

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

18-401

Trade Name: **Buprenex**

Generic Name: **Buprenorphine Hydrochloride**

Sponsor: **Norwich Eaton Pharmaceuticals**

Approval Date: **December 29, 1981**

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APPLICATION NUMBER:

18-401

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CENTER FOR DRUG EVALUATION AND RESEARCH

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18-401

APPROVAL LETTER

NDA 18-401

Norwich-Eaton Pharmaceuticals
Division of Morton-Norwich Products, Inc.
Attention: Alexander B. Neill, Ph. D.
P.O. Box 191
Norwich, New York 10016

DEC 29 1981

Gentlemen:

Please refer to your new drug application dated October 31, 1979 submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Buprenex (buprenorphine hydrochloride injectable).

We acknowledge receipt of your communications dated July 14 and 23, 1981 and August 28, 1981.

We have completed the review of this application and have concluded that the drug is safe and effective for use as recommended in the labeling. As discussed in a telephone conversation between Dr. Alexander Neill and Dr. Marion J. Finkel on December 22, 1981, you have agreed to the conditional Phase IV bioavailability study and the labeling revisions outlined in our October 14, 1981 letter. Accordingly, the application is approved.

As you know, the Division is preparing documents to affect lesser controls for buprenorphine. This, however, in no way impairs your approval to market buprenorphine in its current controlled substances schedule.

The enclosures summarize the conditions relating to the approval of this application.

Please submit copies of your final printed labeling and one market package of the drug when available.

Sincerely yours,

M J F

Marion J. Finkel, M.D.
Associate Director
for New Drug Evaluation
Bureau of Drugs

Enclosures: Records and Reports Requirement
Conditions of Approval of NDA

43.V. for ETOCUS 12/28/81
dc
Jc 12/28/81

NDA 18-401

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cc:

NYK-DO

NDA

HFL-10

HFD-616

HFD-100/Dr. Finkel

HFD-120

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HFD-120/Rev: FVocc1/12/24/81

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APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-401

LABELING

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-401

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data

Original NDA 18-401

Sponsor: Eaton-Reccol, Inc.
Norwich, New York

Drug: Buprenorphine Hydrochloride injectable

Category: Mixed agonist-antagonist analgesic for the relief of moderate to severe pain

Date of Submission: October 31, 1979

Date of Review: April 25, 1980

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1. General Information

a. Name of Drug

- (1) Generic name; buprenorphine hydrochloride injectable
- (2) Trade name; not available at this time
- (3) Structural Formula and Description

Chemical Name: [5 ,7 (S)]-17-(cyclopropylmethyl)- - (1,1-dimethyl- ethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy- α -methyl-6,14-ethenomorphinan-7-methanol Hydrochloride

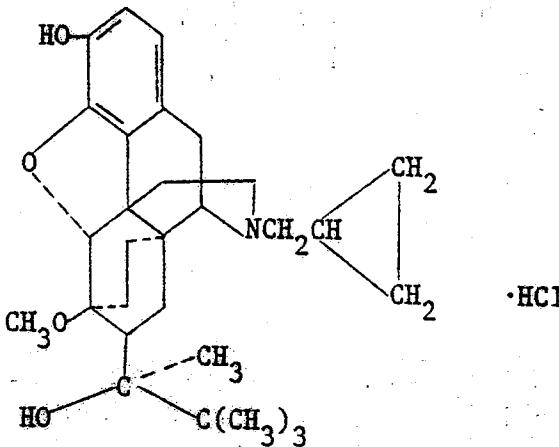
Alternate Name: N-Cyclopropylmethyl-7-(1-(S)-hydroxy-1,2,2-trimethyl-propyl-6,14-endoethano-6,7,8,14-tetrahydronororipavine

CAS Register
Number: 53152-21-9
52485-79-7 (Free base)

Molecular formula: C₂₉H₄₁NO₄ HCl

Molecular Weight: 504.11

Structure:



Buprenorphine is a ring-C-bridged oripavine derived from thebaine with high affinity for the opiate receptor. However, it exhibits a relatively low intrinsic activity. These properties result in both opiate agonist and antagonist effects. As a partial agonist on the opiate receptor it produces analgesia and antagonist effects. Its analgesic potency is approximately 30 times that of morphine, but its partial agonist profile and particularly its slow receptor kinetics impart pharmacological properties that are distinct from morphine on the one hand and the marketed drugs butorphanol (marketed as STADOL by Bristol Laboratories) and nalbuphine (marketed as NUBAIN by Endo Laboratories) on the other hand.

1. a. Clinical Studies:

Buprenorphine is synthesized in the U.K. by Reckitt and Colman and was originally sponsored by Lederle Laboratories in its early development within the United States.

When early data generated at NIDA's Addiction Research Center indicated some "euphoria," the U.S. sponsor, Lederle Laboratories, dropped the drug for injectable or sublingual use. The investigation of the safety and efficacy was pursued, however, by the parent company in England. In the following discussion of the pivotal data, I will indicate those studies that were monitored by Lederle Laboratories and those that were conducted and monitored by the sponsor, Eaton-Reccol.

- b. Pharmacologic category; mixed agonist-antagonist
 - c. Proposed indication; potent injectable analgesic for the relief of moderate to severe pain.
 - d. Dosage form and routes of administration; injectable to be given by intramuscular administration or by intravenous administration.
 - e. Related drugs; morphine, butorphanol injectable (NDA 17-857), nalbuphine injectable (NDA 18-024).
2. Manufacturing Controls (refer to Chemistry Review)
3. Pharmacology (refer to Pharmacology Review)
4. Clinical Background

Buprenorphine is a new potent analgesic of the mixed agonist-antagonist class which differs from marketed compounds both in its clinical and pharmacological profile. The INDICATION section of the proposed labelling simply states "(Tradename) is indicated for the relief of moderate to severe pain." The DESCRIPTION Section states "The duration of analgesia is up to eight hours. (Tradename) is approximately thirty times more potent than morphine. Clinically, 0.3 mg (Tradename) provides pain relief equivalent to 10 mg morphine or 75 mg meperidine. The onset time for analgesia is within 15 minutes following intramuscular administration, and more rapidly following intravenous administration. Peak analgesic activity is usually obtained 1 hour following intramuscular injection."

The clinical development of buprenorphine was carried out in the U.S.A., Britain, Continental Europe, New Zealand, and South Africa. This submission contained the results of a wide variety of clinical trials involving 1,022 subjects. These subjects were administered buprenorphine either intramuscularly or intravenously in open or double-blind fashion. The drug is currently marketed in the United Kingdom, and the data obtained from a monitored post-marketing report on more than 17,000 administrations is also included in this submission (9123 subjects).

The clinical section of this submission contains seventy-four clinical studies performed and described by fifty-five physicians and included clinical pharmacology studies to evaluate safety and tolerance, including evaluation of the respiratory effects of buprenorphine (74 subjects), pharmacokinetic studies in both healthy volunteers and in patients (21 subjects). The dose range studies to establish a clinically useful dose range involved 310 subjects. The pivotal efficacy comparisons were

obtained with morphine, pentazocine, pethadine, and Omnopon (a trade name for a drug marketed in the United Kingdom) (417 subjects). A series of open trials were also undertaken to broaden the clinical experiences with the drug by the intramuscular and intravenous routes of administration (221 subjects). Case record forms are included for the patients who received buprenorphine and the 388 subjects who received other drugs in these studies.

Physical dependence liability in man has been assessed and the data submitted for review.

The section noted "Other Clinical Reports" contains summary information on 760 subjects given buprenorphine for a variety of indications. Dr. Forrest and Dr. Quack's case report forms are included in this submission and are in addition to the 1,022 case report forms noted above. In addition, a report on a United Kingdom monitored post-marketing program contains information on an additional 9,123 subjects as described above. Also submitted is a clinical literature review consisting of 63 manuscripts and/or abstracts.

I. General Information

A. Demographic Data

1. Etiology of Pain

Table I denotes the etiology of pain for the 1,022 subjects given buprenorphine (435 males and 587 females) included in the clinical pharmacology, dose range, controlled double-blind comparisons and open label studies.

Table I
Population Summary by Etiology of Pain

<u>Etiology of Pain</u>	<u>Total</u>	<u>Males</u>	<u>Females</u>
Acute Postoperative	867	320	547
Phase I (Pain Free Volunteers)	74	74	0
Cancer	50	19	31
Renal Colic	7	6	1
Miscellaneous	24	16	8
Total	1022	435	587

Table 2 denotes the etiology of pain for the 684 patients (329 male, 342 female, and 13 sex unspecified) given buprenorphine and included in the "Other Clinical Studies" section. Dr. Forrest's patients are not included in this table; however, the study is discussed later in this review.

Table 2
Population Summary by Etiology of Pain
for "Other Clinical Studies"

<u>Etiology of Pain</u>	<u>Total</u>	<u>Males</u>	<u>Females</u>	<u>Sex Unspecified</u>
Acute Postoperative	313	96	217	0
Myocardial Infarction	103	91	12	0
Cancer	159	103	56	0
Miscellaneous	109	39	57	13
Total	684	329	342	13

2. Age Range and Sex

Table 3 denotes the population summary by age and sex for the subjects given buprenorphine.

Table 3
Buprenorphine Studies
Population Summary by Age and Sex

<u>Age</u>	<u>Males</u>	<u>Females</u>	<u>Total</u>	<u>% of Total</u>
Unknown	27	18	45	4.4
11-20	16	17	33	3.2
21-40	162	235	397	38.9
41-60	150	222	372	36.4
61-80	77	93	170	16.6
81	3	2	5	0.5
Total	435	587	1022	100.0

B. Dosage Schedules

Tables 4 and 5 include the intramuscular injection dosage schedules for the open and controlled Phase II and III investigations. The majority of the patients received one I.V. or I.M. dose. The doses most often used were 0.3 - 0.6 mg, which is the therapeutic dose range for pain relief.

Table 4

Number of Patients Receiving One or More Intramuscular Injections of Buprenorphine (x)

<u>Dosage (mg)</u>	<u>Number of Injections</u>				<u>Total No. of Injections</u>
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	
≤ 0.05	14				14
$0.05 < x \leq 0.1$	17	1			19
0.1	68	2	1		75
$0.1 < x \leq 0.2$	77				77
0.2	169				179
$0.2 < x \leq 0.3$	41				41
0.3	80	30	6	7	186
$0.3 < x \leq 0.4$	9				9
0.4	213				221
$0.4 < x \leq 0.5$	10				10
0.5	6				6
$0.5 < x \leq 0.6$	7				7
0.6	60	1			62
$0.6 < x \leq 0.7$	10				10
0.7	0				0
$0.7 < x \leq 0.8$	4				4
0.8	31	2			35
1.6	15				15
Total				=	970

Table 5

Total Number of Injections of Intramuscular Buprenorphine (x)

<u>Dosage (mg)</u>	<u>No. of Injections</u>	<u>Percent of Total</u>
$x < 0.3$	405	41.7
$0.3 \leq x \leq 0.6$	501	51.6
$x > 0.6$	64	6.6

C. In all cases, the .05 level of confidence was the criterion for significance and two tailed tests were used.

D. Laboratory studies, vital signs, and adverse reactions were included in all studies. A brief review of the safety studies and a summary of adverse reactions will be presented following the efficacy section.

II. Clinical Pharmacology

The clinical pharmacological profile for both single and multiple doses of buprenorphine was assessed in normal volunteers. This included safety and tolerance studies (2 single dose volunteer studies, 2 multiple dose volunteer studies), 5 studies for the assessment of respiratory effects, 3 pharmacokinetic studies and 4 physical dependence studies.

1. Safety and Tolerance Studies

Table 6 reviews the study design, parameters measured, number of subjects and investigators involved in the studies.

In the initial safety and tolerance studies carried out in volunteers, buprenorphine was shown to possess a pharmacologic profile which could be described as opiate like and included such pharmacological effects as varying degrees of drowsiness, occasional alterations in CNS perception, miosis, nausea/vomiting, occasional transient euphoria, and minor degrees of cardiopulmonary function depression. As will be discussed in the section on physical dependence of this review, the volunteer who has a past history of opiate dependence recognizes more than "occasional alterations in CNS perception."

These are consistent with the animal pharmacological profile and with effects common to other potent analgesic agents. The only unexpected occurrence was the development of an abnormal ECG in Subject 020 in the study of Okun/Elliott. This subject was a 55 year old, black male without history of cardiovascular system disease. Baseline ECG was unremarkable. Approximately 7 hours after receiving 0.025 mg/kg intramuscular buprenorphine (1.36 mg), the ECG revealed slight ST segment elevation and deep symmetrical T wave inversions in Leads V₂-V₃. This abnormality had lessened by the following day and ECG was entirely normal and identical with the pre-drug tracings by approximately 3 days post-dosing. The subject did not experience either chest pain or dyspnea. Serial cardiac enzymes (CPK, SGOT, and LDH isoenzymes) did not suggest myocardial damage. Further, neither post-drug response of pulse and blood pressure to tilt table evaluation nor evaluation of systolic time intervals reveals acute myocardial insult. The investigator concluded that although the ECG abnormality was possibly caused by buprenorphine, clinical hemodynamic and laboratory data revealed neither evidence of myocardial damage nor impaired contractility. I agree with this evaluation and feel this does not present a major safety problem.

2. Respiratory Studies

Table 7 reviews the study design, parameters measured, and investigators involved in the studies.

Of particular interest in the profile of any potent narcotic is the degree of respiratory depression it produces. As noted this was evaluated in depth in a series of 5 studies by Dr. Orwin. In these studies he measured the displacement of carbon dioxide respiratory response curves at an alveolar ventilation of 20 liters/min. A rebreathing technique was used. Shifts in the response curve are believed to result from decreased responsiveness of CO_2 receptors. The technique is considered sensitive and will often detect changes well below the level of clinical significance. Initial comparison of intramuscular buprenorphine (0.3 mg) to morphine (12.5 mg) failed to produce differences. Further comparisons of intramuscular buprenorphine (0.15 mg, 0.3 mg, and 0.6 mg) to morphine (5.0 mg and 10.0 mg) were made. Peak values obtained were used to determine a relative potency of buprenorphine to morphine (44:1) with confidence limits of 21:1 to 92:1 in terms of respiratory depressions at peak. In this study, a plateau in curve displacement appears to occur between 0.3 mg and 0.6 mg. Evaluating this situation further, doses of 1.2 mg buprenorphine were administered to 5 of the 6 volunteers in this study and this dose demonstrated further displacement. None of these changes resulted in manifestations that were of clinical concern.

Subsequent studies demonstrated that naloxone in rather high intravenous doses of 2.4 mg to 16.0 mg produced on the average 50% reversal of a 0.3 mg buprenorphine dose. However, doxapram when given at 1.0 mg/kg intravenously significantly reversed 0.3 mg of intravenous buprenorphine within 2 - 3 minutes. It was therefore concluded that recommended doses of doxapram successfully counteract the respiratory depressant affects of buprenorphine measured by CO_2 curve displacement.

3. Pharmacokinetic Studies

Table 8 reviews the study design, parameters measured, number of subjects and investigators involved in the studies. Preliminary pharmacokinetic and metabolic studies were done to assess the half-life and excretion pattern after buprenorphine was administered intramuscularly. After intramuscular administration of ^3H -buprenorphine (2 g/kg) (N = 1 volunteer), the high initial plasma level of radioactivity rapidly declined to low levels by 4 hours. In another single patient study, after an oral dose (15 g/kg) the peak plasma levels of radioactivity was found 2 hours after dosing. The level then declined rapidly up to 6 hours, after which time further decline was slow. The drug was excreted predominantly in the feces as free buprenorphine with traces of the N-desalkylbuprenorphine after both intramuscular and oral administration (N = 2). Slightly higher levels of urinary excretion are found

in man than in animals (15% oral, 27% i.m.). Radioactivity in human urine was present as polar glucuronide conjugates of the unchanged drug and the N-desalkylmetabolite. In another small preliminary study, additional human kinetics data were obtained by investigator Hovell. Plasma concentrations, as determined by radioimmunoassay, were obtained after intramuscular and intravenous administration (N=12). For both routes considerable inter-subject variation existed. The pharmacokinetic pattern noted was complex. The half-life for the initial elimination phase after intravenous administration of the drug in one subject was estimated as 6 minutes.

Subsequent plasma elimination half-life ranged from 60 - 180 minutes. After intramuscular administration, peak plasma concentrations occurred within 15 minutes. As will be seen later, this rapid attainment of peak plasma concentrations is consistent with an onset of pain relief of 15 - 30 minutes. Although the initial elimination phase could not be estimated, the terminal phase appeared to be similar to that found after intravenous dosing.

Formal bioavailability studies as required for NDA approval have not been submitted.

4. Abuse potential studies

The abuse potential of buprenorphine was evaluated in a series of studies of Dr. Donald Jasinski. Table 9 reviews the study design, parameters measured, and the study's location within the NDA submission. This information is based on a published report rather than a series of studies commissioned by the firm for this NDA. The reference is: Jasinski, D.R.; Pevnick, J.S.; Griffith, J.D.; Gorodetzky, C.W., and Cone, E.J. Progress Report on Studies from the Clinical Pharmacology Section of the Addiction Research Centre. Assessment of Buprenorphine for Morphine-Like Effects in Man and Evaluation As a Maintenance Drug in the Treatment of Narcotic Addiction. Reported to the Committee on Problems of Drug Dependence, Richmond, Virginia, 1976, p. 131 - 148.

In the first study, subcutaneous buprenorphine, 0.2, 0.4, and 0.8 mg; subcutaneous morphine, 15 and 30 mg and placebo were compared in nine subjects using a double-blind crossover design. Buprenorphine was found to produce typical morphine-like subjective effects which were of slower onset and longer duration than those obtained with morphine.

In the second study, subcutaneous buprenorphine, 0.6 and 1.2 mg, and subcutaneous morphine, 20 and 40 mg, were compared to determine if the morphine-like subjective effects of buprenorphine reached a plateau. For all parameters, the responses to 1.2 mg of buprenorphine were less than the responses to 40 mg of morphine and using the MBG (Morphine-Benzedrine Group) scale scores and the opiate symptoms scores, the responses to 1.2 mg of

buprenorphine were found to be less than those produced by 0.6 mg of buprenorphine. The results suggest the existence of a plateau with a maximum effect at the 1.0 mg level, at least, as far as the parameters assessed in this study.

In the third and final single dose study, buprenorphine 1.0 mg, morphine 30 mg, methadone 30 mg, and placebo were administered at weekly intervals to 14 subjects using a randomized double-blind crossover design. Observations were made at 0.5, 1, 2, 3, 4, 5, 6, 12, 24, 30, 36, 48, 54, 60, and 72 hours after drug administration. Both buprenorphine and methadone produced sustained miosis which lasted throughout the entire period of observation (72 hours) and a less pronounced but similarly long-lasting response was obtained in some subjective effects.

The multiple dose trial was a direct dependence study involving five subjects. Buprenorphine was given as a single daily injection. After two weeks on saline placebo, buprenorphine was introduced and during the following 15 days the single daily dose was increased from 0.5 mg to 8.0 mg. This dose, which was considered equivalent to 240 mg of morphine, was then administered once daily for the remainder of the study. During the period of chronic administration two sets of experiments were performed. Single doses of morphine and placebo were administered and their effects compared to those obtained with similar doses during the control phase when subjects were receiving saline. In the other experiment, naloxone was administered to test if this would precipitate a morphine-like abstinence syndrome. In the first experiment, buprenorphine blocked the effects of morphine and this effect persisted undiminished for at least 25 to 30 hours after drug administration. In the second experiment, naloxone in doses of up to 4 mg failed to precipitate any discernible abstinence as measured by abstinence score by subject's reports of withdrawal illness. Two of the five subjects withdrew from the study prematurely (after 42 and 47 days of chronic administration, respectively). Persistent nausea and occasional vomiting was the reason for withdrawing in one of the subjects; the other subject complained of increasing nervousness and irritability. After completion of the precipitation tests, the three remaining subjects were stabilized on buprenorphine for 8 more days and then saline placebo was substituted under double-blind conditions.

During the first ten days of withdrawal, Himmelsbach scores indicated the presence of mild abstinence which was below the level of clinical significance for morphine withdrawal and less than that observed with other drugs which have produced mild abstinence syndromes in direct dependence tests. On the 14th day of withdrawal there was an increase in abstinence signs and Himmelsbach scores increased from a mean of 9 points on the 13th day to a mean of 23 points on the 14th day. Subjects reported feeling bad, were depressed and demanded relief of their symptoms with morphine. Nausea, vomiting, restlessness, insomnia and diarrhea were present for the first time, indicating more severe withdrawal. These two patients were able to be medically managed without the administration of narcotics.

III. Effectiveness

1. Dose range studies

The dose range studies were designed to establish a dose range for injectable buprenorphine which is effective and caused minimal side effects in a variety of painful conditions. Buprenorphine's potency relative to injectable morphine was also established. Six studies including a total of 328 patients of which 310 received buprenorphine were undertaken to meet these goals. Of these patients 166 were involved in the open label dose range trials and the remaining 162 participated in a double-blind controlled bioassay study.

The doses of buprenorphine which were evaluated ranged from 0.025 to 1.6 mg and were always administered by the intramuscular route. The parameters assessed in these studies included pain intensity, pain relief, 50% relief, sedation, time to remedication, vital signs (blood pressure, pulse, and respiratory rate), side effects and injection site tolerance.

The details of the design of these trials are highlighted in Table 10.

The findings of the open label dose ranging studies are presented in Table 11.

Table 11
Summarization of Results of Five Open Label Dose Range Studies
for Injectable Buprenorphine

<u>Investigator</u>	<u>Dose range Producing Measureable and Satisfactory Analgesia</u>	<u>Time to Onset of Action (Post-Injection)</u>	<u>Duration of Analgesia</u>
Dr. Ouellette	0.2 - 0.6 mg	Within 30 min	4 - 6 hours
Dr. Dobkin	0.2 - 0.6 mg	By 30 min	4 - 6 hours
Dr. Sunshine	0.2 - 0.6 mg	Within 30 min	4 - 6 hours
Dr. Kantor	0.1 - 0.4 mg	Within 30 min	3 hours
Dr. Robbie	0.025 - 0.72 mg	Within 1 hour	5 hours

Although Table 11 is presented only for visual comparison of the results of several investigators, it is supportive of the interpretation that intramuscular doses of 0.2 - 0.6 mg buprenorphine produce analgesia for 4 - 6 hours after injection.

The doses of buprenorphine which were evaluated in the uncontrolled studies ranged from 0.025 to 0.72 mg and evidence of measurable analgesic activity [based on Sum of Pain Intensity Difference (SPID) and Total Pain Relief (TOTPAR)] was found by all the investigators and with all the doses tested. However, differences in the degree of analgesic activity with 0.2 - 0.7 mg doses was less apparent than doses below 0.2 mg which were found to be significantly less effective. Onset of action within 30 minutes of intramuscular administration was a consistent finding throughout all the studies and for all the doses tested. Duration of action, based on the hourly Pain Intensity Decrease (PID), pain relief scores and on the remedication time also showed overall consistency. A duration of 4 - 6 hours was generally obtained with the doses of 0.2 mg and above. The lower doses had a significantly shorter duration of action with most patients receiving remedication within 3 hours of dosing. The analgesic effect of buprenorphine was found to be sufficiently adequate to cope with the various painful conditions included in the studies.

The other study included in this category is a double-blind controlled relative potency assessment conducted by Houde. This analgesic potency assay of intramuscular buprenorphine and intramuscular morphine was conducted in patients with post-operative pain or chronic pain due to cancer. The study consisted of a series of seven twin crossover comparisons, each patient received two doses, a lower dose of one drug and a higher dose of the other drug. In all comparisons the doses of morphine used were 8 and 16 mg while the doses of buprenorphine were 0.05 and 0.1 mg (two comparisons), 0.1 and 0.2 mg (two comparisons), 0.2 and 0.4 mg, 0.4 and 0.8 mg, and 0.8 and 1.6 mg.

A total of 162 patients participated in the various comparisons. Prior to dosing, each patient's pain was evaluated as to its site, character, and intensity. After the administration of the test drugs the parameters assessed were pain intensity, pain relief, 50% relief, acceptability, side effects and injection site reaction.

The analgesic potency was evaluated based on SPID, TOTPAR, maximum PID and maximum pain relief for the four comparisons which used buprenorphine doses of 0.1 and 0.2 mg, 0.2 and 0.4 mg, 0.4 and 0.8 mg, and 0.8 and 1.6 mg. The lowest doses of buprenorphine (0.05 and 0.1 mg) were not analyzed because they did not produce adequate pain relief. A weighted single potency estimate for each parameter was constructed from the estimates of these studies. Based on TOTPAR, the estimate of the potency of buprenorphine relative to morphine was 29 (95% confidence limits: 19-40). ←

The bioassay study demonstrated a potency ratio between buprenorphine and morphine of approximately 30:1. Thus, a 0.30 mg intramuscular dose of buprenorphine would be expected to produce analgesia similar to that of 10 mg morphine.

2. Controlled Double-Blind Studies

The controlled clinical trials are divided into two subcategories, comparisons with morphine (N = 5) and comparisons with other potent analgesics (N = 3). These studies included patients needing analgesia for various painful conditions.

Laboratory studies, vital signs, level of sedation and adverse reactions were included as study parameters in all eight studies. A brief review of the safety data and specifics of the adverse reactions will be presented in the review of each study. An overall review of the safety issues will follow this efficacy section.

Two overall measures of treatment efficacy were derived from the pain intensity and pain relief scores. The sum of the pain intensity differences (SPID) was calculated by adding the product of the difference between each post-drug and pre-drug pain intensity scores (denoted PID) and the corresponding elapsed time interval since the previous observation, discarding negative values. Total pain relief (TOTPAR) was calculated by adding the product of each pain relief score and the corresponding time interval since the previous observation. SPID's and TOTPAR's were obtained for each patient. For patients requiring remedication before 6 - 8 hours, depending on the study, SPID's and TOTPAR's up to the time of remedication were obtained.

To further characterize analgesic effect over time, two additional parameters were defined. PEAK PID was the maximum observed pain intensity difference. REMEDHR was the time to administration of additional analgesic medication and reflected duration of action.

For PEAK PID, contingency table chi-square methods were used to compare the treatment groups. Lifetable techniques with adjustment for baseline pain intensity were used to compare the times to remedication among the four treatments.

The patient's and investigator's assessments of the overall relief provided by each test medication were analyzed by assigning scores to the ordered outcome categories and using analysis of variance.

To characterize the overall extent of sedation, the sum of sedation level differences (SSLD) was defined as the sum of the product of the difference between each post-drug and pre-drug sedation level score and the corresponding time interval since the previous observation, discarding negative values. Analysis of covariance using BMDP7V was used with baseline sedation level score and age as covariates to examine any treatment differences for this variable.

For respiratory rate, pulse rate, and blood pressure, mean changes from baseline values were computed at each post-drug evaluation time within each

treatment group and the significance of the changes assessed by paired t-tests. Analysis of variance was used to compare the mean changes among the treatment groups at each evaluation time. Duncan's multiple range procedure was used to identify significant pairwise treatment differences when the overall test from the one-way ANOVA was significant (i.e. $p < 0.05$).

The safety considerations are basically the same for all eight studies. The data collected is as follows with the minor differences addressed in the review of each study: medical and surgical history, preoperative laboratory examinations (hemoglobin, hematocrit, WBC with differential count, RBC, complete urinalysis, blood urea nitrogen, SGOT, SGPT, and serum alkaline phosphatase), and physical examination, and admission diagnosis documented for each patient.

At each observation period the following was assessed or measured:

A. Degree of Sedation

- 1 = Alert
- 2 = Mildly Drowsy
- 3 = Moderately Drowsy
- 4 = Asleep

B. Blood pressure (supine)

C. Pulse Rate (supine)

D. Respiratory Rate

E. Side Effects

At each observation point, after asking about pain, the "observer asked routinely" all patients, "Is anything else bothering you?" Any overt or volunteered emergent symptom were recorded, noting severity, time of onset and duration, and probable relationship to study drug administration.

a. Comparisons with Morphine

This category includes five randomized, parallel, double-blind controlled studies using morphine as the reference agent. A total of 479 patients experiencing moderate to severe post-operative pain were involved and both test drugs were given by the intramuscular route only.

All five studies involved single dose administration. The doses of buprenorphine ranged from 0.15 mg to 0.6 mg and the dose of morphine ranged from 5 mg to 15 mg. All patients were assessed for pain intensity, pain relief, vital signs (blood pressure, pulse and respiratory rate) and side effects before and at various times for up to 8 hours after dosing.

Tables 12 and 13 summarize the five studies

I. Principal Investigator:

a. Robert Ouellette, M.D.
St. Vincent Hospital
Worcester, Massachusetts

Harriet Kiltie, M.D. - Monitor
Lederle Laboratories

Title of Study:

Comparison of the Analgesic Activity of Buprenorphine with Morphine Given as a Single Intramuscular Injection to Post-Operative Patients Experiencing Moderate to Severe Pain

(1) Objective of the Study

The purpose of this study was to compare the analgesic activity of 0.15 and 0.3 mg of buprenorphine with that of 5 mg and 10 mg of morphine in post-operative patients experiencing moderate to severe post-operative, fracture or somatic pain requiring parenteral analgesia.

(b) Experimental Design**(1) Patient Population****(a) Demography**

This was a randomized, double-blind parallel study with 69 patients enrolled. A total of 80 drug administrations were given to these patients, with 11 patients receiving two administrations of test medication. Only the observations for the first administration have been included in the analyses of this report. Additionally, 2 patients who had a history of narcotic addiction have been excluded from the analysis because, according to the protocol, these patients should not have been enrolled in the study. Thus a total of 69 individual patient drug administrations have been analyzed in this report.

The numbers of patients analyzed for each treatment are as follows:

<u>Treatment</u>	<u>Number of Patients</u>
0.15 mg buprenorphine	17
0.30 mg buprenorphine	16
5 mg morphine	17
10 mg morphine	17

Among the 67 patients analyzed, there were 28 males and 39 females.

The comparability of the four treatment groups with respect to weight and age was assessed separately using a two-way analysis of variance model with sex as a blocking factor. The chi-square test was used to compare the sex distributions in the treatment groups.

The sex distributions in the four treatment groups were comparable. The chi-square value for testing the homogeneity of sex distributions was 0.743 (d.f. = 3, p = 0.86). The mean weights were not significantly different ($p > 0.50$) in the four treatment groups.

The mean ages in the four treatment groups differed significantly ($p < 0.05$). Pairwise comparisons of means using Duncan's multiple range procedure revealed that the mean age in the 5 mg morphine group was significantly greater than the mean ages of the three other treatment groups. There were no significant differences in mean ages among these three other treatment groups. Age was used as a covariate in the analysis of SPID, TOTPAR, and SSLD values in an attempt to adjust for any differences in response among the treatment groups which might be attributable to differences in age.

(b) Clinical Characteristics for Inclusion:

- A. Over 18 years of age, weighing between 100 and 225 pounds.
- B. Undergoing a major abdominal, thoracic, or orthopedic surgical procedure.
- C. Experiencing moderate to severe postoperative, fracture, or somatic pain and requiring parenteral analgesic medication.
- D. Fully responsive with a clear sensorium following general anesthesia.

Patients were assessed by medical history and physical examination prior to enrollment in this study. Pre-study laboratory tests included hematology (hemoglobin, hematocrit, red cell count and white cell count with differential), blood chemistry profile (including SGOT, SGPT, alkaline phosphatase, BUN) and urinalysis (including specific gravity, pH, albumin, glucose, acetone, and microscopic). These parameters are adequate measurements for this study.

(c) Exclusions

- A. Women who are pregnant, lactating or of childbearing potential.
- B. Patients undergoing methadone or other narcotic maintenance treatment or having a history of narcotic drug tolerance or addiction.
- C. Patients undergoing neurosurgery or cardiac surgery.
- D. Any patient who on the basis of clinical history, physical examination and preoperative laboratory examination, has or is suspected of having severe renal, hepatic, respiratory, cardiac, prostatic or endocrine disease, phaeochromocytoma, or hematologic disease will be excluded from the study.
- E. Patients who have limited mental competence and/or who may have difficulty answering questions at interview.

(2) Procedure

(a) Specific Formulation(s) used in Study:

Patients were assigned one dose of test medication provided in identical appearing amber glass ampuls. The drugs were supplied as follows:

Buprenorphine	0.15 mg/ml	1 ml ampul
Buprenorphine	0.30 mg/ml	1 ml ampul
Morphine	5 mg/ml	1 ml ampul
Morphine	10 mg/ml	1 ml ampul

All ampules were labeled to show only the patient's study number; a sealed, tear-off portion of the label concealed the identification of the drug and the strength. This tear-off portion was to be opened only in the event of emergency. All envelopes remained unopened.

(b) Type of Experimental Controls:

This was a double-blind parallel study in 69 patients who were randomly divided into four treatment groups. Randomization was accomplished in blocks of 20 to permit interim analyses of successive groups of patients.

This procedure is not appropriate or adequate for this study. See reviewer's comments.

(c) Dosage schedule: See table 12 and 2 (a) above.

(d) List desirable concomitant medication: none

(3) Safety Considerations: Observations prior to, during, and after study.

(a) Clinical Studies: see introduction to this section, Table 12.

(b) Laboratory Studies: see introduction of this section, page 21.

(c) Indications for removing a patient from the study are listed in exclusion criteria above. Two patients with a history of narcotic addiction were excluded from the efficacy analysis; however, safety data was obtained.

(d) Study Observations:

Four patients reported undesired side effects during the observation period. Only one of these received buprenorphine (0.30 mg) and this patient reported mild nausea which developed at two and one-half hours after drug administration and lasted for one hour. No treatment was required.

(4) Efficacy Considerations

(a) Clinical and laboratory measurement used to characterize efficacy or comparability:

Evaluations were made over a 6 hour study period. Immediately prior to, and at 1/6, 1/3, 1/2, 1, 2, 3, 4, 5, and 6 hours after drug administration the following measures were assessed by a trained observer.

a) Pain intensity

0 = none
1 = mild
2 = moderate
3 = severe
4 = very severe

b) Pain relief

0 = none
1 = slight
2 = moderate
3 = good
4 = complete

c) Level of sedation

1 = alert
2 = mildly drowsy
3 = moderately drowsy
4 = asleep

The following vital signs were recorded at all the above listed times with the exception of the 1/6 and 1/3 hour points.

- d) Respiratory rate
e) Pulse rate (supine)
f) Blood pressure (systolic and diastolic, supine)

The patients were also observed for treatment emergent signs and symptoms over the evaluation period.

At the six hour observation interval, the overall pain relief provided by the medication was assessed first by the patient and then by the investigator as poor, fair, good or excellent.

Clinical evaluations were discontinued following remedication for those patients who received additional analgesic medication before the end of the 6 hour study period.

(b) $\alpha = .05$ is the degree of significance.

(c) The endpoints for efficacy evaluation are appropriate.

(5) Results of Statistical Consultation:

a. Statistical methods in the comparability of demographic variables and baseline sedations are acceptable. For baseline pain intensity, the standard chi-square test would have been more appropriate than the analysis of variance method because of the categorical nature of the data and concentration of most of the data in two categories. However, both methods yielded non-significant results in this study.

b. Within the 6-hour study period, clinical evaluations for pain and vital signs were discontinued after remedication. The applicant explained that this was to avoid the effects of the additional analgesics administered on remedication from entering into the analyses. However, over half of the patients received pre-study analgesics within 6 hours prior to the start of administrations of the study drugs. Ten patients received pre-study analgesics as late as 2 to 3 hours prior to the study drugs (pages 38-44, Volume 1.8 of the NDA submission). The applicant ignored the possible influences of pre-study analgesics in all the analyses. According to the reviewing medical officer, the consequences of this are important. The applicant should either have stratified or made adjustments in the analyses for the type of and elapsed time since the administration of pre-study analgesics.

c. In this study there was no distinction made between pain at rest and pain on motion. This distinction was made in study number 5 discussed later in this review and the results of some of the analyses were different between pain at rest and pain on motion. The reviewing medical officer agreed that the applicant should demonstrate the role this distinction plays in all these studies.

d. Methods of assessments for pain intensity and pain relief were not clearly specified when patients were asleep. The buprenorphine groups appeared to have higher mean sedation levels than the 5 mg morphine group although this difference was not statistically significant. A comparison of the individual patient's pain relief scores with sedation levels revealed that most of the patients who obtained complete pain relief were patients who were asleep. The following table shows the number of patients cross-classified by pain relief scores and sedation levels at 3 hours after administration of study drugs.

		Pain Relief Score					Morphine				
		Buprenorphine									
Sedation Level	1	0	1	2	3	4	0	1	2	3	4
	2	0	2	1	6	1	2	3	0	12	0
	3	1	0	0	4	0	0	0	2	4	0
	4	0	0	0	3	0	0	0	0	0	1
		0	0	0	1	12	0	0	0	0	8

This table demonstrates that of the 22 patients who had complete relief (score = 4), 20 were asleep (sedation = 4). The table illustrates clearly the importance of the investigator's rousing a sleeping patient to assess the pain relief. In the case illustrated by the table one cannot entirely separate out sedation effects from pain relief effects. The medical officer agreed that in the opinion of some experts in this field this distinction must be made and the clinical way is to rouse the patients. The sponsor has not done this. One would have to conclude from the sponsor's analyses that in terms of both SSLD and TOTPAR separately as well as SSLD and SPID jointly buprenorphine is significantly superior to morphine. One cannot, however, make the analogous statements for the efficacy variables SSLD, TOTPAR, or SPID separately because of the correlation structure and the way the data were collected. The clinical importance of this observation is left to the medical officer for interpretation.

e. The reviewing medical officer indicated that changes in vital signs due to morphine usually depend on the baseline values. The applicant did not adjust for the baseline values in these analyses either.

f. The nature of side effects was comparable among treatment groups with slightly higher occurrences in the morphine groups. However, it should be noted that side effects might be masked or complicated by the pre-study medications including type and amount of anesthetic.

(6) Results of Study

a. Sponsor's evaluation

All four treatments produced analgesic effects in varying degree during the six hour observation period.

Plots of average pain intensity and pain relief scores showed rapid and substantial analgesia following drug administration for all treatments. Reduced pain was evident by 10 minutes in all drug groups. Peak levels occurred by the one hour evaluation and subsequently gradually returned toward baseline values. The return to baseline was much more rapid and complete for the 10 mg morphine group.

Analyses of the summary efficacy variables SPID and TOTPAR showed the overall effects of the 0.15 mg buprenorphine, 0.30 mg buprenorphine, and 5 mg morphine to be approximately equal in magnitude and greater than those

demonstrated by 10 mg morphine. The only statistically significant ($p < 0.05$) differences, however, were between the 0.30 mg buprenorphine and 10 mg morphine groups.

The overall pain relief provided by the test medications was rated as good or excellent both by the investigator and by the patient for the majority of patients.

Most patients achieved the no pain level at some time during the observation period. There were no significant differences among the treatment groups in the rates of medication.

About half of the patients in the 5 mg morphine and the 0.30 mg buprenorphine groups did not require additional analgesic medication during the 6-hour period. The other two treatment groups had proportionally fewer patients finish the 6-hour period without requiring an additional analgesic. Although suggesting that the 0.30 mg buprenorphine and 5 mg morphine had a longer duration of action the differences were not statistically significant. No tissue reactions were observed during this study.

Sedation was seen in all drug groups with no significant differences in overall extent. All drug groups showed some decrease in respiratory rates and blood pressure but there were generally no significant differences among the treatment groups. Pulse rates remained relatively constant over time. Treatment emergent symptoms were reported in 4 patients. One of these patients received buprenorphine. This patient had mild nausea which did not require treatment.

These results are summarized in Table 13.

(b) Reviewer's Evaluation

1. The test and control groups were comparable by the statistical methods used in the analysis. Proper techniques were applied to assess baseline differences between groups, i.e., age, sex, number of patients per group, etc.

2. The documentation and analysis of results were not sufficient to justify the conclusion.

(c) The data appears to support the sponsor's conclusion as stated above with the reservation that further statistical analysis is required prior to accepting the results as supportive of safety and efficacy.

1. The sponsor ignored the influence of pre-study analgesics in the statistical analysis. Ten patients received pre-study analgesics as late as 2 to 3 hours prior to the study drugs (pages 38-44, Volume 1.8). I recommend the data be stratified or adjustments made in the analyses for the type of pre-study analgesics and elapsed time since the administration of drug.

2. Methods of assessments for pain intensity and pain relief were not clearly specified when patients were asleep. The buprenorphine groups appeared to have higher mean sedation levels than the 5 mg morphine group although this difference was not statistically significant. A comparison of the individual patient's pain relief scores with sedation levels revealed that most of the patients who obtained complete pain relief were patients who were asleep. The sponsor failed to wake up the patients to complete the pain rating forms. Being asleep or awake does not relate to pain or lack of pain and the sponsor should explain why the conclusions are void in regard to efficacy even with this design error.

3. Changes in vital signs due to morphine relate to baseline values and this is presumably true for buprenorphine. The sponsor did not adjust for baseline values in the analysis and the data should be reanalyzed.

4. The nature of side effects was comparable among treatment groups with slightly higher occurrences in the morphine groups. However, it should be noted that side effects might be masked or complicated by the pre-study medications including type and amount of anesthetic. Reanalysis is needed.

5. In this study there was no distinction made between pain at rest and pain on motion. This distinction was made in study number 5 discussed later in this review and the results of some of the analyses were different between pain at rest and pain on motion. The applicant should demonstrate the role this distinction plays in all of these studies.

(d) I disagree with the sponsor's evaluation in that the conclusions are premature. Further analyses are required, and if after that the conclusions still hold validity this study might support efficacy

C. Conclusions

1. Scientific: This submission contains some evidence supporting the sponsor's claim; however, the evidence as presented cannot be considered substantial since there are flaws in the design and serious omissions in the analyses of the data. The points to be addressed and the analyses to be performed are listed above.

2. Deficiencies/Problems in this study as listed above.

II. Principal Investigator:

Robert Ouellette, M.D.
Department of Anesthesiology
St. Vincent's Hospital
Worcester, Massachusetts

Harriet Kiltie, M.D. - Monitor
Lederle Laboratories

Title of Study:

Comparison of Analgesic Activity of 0.2 mg and 0.4 mg of Buprenorphine
Against 5 and 10 mg of Morphine as Intramuscular Injection in Post-
Surgical Patients with Moderate to Severe Pain

(1) Object of the Study:

The purpose of this study is to compare the analgesic activity of 0.2 mg and 0.4 mg of buprenorphine against each other and also against 5 mg and 10 mg of morphine sulfate; each given as a single intramuscular injection following major surgical procedures associated with moderate to severe pain.

(b) Experimental Design

1. Patient population

a. Demography

One hundred thirty-three patients participated in the study and received a total of 159 doses of test medication. Patients who received more than one administration of study drug were entered under a new patient number for subsequent administrations.

The age of the patients ranged from 17 to 71 years with a mean age of 46.4 years for 50 males and 50.5 years for 83 females. Patients' weights ranged from 85 to 236 pounds with a mean weight of 170 lbs for 50 males and mean weight of 144 pounds for 83 females.

Sex distribution for the four treatments were comparable. After adjustment for sex, no differences in treatment groups with respect to age, weight, and height were demonstrated by analysis of variance. Three patients were not Caucasian and the race of one patient was not recorded.

Each patient was to have undergone a major abdominal, thoracic or orthopedic surgical procedure and experiencing moderate to very severe pain. All were to be fully responsive after recovering from general anesthesia.

(b) Clinical characteristics for inclusions:

Hospitalized patients who satisfy the following criteria:

Inclusion Criteria

Each patient will be:

- A. Over 18 years of age, weighing between 100 and 200 lbs.
- B. Undergoing a major abdominal, thoracic or orthopedic surgical procedure
- C. Fully responsive following general anesthesia and experiencing moderate to very severe pain.

Each patient's health status was assessed by medical and surgical history and physical examination upon enrollment in this study. Pre-study laboratory tests included hematology consisting of RBC, hemoglobin, hematocrit, WBC with differential; blood chemistry profile including glucose, total bilirubin, SGOT, SGPT, alkaline phosphatase and BUN; and urinalysis including specific gravity, albumin, glucose, microscopic and pH.

Exclusion Criteria

- A. Women who are pregnant, lactating, or of childbearing potential.
- B. Patients undergoing methadone or other narcotic maintenance treatment or having a history of narcotic drug tolerance or addiction.
- C. Patients undergoing neurosurgery or cardiac surgery.
- D. Any patient who on the basis of clinical history, physical examination and preoperative laboratory examination, has or is suspected of having severe renal, hepatic, respiratory, cardiac, prostatic or endocrine disease, phaeochromocytoma, hematologic disease will be excluded from the study.
- E. Patients who have limited mental competence and/or who may have difficulty answering questions at interview.

(2) Procedure

a. Specific Formulation(s) Used in Study

Each of the patients in this study received a single intramuscular injection of either buprenorphine (0.2 or 0.4 mg) or morphine (5 mg or 10 mg). The study drugs were supplied in amber colored glass ampuls as follows:

Buprenorphine	0.2 mg/ml	1 ml ampuls
Buprenorphine	0.4 mg/ml	1 ml ampuls
Morphine	5 mg/ml	1 ml ampuls
Morphine	10 mg/ml	1 ml ampuls

All ampuls were identical in appearance and were labeled only with the patient's study number; a sealed, tear-off portion of the label concealed the identification of the drug and the strength. This was to be opened only in the event of medical necessity.

(b) Type of Experimental Controls:

Under the procedures of this study, post-surgical patients experiencing moderate to very severe pain were randomly given, in a double-blind fashion, a single injection of 0.2 or 0.4 mg buprenorphine or 5 or 10 mg morphine. Evaluations of analgesic efficacy and safety were then made over a six hour period. In addition it was specified that when a patient was asleep and in no obvious pain, ratings of zero for pain intensity and 4 for pain relief were assigned. If the patient was asleep but appeared to be in pain, he/she would be roused for the usual ratings.

This procedure is not appropriate and adequate for this study. See reviewer's comments.

(c) Dosage schedule: See table 12 and 2 (a) above.

(d) List desirable concomitant medication: none

(3) Safety considerations - Observations prior to, during, and after study.

a. Clinical studies: See introduction and Table 12

b. Laboratory studies: See introduction of this section.

c. Indications for removing a patient from the study are listed in exclusion criteria above.

d. Study observations:

Somnolence was the most frequent side effect, occurring in 89% and 75% of the patients receiving buprenorphine and morphine, respectively, regardless of dose. The incidence of somnolence was dose-related with both drugs. Nausea of vomiting or both was reported in 2 patients after buprenorphine and in 6 patients after morphine. Decreased respiratory rate, classified as mild respiratory distress, was recorded in 1 patient (#127) in the 0.4 mg buprenorphine group. The respiratory rate decreased from 20 to 8 after buprenorphine. One patient (#126) receiving 10 mg morphine also experienced a decrease in respiratory rate from 20 to 6 which was classified as mild hypoventilation. Neither of these conditions required treatment or withdrawal from the study. A mild hypotensive episode was recorded for one patient (#120) receiving 10 mg morphine (blood pressure decreased from 110/0 to 82/40). The episode was transient and blood pressure returned to normal levels three hours after drug. Single occurrences of headache, blurred vision and urinary retention (difficulty voiding) were reported after bupmorphine while single incidences of dizziness and urinary abnormality (difficulty voiding) were recorded after morphine administration.

(4) Efficacy considerations

a. Clinical and laboratory measurements used to characterize efficacy or comparability:

Each patient was interviewed by the trained observer for pain intensity, pain relief, level of sedation, and vital signs pre-drug and at 0, 2, 3, 4, 5, and 6 hours after dosing. The data base was the same as in previous study except for the additional time points of 1/6 and 1/3 hour.

b. $\alpha = .05$ is the degree of significance.

c. The endpoints for efficacy evaluation are appropriate.

(5) Results of Statistical Consultation:

Comments of (ii) through (vi) [except for the first statement (iv)] for study number 1 above are applicable here. In addition, in this study were recorded after remedication and these observations, contrary to the protocol, were included in the analyses (patients numbered 107, 179, 192, 126 and 255). There were also missing data prior to remedication.

(patients numbered 199, 132, and 151). Although the small number of data points involved is not likely to affect our conclusions, these inconsistencies should be explained by the applicant.

(6) Results of Study:

a. Sponsor's evaluation

Statistical techniques similar to those in study number 1 were used in this case. All of the demographic variables were comparable among treatment groups.

All four drug treatments produced analgesia during the study. Onset of action occurred as early as one-half hour with a peak effect by 1 hour. Based on SPID and TOTPAR, 0.4 mg buprenorphine produced significantly greater pain reduction and pain relief than 5 or 10 mg morphine. Similarly, 0.2 mg buprenorphine produced greater pain reduction and pain relief than 5 mg morphine.

Most patients in the buprenorphine groups achieved the maximum possible pain reduction at some time during the observation period. Buprenorphine 0.4 mg was statistically superior to 5 or 10 mg morphine in this regard. The median time to remedication was greater for the buprenorphine groups than for the morphine groups.

The most common effect was somnolence (recorded or observed as sedation). Sedation generally increased after buprenorphine or morphine administration. Morphine 5 mg had the least sedative effect. All doses of medication had an effect upon respiratory rate, and blood pressure. There was no consistent effect on pulse rate.

No tissue reactions were observed for any of the study groups in this study.

Overall, buprenorphine (0.2 mg and 0.4 mg) and morphine (10 mg) provided adequate analgesia and appeared equally safe at the doses used in this study. However, in general, 0.4 mg buprenorphine produced significantly better pain relief than did the 5 mg or 10 mg doses of morphine. These results are summarized in Table 13.

(6) Reviewer's Evaluation

(i) The test and control groups were comparable by the statistical methods used in the analysis. Proper techniques were applied to assess for baseline differences between groups, i.e., age, sex, number of patients per group, etc.

(ii) The documentation and analysis results were not sufficient to justify the conclusions.

(c) The data appears to support the sponsor's conclusion as stated above with the reservation that further statistical analysis is required prior to accepting the results as supportive of safety and efficacy.

(i) The sponsor ignored the influence of pre-study analgesics in the statistical analysis. I recommend the data be stratified or made adjustments in the analyses for the type of and elapsed time since the administration of pre-study analgesics.

(ii) Methods of assessments for pain intensity and pain relief were not adequate when patients were asleep. The sponsor failed to wake up the patient to complete the pain rating forms. Being asleep or awake does not relate to pain or lack of pain and the sponsor should explain why the conclusions are void in regard to efficacy even with this design error. One would have to conclude that the firm needs to address the question raised in statistical review p. 5 section iv.

(iii) Changes in vital signs due to morphine relate to baseline values and this is presumably true for buprenorphine. The sponsor did not adjust for baseline values in the analysis and the data should be reanalyzed.

(iv) Side effects might be masked or complicated by the pre-study medications including type and amount of anesthetic. Reanalysis is needed.

(v) In this study there was no distinction made between pain at rest and pain on motion. This distinction was made in study number 5 discussed later in this review and the results of some of the analyses were different between pain at rest and pain on motion. The applicant should demonstrate the role this distinction plays in all of these studies.

(d) I disagree with the sponsor's evaluation in that the conclusions are premature. Further analysis is required and if after that the conclusions still hold validity this study would support efficacy.

C. Conclusions

(1) Scientific - this submission contains some evidence supporting the sponsor's claim; however, the evidence as presented cannot be considered substantial since there are flaws in the design and serious omissions in the analyses of the data. The points to be addressed and the analysis to be performed are listed above.

(2) Deficiencies/problems in this study as listed above.

III. a. Principal Investigator:

Allen B. Dobkin, M.D.
Department of Anesthesiology
State University of New York
Upstate Medical Center
Syracuse, New York

Harriet Kiltie, M.D.
Monitor - Lederle Laboratories

Title of Study:

Comparison of the Analgesic Activity of Two Doses of Buprenorphine Against Two Doses of Morphine Each Given as a Single Intramuscular Injection to Patients Experiencing Post-Surgical Pain.

(1) Objective of the Study:

The purpose of this study is to compare the analgesic activity of 0.2 mg and 0.4 mg of buprenorphine against each other and also against 5 mg and 10 mg of morphine sulfate; each given as a single intramuscular injection following selected major surgical procedures associated with moderate to severe pain.

(b) Experimental Design

1. Patient Population
 - a. Demography

This was a randomized, double-blind parallel study with 160 patients enrolled.

Each patient had undergone a major abdominal, thoracic or orthopedic surgical procedure and was fully responsive after recovering from general anesthesia.

Distributions of sex for the four treatment groups were comparable. The chi-square statistic for testing the homogeneity of sex distributions was 0.36 (.9 < p < .95).

The analysis of variance after adjusting for the effect due to sex as indicated in Tables 2 to 4 shows that the treatment groups were comparable with respect to age, weight, and height. Among 12 Blacks, 6 received .2 mg of buprenorphine, 3 received 10 mg of morphine, 2 received 5 mg of morphine and 1 received .4 mg of buprenorphine. Race status for three other patients was unknown. The remainder of the patients were Caucasian.

Thus, there is no evidence to suggest any imbalance in distributions of demographic characteristics among treatment groups.

(b) Clinical Characteristics for inclusion:

- A. Over 18 years of age, weighing between 100 and 200 pounds.
- B. Undergoing a major abdominal, thoracic or orthopedic surgical procedure.
- C. Fully responsive following general anesthesia and experiencing moderate to very severe pain.
- D. Having been satisfactorily screened by the following laboratory tests: CBC with differential; complete urinalysis; BUN; SGOT or SGPT; serum bilirubin, direct and indirect; serum alkaline phosphatase.

Laboratory studies are as described in the previous study. These parameters are basically the same for all 8 pivotal studies.

(c) Exclusions:

- A. Women who are pregnant, lactating, or of childbearing potential.
- B. Patients undergoing methadone or other narcotic maintenance treatment or having a history or narcotic drug tolerance or addiction.
- C. Patients undergoing neurosurgery or cardiac surgery.
- D. Any patient who has or is suspected of having severe renal, hepatic, respiratory, cardiac, prostatic or endocrine disease, phaeochromocytoma, hematologic disease will be excluded from the study.
- E. Patients who have limited mental competence and/or who may have difficulty answering questions at interview.

(2) Procedures

(a) Specific Formulations Used in Study:

The drugs were supplied in amber glass ampuls as follows:

Buprenorphine	0.2 mg/ml	1 ml ampul
Buprenorphine	0.4 mg/ml	1 ml ampul
Morphine	5 mg/ml	1 ml ampul
Morphine	10 mg/ml	1 ml ampul

All ampuls were identical in appearance and labeled to show only the patient's study number. A sealed, tear-off portion of the label concealed the identity of the drug and its strength. The tear-off portion was opened only in the event of a medical emergency.

(b) Type of Experimental Controls:

Under the procedures of this study, 160 post-surgical patients were randomly assigned to one of four treatment groups of 40 patients each. Buprenorphine and morphine were administered in single intramuscular injections and the effects compared using a parallel, double-blind study design.

This procedure is not appropriate nor adequate for this study. See reviewer's comments.

(c) Dosage schedule: See Table 12 and 2 (a) above.

(d) List desirable concomitant medication: None

(3) Safety Considerations - Observations prior to, during, and after study

(a) Clinical studies: see introduction of this review and Table 12.

(b) Laboratory Studies: see introduction of this section.

(c) Indications for removing a patient from the study are listed in exclusion criteria above. Two patients with a history of narcotic addiction were excluded from the efficacy analysis; however, safety data was obtained.

(d) Study observations:

The missing values were excluded from the calculations. Patients were included in the computation of change from baseline means only if observations were available at both baseline and the post-injections time under consideration.

In regard to treatment emergent symptoms, 19 symptoms were reported. The onset for all symptoms was within 50 minutes after receiving treatment. Seven patients were in buprenorphine groups and twelve patients were in morphine groups. Three patients experienced hypotension and there was one report of hypertension. Only one of these four instances, a report of hypotension for a patient treated with .2 mg of buprenorphine, was described as possibly drug-related. The other symptoms reported were 2 instances of vomiting in the 10 mg morphine group and 13 instances of nausea in all groups.

(4) Efficacy considerations:

Each patient was interviewed by a trained observer, pre-drug (control) and at 0.5, 1, 2, 3, 4, 5, and 6 hours post-injection to determine the information as outlined in Table 12. This protocol is essentially identical to the other seven pivotal studies.

(b) $\alpha = .05$ is the degree of significance.

(c) The endpoints for efficacy evaluation are appropriate.

(5) Results of Statistical Consultation:

Since the protocol and the statistical methods in this study were practically identical to those of study number 2, all of the comments in study number 2 apply equally here.

It is interesting to note that the results of study number 2 and this study were not comparable though they had nearly identical protocols.

The mean values of SPID and TOTPAR in study number 2 were almost twice those in this study and the average times to remedication in study number 2 were also much longer. The mean values of SSLD in study number 2 were 5 to 18 times larger than those in study number 3. The following table provides a summary comparison:

Treatment	SPID Study		TOTPAR Study		Duration (hr) Study		SSLD Study	
	2	3	2	3	2	3	2	3
0.2 mg Bupr.	11.0	6.0	13.7	8.3	6	4	4.7	0.72
0.4 mg Bupr.	12.5	6.6	13.6	9.1	6	4.5	5.1	0.89
5 mg Morp.	8.2	3.2	10.6	4.6	6	3	3.0	0.21
10 mg Morp.	9.5	5.0	12.8	6.6	6	3.5	5.1	0.28

The applicant needs to explain this further. There were more patients with severe initial pain intensity in this study than in study number 2. This might account for some of the differences. Different nurse observers in different studies might be another reason for this difference. It should be noted that the table also shows good general agreement between studies 2 and 3 on the relative effect of buprenorphine to morphine despite the disparity in response level.

Observations (mostly in vital signs) that were either missing for no reason or recorded after remedication and later incorporated into the calculations (contrary to the protocol) included the following patients' numbers: 174, 203, 242, 248, 256, 304 (0.2 mg buprenorphine); 219, 243, 272, 283, 287 (0.4 mg buprenorphine); 196, 244, 249, 255, 281, 309 (5 mg morphine); and 245, 246, 251, 268, 278, 286, 297 (10 mg morphine).

(6) Results of Study:

(a) Sponsor's evaluation:

Comparisons between treatment groups showed that both buprenorphine groups had significantly greater pain relief as measured by the Sum of Pain Intensity Difference (SPID) and Total Pain Relief (TOTPAR) than did the morphine 5 mg group. Buprenorphine also produced greater (however not statistically significant) pain relief than 10 mg morphine. The median remedication times were 3 hours for 5 mg morphine, 3.5 hours for 10 mg morphine, 4 hours for 0.2 mg buprenorphine, and 4.5 hours for 0.4 mg buprenorphine.

The type and incidence of side effects for buprenorphine and morphine were similar with somnolence and nausea being the most common.

Overall, patients treated with buprenorphine had significantly greater pain reduction and pain relief than did the 5 mg morphine group. Although not significant, the buprenorphine groups also seemed to provide more analgesia than the 10 mg morphine group. Both drugs appeared to be equally safe. These results are summarized in Table 13.

(b) Reviewer's evaluation

(i) The test and control groups were comparable by the statistical methods used in the analysis. Proper techniques were applied to assess baseline differences between groups, i.e., age, sex, number of patients per group, etc.

(ii) The documentation and analysis of results were not sufficient to justify the conclusion.

(c) The data appears to support the sponsor's conclusion as stated above with the reservation that further statistical analysis is required prior to possibly accepting the results as supportive of safety and efficacy.

(i) The sponsor ignored the influence of pre-study analgesics in the statistical analysis. I recommend the data be stratified or made adjustments in the analyses for the type of and elapsed time since the administration of pre-study analgesics.

(ii) Methods of assessments for pain intensity and pain relief were not clearly specified when patients were asleep. The sponsor failed to wake up the patient to complete the pain rating forms. Being asleep or awake does not relate to pain or lack of pain and the sponsor should explain why the conclusions are void in regard to efficacy even with this design error. One would have to conclude that the firm needs to address the question raised in statistical review of page 5, section iv.

(iii) Changes in vital signs due to morphine relate to baseline values and this is presumably true for buprenorphine. The sponsor did not adjust for baseline values in the analysis and the data should be reanalyzed.

(iv) The nature of side effects was comparable among treatment groups with slightly higher occurrences in the morphine groups. However, it should be noted that side effects might be masked or complicated by the pre-study medications including type and amount of anesthetic. Reanalysis is needed.

(v) In this study there was no distinction made between pain at rest and pain on motion. This distinction was made in study number 5 discussed later in this review and the results of some of the analyses were different between pain at rest and pain on motion. The applicant should demonstrate the role this distinction plays in all of these studies.

(d) I disagree with the sponsor's evaluation in that the conclusions are premature. Further analysis is required and if after that the conclusions still hold validity this study would support efficacy.

C. Conclusions

(1) Scientific - this submission contains some evidence supporting the sponsor's claim; however, the evidence as presented cannot be considered substantial since there are flaws in the design and serious omissions in the analyses of the data. The points to be addressed and the analysis to be performed are listed above.

(2) Deficiencies/Problems in this study as listed above.

IV. a. Principal Investigator:

J.W. Downing MB BCH FFARCS,
Professor of Anaesthetics,
University of Natal
Durban
South Africa

Monitor: R.C. Hoare, Clinical Research Director, Reckitt and Colman

Title of Study:

A Double-Blind Study of Buprenorphine and Morphine for the Treatment of Patients with Post-Operative Pain

(1) Objective of the study:

The purpose of this study was to compare the analgesic activity of buprenorphine with that of morphine when each medication was administered as a single intramuscular injection to patients suffering from moderate to severe post-operative pain.

STUDY DESIGN:

The original design of this study was a single-dose, double-blind, between patient comparison of buprenorphine (0.3 mg and 0.6 mg) and morphine (7.5 mg and 15 mg). Following a small, open pilot study (results not available) and consideration of the results from the first two patients receiving buprenorphine (0.3 mg) (see later), the study design was modified to compare only buprenorphine (0.6 mg) and morphine (15 mg) on a double-blind basis.

Initially it was proposed to compare buprenorphine (0.3 mg and 0.6 mg) with morphine (15 mg) but due to lack of analgesia produced by buprenorphine (0.3 mg) in the first two patients (nos. 14 and 16) receiving this dose, the treatment group was dropped from the study. Fifty-eight patients were randomly allocated to the other treatment groups. It was subsequently decided to study the buprenorphine patients for 8 hours posts-therapy as opposed to 4 hours, and 9 of the 58 patients were studied for an additional 4 hours on an open basis. A further 6 patients received buprenorphine (0.6 mg) on an open basis and were studied for 8 hours. (Patient nos. 121 - 126 inc.)

(b) Experimental Design

Patient Population

(a) Demography

PATIENT POPULATION:

A total of 66 female patients experiencing moderate to severe post-operative pain following elective Caesarean section were admitted into the trial. Age of the patients ranged from 19 to 40 years with a mean age of 26.7 years. Patients' weights ranged from 45 to 100 kg with a mean weight of 70.5 kg based on 65 patients. For the 58 patients involved in the double-blind comparison of buprenorphine (0.6 mg) and morphine (15 mg), ages ranged from 19 to 40 years with a mean age of 26.4 years and weights ranged from 54 to 95 kg with a mean weight of 69.9 kg. For the 15 patients who received buprenorphine (0.6 mg) and were studied for 8 hours, ages ranged from 19 to 35 years with a mean age of 24.4 years and weights ranged from 45 to 96 kg with a mean weight of 69.3 kg.

For one patient (no. 14) body weight was not recorded.

(6) Clinical characteristics for inclusion:

This was a double-blind, single dose comparison of buprenorphine (0.6 mg) and morphine (15 mg) given intramuscularly to patients suffering moderate to severe pain following elective Caesarean section. The inclusion criteria are the same basically as the other seven pivotal studies. This information is described adequately in the protocol and was adhered to.

(C) Exclusion:

As in the other seven pivotal studies, this information was adequate in the protocol and was adhered to in conducting the study.

(2) Procedures

(a) Specific formulation(s) used in the study:

Each patient was assigned one ampoule of test medication, the total

contents of the ampoule being administered. The drugs were supplied in the following concentrations:

Buprenorphine	0.15 mg/ml	2 ml ampoule
Buprenorphine	0.3 mg/ml	2 ml ampoule
Morphine	7.5 mg/ml	2 ml ampoule

The study was conducted as per protocol with the modifications detailed above.

(b) Type of Experimental Controls:

Fifty-eight female patients were admitted to the double-blind study, nine of whom had their code broken and were openly assessed along with a further six patients who entered the open study directly. Prior to, and at intervals following drug administration patients were assessed for pain intensity, pulse rate, blood pressure, vital capacity, peak flow, and side effects. Time to remedication and pain relief were also recorded following drug administration. Pain intensity difference (PID), sum of pain intensity differences (SPID) and total pain relief (TOTPAR) were calculated.

This procedure is not appropriate nor adequate for this study. See reviewer's comments.

(c) Dosage schedule: See Table 12 and 2 (a) above.

(d) List desirable concomitant medication: None.

(3) Safety Considerations - Observations prior to, during, and after study:

a. Clinical studies: See Introduction of this section and Table 12.

b. Laboratory Studies: See Introduction of this section.

c. Indications for removing a patient from the study are listed in exclusion criteria above.

d. Study observations:

Pulse rate and blood pressure by patient at each observation time were tabulated. For both treatments there was a significant fall in pulse rate one hour after administration followed by a gradual return to baseline. For systolic blood pressure, buprenorphine (0.6 mg) shows a fall for one to two hours followed by gradual return to baseline, and morphine (15 mg) shows a decrease over the four-hour period. For diastolic blood pressure both treatments show a significant fall over the four-hour period. For each of these parameters there is no significant difference between treatments.

Clinically, neither treatment caused any meaningful changes. Vital capacity and peak flow for each patient at each observation time was obtained. For both these parameters both treatments caused a significant increase over the four-hour treatment period but there was no significant difference between the treatments. Volume of both vital capacity and peak flow can be markedly reduced by pain and analgesia will cause an increase in volume.

Side effects which occurred only after drug administration are separated from those that were present prior to drug administration and continued during part or all of the study period in the sponsor submission. The incidence of side effects was low, with no significant differences between the treatments. Sedation was most common and nausea and vomiting were only reported by one patient (treatment number 71) who had received morphine (15 mg).

(4) Efficacy considerations:

(a) Clinical and laboratory measurements used to characterize efficacy or comparability:

Each patient was evaluated according to the protocol by a trained nurse observer at each observation period (pre-therapy 0.25 hours, 1 hr, 2 hrs, 3 hrs, and 4 hrs post-therapy). Fifteen patients were also observed at 5 hrs, 6 hrs, 7 hrs, and 8 hrs post-therapy. The details of the protocol are the same as the other seven pivotal studies and were basically adequate and appropriate for the issue at hand.

(b) $\alpha = .05$ is the degree of significance.

(c) The endpoints for efficacy evaluation are appropriate.

(5) Results of Statistical Consultation:

(i) The comparability of age and weight between treatment groups was based on all patients including the six patients in the open study. The p-value for age would have been 0.06 (2 sided t-test) instead of 0.09 when those six patients were excluded from the calculation. This indicated that more younger patients were assigned to the buprenorphine groups. The p-value for the comparison of weight would also be lower but is still not statistically significant.

(ii) As a consequence of comment (i), it would be more appropriate to adjust for age when analyzing the efficacy and safety variables. The applicant has not done this.

(iii) The applicant's claim that 0.6 mg buprenorphine had longer duration of action than 15 mg morphine is not acceptable since it was based on the

significant later time to maximum PID of buprenorphine than morphine and also on the assessment of the 8 hour open study of buprenorphine alone. Only direct comparison of time to remedication over an extended period of time could substantiate this claim.

(iv) Because of the uniform nature of operations and pre-study medications, the issue of pain at rest and pain on motion raised in connection with the previous study appears not as important in this case.

(v) The proportion of patients who suffered from sedation was small (6 patients in the buprenorphine group and 4 in the morphine group) and these 10 patients had only mild to moderate sedation. Thus, the effects of sedation in this study would not be expected to affect the analyses seriously as in the previous studies.

(vi) Comparisons of changes in vital signs should have been adjusted for baseline values but were not.

(vii) Both drugs appeared to be equally safe at their respective doses since only one patient who received morphine experienced nausea and vomiting.

(6) Results of Study

(a) Sponsor's evaluation:

Both buprenorphine 0.6 mg and morphine 15 mg produced increasing analgesia over the first hour following drug administration. Maximum relief occurred earlier with morphine (1 - 3 hours after administration) than with buprenorphine (4 - 5 hours), but this maximum was significantly greater with buprenorphine. Treatment efficacy parameters SPID and TOTPAR showed evidence of greater analgesia after buprenorphine 0.6 mg than after morphine 15 mg. The proportion of patients experiencing no pain at some time during the post-drug evaluation period, however, was not significantly different between the treatment groups.

A fall in pulse rate occurred with both drugs over the first hour after administration, and subsequently the level increased towards the baseline value. Systolic and diastolic blood pressure decreased from the pre-drug level and thereafter showed evidence of levelling off or returning towards the baseline level for both treatments. Both vital capacity and peak flow increase sharply following administration for both buprenorphine 0.6 mg and morphine 15 mg. However, for buprenorphine a levelling off of vital capacity and a reversal of the trend for peak flow was indicated over the extended 8 hour evaluation period. For all of the vital signs recorded, the comparison of treatment groups showed no evidence of a difference in response.

The low incidence of side effects was similar for buprenorphine 0.6 mg and for morphine 15 mg.

These results are summarized in Table 13.

(6) Reviewer's Evaluation:

(i) The treatment groups were comparable with respect to demographic variables, according to the applicant. All patients in the double-blind study had severe initial pain. The additional six patients in the open study had moderate/severe initial pain. Analyses of efficacy variables where these six patients were included were adjusted for initial pain intensity. Only 4 patients (2 in each treatment group) needed remedication during the 4 hour study period.

The comparability of age and weight between treatment groups was based on all patients including the six patients in the open study. The p-value for age would have been 0.06 (2 sided t-test) instead of 0.09 when those six patients were excluded from the calculation. This indicated that more younger patients were assigned to the buprenorphine groups. The p-value for the comparison of weight would also be lower but is still not significant. It would be more appropriate to adjust for age when analyzing the efficacy and safety variables. The applicant has not done this, and I recommend the sponsor be requested to supply this information.

(ii) The documentation and analysis of results were not sufficient to justify the conclusions.

(c) The data appears to support the sponsor's conclusion as stated above with the reservation that further statistical analysis is required prior to accepting the results as supportive of safety and efficacy.

(i) SPID was significantly higher for the buprenorphine group with or without the six additional patients in the open study. TOTPAR also favored the buprenorphine group ($p = 0.07$) in both instances. Maximum PID was compared using a Mann-Whitney U-test. The buprenorphine group was favored ($p = 0.02$) in the double-blind study. Inclusion of the six additional patients reduced the significance level to 0.12. Time to maximum PID indicated that maximum pain relief occurred at a significantly later time in the buprenorphine group than in the morphine group ($p = 0.0001$) whether the six patients were included or not.

(ii) The number of patients suffering from sedation (mostly mild) was comparable between treatment groups. Over the 4 hour evaluation period, pulse rate, systolic and diastolic blood pressure decreased significantly below baseline while vital capacity and peak flow rose significantly in both treatment groups. Nausea and vomiting were observed in only one patient.

The applicant concluded that "0.6 mg buprenorphine gave a higher level of analgesia, with a longer duration of activity than 15 mg morphine with no increase in unwanted effects." I feel this is not acceptable since it was based on the significant later time to maximum PID of buprenorphine than morphine and also on the assessment of the 8 hour open study of buprenorphine alone. Only direct comparison of time to remedication over an extended period of time could substantiate this claim.

The proportion of patients who suffered from sedation was small (6 patients in the buprenorphine group and 4 in the morphine group) and these 10 patients had only mild to moderate sedation. Thus, the effects of sedation in this study would not be expected to affect the analyses seriously as in the previous studies.

(iii) Comparisons of changes in vital signs should have been adjusted for baseline values but were not. I recommend the sponsor supply this information.

(d) I disagree with the sponsor's evaluation in the the conclusions are premature. Further analysis is required and if after that the conclusions still hold validity this study would support efficacy.

C. Conclusions

(1) Scientific - this submission contains some evidence supporting the sponsor's claim; however, the evidence as presented cannot be considered substantial since there are flaws in the design and serious omissions in the analyses of the data. The points to be addressed and the analysis to be performed are listed above.

(2) Deficiencies/problems in this study as listed above.

V. Principal Investigator

B.C. Hovell, M.B., Ch.B., F.F.A.R.C.S.
Consultant Anæsthetist
Hull Royal Infirmary
Kingston-Upon-Hull
United Kingdom

Monitor: Dr. J.A. Buylla, Clinical Research Director, Reckitt and Colman

Title of Study:

Comparative Study of Buprenorphine and Morphine Given Intramuscularly to Patients Suffering Acute Post-Operative Pain

(1) Objective of the Study

The purpose of this study was to compare the analgesic activity, incidence of unwanted effects and effect on vital signs of buprenorphine (0.3 mg) and

morphine (10 mg), when given as a single intra-muscular injection to patients experiencing moderate to severe post-operative pain following general surgical procedures.

(b) Experimental Design

(1) Patient population

(a) Demography

A total of fifty-one patients experiencing moderate to severe pain following general surgical procedure, who would normally require an injected analgesic for the relief of pain, were selected for participation in the study. The age of the patients ranged from 22 to 81 years with a mean age of 42.0 years for 21 males and 48.3 years for 30 females. Patients' weights ranged from 45 to 98 kg with a mean weight of 75.1 kg based on data from 20 males and 60.2 kg based on data from 25 females. As data from one male patient (Treatment No. 47) was excluded from the efficacy analysis, the remaining 20 males had a mean age of 43.0 years and a mean weight of 75.1 kg.

Coparability of the two treatment groups with respect to age and weight was examined using analysis of variance. Differences in the sex distributions of the parameters were investigated in the analysis. The sex distribution in each of the treatment groups was compared using the chi-square test.

The number of patients in each treatment group were as follows:

	<u>No. of Patients</u>
Buprenorphine 0.3 mg	26
Morphine 10 mg	25

For six patients body weight was not recorded; three patients in each of the two treatment groups.

Of the study population 59% were females and 41% males and the sex distributions in the treatment groups were comparable.

The mean ages and weights of patients in the two groups are shown in the NDA submission. Means in each of the two treatment groups, after removing the effect due to sex, show that the groups were comparable with respect to age and weight.

There is no evidence to suggest any imbalance in the distribution of demographic variables between the treatment groups.

The distribution of pre-drug (baseline) pain intensity scores (move and rest) for each treatment group are shown in the submission. Chi-square tests for homogeneity showed that the groups were comparable. However, in the

analysis of efficacy the minor differences in pre-drug pain scores were controlled by using this score as the concomitant variable in an analysis of covariance.

For the vital signs (respiration rate, pulse rate and blood pressure) the treatment groups were compared using a partially hierarchical analysis of variance on the difference between pre-drug and post-drug findings. Trends in these parameters from baseline up to six hours after drug administration were also investigated, and both the absolute values and changes from baseline values were examined.

(6) Clinical characteristics for inclusion:

Same criteria as on previous studies.

Patients were assessed by medical history and physical exam prior to the study. Pre-study laboratory tests are the same as in the previous study.

(c) Exclusions:

The criteria are the same as in the previous study.

(2) Procedure

(a) Specific formulation(s) used in the study:

The two test medications compared were buprenorphine and morphine. Each patient was assigned one ampoule of test medication, the total contents of the ampoule being administered. The drugs were supplied in the following concentrations:

Buprenorphine	0.3 mg/ml	1 ml ampoule
Morphine	10 mg/ml	1 ml ampoule

(6) Type of Experimental Controls:

This was a single dose, double-blind, between patient study in 51 patients who were randomly allocated to one of the test medications. Subsequently one patient (Treatment No. 47) was excluded from the efficacy analysis.

The procedure, had the design been followed, would have been basically appropriate and adequate for this study. See reviewer's comments.

(c) Dosage schedule: See Table 12 and 2 (a) above.

(d) List desirable concomitant medication: None.

(3) Safety considerations - Observations prior to, during and after study

a. Clinical studies: see introduction of this section and Table 12.

b. Laboratory studies: see introduction of this section.

c. Indications for removing a patient from the study are listed in exclusion criteria above.

d. Study observations:

Data was obtained on vital signs including pulse rate, blood pressure and respiration rate. In a number of patients these parameters were not recorded after one hour post-drug because of a misunderstanding by the nurse observers. With regard to pulse rate there were no significant changes in mean post-drug values relative to the mean pre-drug values for either treatment. With regard to blood pressure, there is evidence of a small but significant fall in the period up to 2 hours for both treatments, but there was no significant difference between treatments. The mean values over the period up to 2 hours post-drug compared to pre-drug values were for buprenorphine (0.3 mg): systolic -7.8 mmHg, diastolic -3.5 mmHg and for morphine (10 mg): systolic -4.4 mmHg, diastolic -4.1 mmHg. With regard to respiratory rate both treatments caused a progressive fall over the initial 3 hours post-drug the lower mean values reached being maintained for the remaining 3 hours. For both treatments, the mean post-drug values over the six hour period were significantly lower than the pre-drug values, the mean decrease over the period 2 - 6 hours being 6.2 min^{-1} for buprenorphine (0.3 mg) and 1.5 min^{-1} for morphine (10 mg). Buprenorphine (0.3 mg) caused a significantly greater decrease than morphine (10 mg) over the six hour period ($p < 0.05$). Clinically neither treatment caused any meaningful changes in pulse or blood pressure. A marked fall in respiratory rate was observed in three patients having received buprenorphine (0.3 mg) (Treatment numbers 27, 29, 48) and in one having received morphine (10 mg) (Treatment number 50). Additional treatment was not required in any of these cases, the respiratory rate returning to normal spontaneously.

Side effects are presented in the submission and listed by patient and dose. The commonest side effect was sedation which was reported by all but two patients in the morphine group, but based on degree of sedation, buprenorphine (0.3 mg) appeared more sedative than morphine (10 mg), the difference being statistically significant ($p < 0.05$). Other side effects were relatively uncommon with no observable difference between treatments.

(4) Efficacy considerations:

(a) Clinical and laboratory measurements used to characterize efficacy or comparability:

Data was obtained immediately prior to and at 1/4, 1/2, 1, 2, 3, ,4, 5 and 6 hours after administration of the drug. The parameters are identical to the other pivotal studies; however, a distinction was made between pain intensity at rest vs with motion.

(b) $\alpha = .05$ is the degree of significance.

(c) The endpoints for efficacy evaluation are appropriate.

(5) Results of Statistical Consultation:

(i) Missing data is a major problem in this study, leading one to question the level of clinical control exercised by the investigator and the reliability of the remaining data. For example, 40% of the patients had no record of anesthetic and/or other drugs used during anesthesia. Five patients had missing pain scores at some observation periods. Estimated values were used in these cases. Nearly half of the patients had missing observations in their signs at some period of observation. Thus, analyses of changes in vital signs would not be reliable.

(ii) Buprenorphine (0.3 mg) appeared to have a higher sedative effect than did morphine (10 mg). As I have illustrated above in study number 1 pain relief and sedation could not fully be separated when comparing the treatment groups. Those comments would also be appropriate for this study.

(iii) Since side effects due to the test drugs might be confounded with those induced by anesthetic or other drugs used during anesthesia, and 40% of the patients had no such records, it is not possible to draw any conclusions regarding the comparability of side effects.

(6) Results of Study:

(a) Sponsor's Evaluation

Statistical methods employed in this study were similar to those in study number 4. There were some missing data due to the misunderstanding of a nurse observer. Demographic factors and baseline pain intensity (motion and rest) were shown to be comparable between treatment groups.

Both buprenorphine 0.3 mg and morphine 10 mg produced increasing analgesia over the first hour following drug administration, reaching maximum pain relief at 2 - 4 hours and thereafter gradually returning towards the baseline value. The treatment efficacy parameters SPID and TOTPAR showed greater analgesia after the buprenorphine 0.3 mg administration than after morphine 10 mg. Maximum pain relief (max. PID) was greater for buprenorphine, as was the proportion of patients experiencing no pain at some time during the post-drug evaluation period for pain (rest). For both time to remedication and time to peak activity there was no evidence of a difference between the two drugs.

Missing data on vital signs were excluded in the analyses of safety variables. Apart from an indication of a decrease over the first hour following buprenorphine treatment little effect on pulse rate was observed. For systolic and diastolic blood pressure, both treatments produced a decrease from the pre-drug level over the first 1 - 2 hours following administration. Thereafter the levels were consistent with the pre-drug levels. A decrease in respiratory rate was observed in both drug groups with buprenorphine showing a greater decrease than morphine.

The side effect profile was similar in both drug groups but the degree of sedation was greater after buprenorphine than after morphine.

These results are summarized in Table 13.

(6) Reviewer's evaluation

(i) The test and control groups were comparable by the statistical methods used in the analyses. Proper techniques were applied to assess baseline differences between groups, i.e., age, sex, number of patients per group, etc.

Statistical methods employed in this study were similar to those in study number 4. There were some missing data due to the misunderstanding of a nurse observer. Demographic factors and baseline pain intensity (motion and rest) were shown to be comparable between treatment groups.

(ii) and (c) The documentation and analysis of results were not sufficient to justify the conclusions.

(i) Missing data is a major problem in this study, leading one to question the level of clinical control exercised by the investigator and the reliability of the remaining data. For example, 40% of the patients had no records of anesthetic and/or other drugs used during anesthesia. Five patients had missing pain scores at some observation periods. Estimated values were used in these cases. Nearly half of the patients had missing observations in their vital signs at some periods of observation. Thus, analyses of changes in vital signs would not be reliable.

(ii) Buprenorphine (0.3 mg) appeared to have a higher sedative effect than did morphine (10 mg). As I have illustrated above in study number 1 pain relief and sedation could not fully be separated when comparing the treatment groups. Those comments would also be appropriate for this study.

(iii) Since side effects due to the test drugs might be confounded with those induced by anesthetic or other drugs used during anesthesia, and 40% of the patients had no such records, it is not possible to draw any conclusions regarding the comparability of side effects.

(d) I disagree with the sponsor's evaluation in that the conclusion can not be drawn from the data because of the points discussed above.

C. Conclusions

(1) Scientific - This submission contains some evidence supporting the sponsor's claim; however, the evidence as presented cannot be considered substantial since there are flaws in the design and serious omissions in the analyses of the data. The points to be addressed and the analysis to be performed are listed above.

(2) Deficiencies/Problems in this study as listed above.

b. Comparison with Other Potent Analgesics

The second sub-category of controlled studies submitted includes three randomized, double-blind, controlled studies using pentazocine, pethidine, or Omnopon as reference agents. A total of 263 patients experiencing moderate to severe post-surgical pain or cancer pain were involved in these studies. Of the 263 patients, 159 patients received buprenorphine for post-surgical pain (137) or cancer pain (22). Each of these three studies employed a single intramuscular dose of the test agents. In two of the studies the doses of buprenorphine ranged from 2 ug/kg to 8 ug/kg and a dose of 0.3 mg was used in the other study. The doses of the comparative drugs used were pentazocine 0.6 mg/kg, pethidine 1 mg/kg and Omnopon 20 mg. All of the patients were assessed for pain intensity, pain relief (after dosing), vital signs and side effects before and at various time up to 8 hours after dosing.

The design of each study is outlined in Table 14 and the summary of efficacy data as presented by the firm is presented in Table 15.

I. Principal Investigator:

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Consultant Anaesthetist
The Royal Marsden Hospital
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United Kingdom

Clinical Monitor: Dr. J.A. Buylla, Clinical Research Director, Reckitt and Colman

Title of Study:

Comparative Study of Buprenorphine and Pentazocine Given Intramuscularly to Patients with Cancer Pain

(1) Objective of the Study:

The purpose of this study was to assess the efficacy and nature and incidence of unwanted effects of intramuscular buprenorphine (2 and 4 ug/kg) relative to intramuscular pentazocine (0.6 mg/kg) in patients with cancer pain.

(6) Experimental Design

(1) Patient Population

(a) Demography

A total of 22 patients were selected from among those with moderate to severe pain of malignant origin and who agreed voluntarily to enter the trial. Those on large maintenance doses of narcotics were excluded due to the possibility that buprenorphine could precipitate a withdrawal syndrome by virtue of its morphine antagonist properties. Age of the patients ranged from 21 to 74 years with a mean age of 54.8 years for eight males and 57.1 for 14 females. Patients' weights ranged from 41 to 83 kg with a mean weight of 65.4 kg for eight males and 57.3 kg for 14 females. A patient weighing 41 kg would receive 82 ug, 164 ug buprenorphine and 24.6 mg pentazocine, whereas an 83 kg patient would receive 176 ug, 332 ug buprenorphine and 49.8 mg pentazocine.

As two female patients (patients numbers 5 and 18) did not complete the full round of three treatments the remaining 12 females had a mean age of 60.3 years and a mean weight of 58.6 kg.

The pre-study medication and medication used during the study by the patients are given in the submission. One patient (patient number 25) had been receiving sublingual buprenorphine prior to the study and the investigator decided to continue this medication between administration of the test treatments. This patient was not included in the efficacy evaluation.

Two patients only received the initial treatment and are not included in the efficacy analysis. One patient (patient number 5) was nauseated prior to and throughout the initial treatment period and subsequently her condition deteriorated due to her disease state (Hodgkin's disease) and further test treatments were not administered. The other patient (patient number 18) was found to have a fractured femur after receiving the initial treatment and was transferred to another hospital. Further test treatments were not administered.

The patients' baseline pain intensity scores (movement and resting) for the three treatments were analysed using a Friedman Two-way analysis of Variance. No significant difference was found between the three treatments for the level of pain intensity at baseline.

(6) Clinical characteristics for inclusion:

Patients were chosen from among those with significant (moderate to severe) pain from malignant disease and who agreed voluntarily to enter the trial. Those on large maintenance doses of narcotics were excluded due to the possibility that buprenorphine could precipitate a withdrawal syndrome by virtue of its morphine-antagonist properties.

The study protocol follows the same types of specific inclusion criteria as the other seven "pivotal" studies.

(c) Exclusions:

See previous study. Exclusions are similar to the other pivotal studies.

(2) Procedures

(a) Specific formulation(s) used in study: with the addition of pentazocine, same as detailed in previous study and is adequate.

(b) Type of Experimental Controls

This was a single-dose, double-blind, within patient comparative study. Twenty-two patients commenced the study and 20 of these received one dose of each of the three treatments on separate days. The order of treatments was randomly assigned (Latin square design). As two patients failed to complete the study and four treatments were not used for other reasons (see above), the original study design is unbalanced and the effect of this on the results was determined. It was shown that for each of the efficacy parameters there was no significant effect due to the order in which the treatments were given.

This procedure is not appropriate nor adequate for this study. See reviewer's comments.

(c) Dosage schedule: see Table 14 and 2(a) above.

(d) List desirable concomitant medication: None

(3) Safety considerations - observations prior to, during, and after study

a. Clinical studies: See introduction and Table 14.

b. Laboratory studies: See introduction of this section.

c. Indications for removing a patient from the study are listed in exclusion criteria above.

d. Study observations:

In the analysis of vital signs no change in systolic and diastolic blood pressure was detected for pentazocine 0.6 mg/kg and buprenorphine 2 ug/kg, but for buprenorphine 4 ug/kg there was evidence of a decrease from the pre-drug level during the period of evaluation. Pulse rate also showed a decrease for all three treatments and remained below the pre-drug level throughout the evaluation period. Respiratory rate showed an initial fall over the first three hours for pentazocine 0.6 mg/kg and buprenorphine 2 ug/kg, followed by a return to the pre-drug level. For buprenorphine 4 ug/kg the decrease was evident for up to five hours before returning to the pre-drug level.

The side effect profile was similar for all three treatments, with sedation showing the highest level of incidence. A comparison of the proportion of sedated patients for each treatment (combining levels of sedation due to the small numbers involved), using a chi-square test, showed no evidence of a drug-related effect.

The overall profile of side effects was similar for all treatments although disorientation (patient number 6) and hallucinations (patient number 14) were only reported following pentazocine administration.

(4) Efficacy considerations:

(a) Clinical and laboratory measurements used to characterize efficacy or comparability are similar to the previous study:

Each patient was evaluated according to the study parameters by a trained nurse observer at each observation point (pre-therapy, 0.25 hrs, 0.5 hr, 1 hr, 2 hrs, 3 hrs, 4 hrs, 5 hrs, 6 hrs, and 7 hours post-therapy).

As in study 5 of the morphine control studies (B.C. Hovell) pain at rest is evaluated separately from pain with motion.

See Table 14 for summary of study design.

(b) $\alpha = .05$ is the degree of significance.

(c) The endpoints for efficacy evaluation are appropriate.

(5) Results of Statistical Consultation:

(i) The design of the trial was a crossover type. The use of a two-way (patients and treatments) analysis of variance in this design is not appropriate. The applicant ought to provide a standard analysis for this design taking into account the treatment effect, period effect, treatment by period interaction and residual effects uncontaminated by patient-to-patient (subjects within sequence) variability).

(ii) No adjustment was made for the baseline values in the analysis of changes in vital signs.

(iii) During the observation period, 25% (5/20) of the patients were given radiotherapy. The effect of this treatment on the patients' pain relief and side effects was not known.

(iv) There was no statement as to whether patients were roused for pain evaluation when they were sleeping.

(v) Some of the patients' entry numbers were not in alignment with their chronological order of entry. For example, if we arrange the patient numbers according to chronological order, then patient #5 should follow patient #9 and patients #16-20 should precede patients #10. The applicant should explain this anomaly.

(vi) The description of the analgesic study forms (p. 141, Vol. 1.10) in the protocol provides assessments for pain site, pain character, and whether a patient had 50% relief. However, such items could not be found either in the case reports or in the study summary itself. The applicant needs to explain this lack of adherence to the protocol.

(vii) All patients received each of the three treatments. The protocol indicated that the spacing in time of treatments was not fixed but would be arranged so that the round would be completed within 6 to 10 days. However, upon examination of the case reports, it was found that only one patient satisfied this requirement. Among the other 19 patients, 15 of them completed the round in 3 days and the other 4 patients completed the round in 4 to 17 days.

(6) Results of study:

(a) Sponsor's evaluation:

All treatments produced pain relief within 30 minutes, but time to peak pain relief was about one hour for pentazocine and two to three hours for the slow onset two buprenorphine doses. Based on time to peak PID buprenorphine (4 ug/kg) had a slower onset of action than pentazocine (0.6 mg/kg). There were no significant differences between the SPID (move), and SPID (rest) and TOTPAR values for each treatment, all treatments producing satisfactory pain relief, nor was there any significant difference between the treatments for time to remedication.

All treatments caused decrease in respiration rate for up to five hours, pulse rate for seven hours, there being no significant difference between the effects of the treatments. Buprenorphine (4 ug/kg) produced a lowering of systolic blood pressure for one to three hours post dose and both systolic and diastolic blood pressure at seven hours post dose.

Fifteen patients reported side effects following pentazocine (0.6 mg/kg), 12 following buprenorphine (2 ug/kg) and 14 following buprenorphine (4 ug/kg) there being no significant difference between each treatment. One patient reported disorientation, and another reported hallucinations. Both had received pentazocine (0.6 mg/kg).

The degree of analgesia, duration of action and side effects were similar for all treatments. Based on time to peak PID pentazocine (0.6 mg) had a faster onset of action than both doses of buprenorphine.

These results are summarized in Table 15.

(6) Reviewer's evaluation

(i) The test and control groups were comparable by the statistical methods used in the analysis. Proper techniques were applied to assess baseline differences between groups, i.e., age, sex, number of patients per group, etc.

(ii) The documentation and analysis of results are not sufficient to justify the conclusions.

The case report forms are not in agreement with the description of data to be collected in the protocol. On Vol. 1.10, page 141 of the submission it is clearly stated data will be collected on "pain site" requiring analgesia and "pain character." These are not mentioned in the final report nor the statistical review. This raises serious questions about how well the study was monitored.

Questions about how well the study was controlled and monitored also arise from the observation that the numbers assigned upon entry into the study are not in chronological order by dates. The sponsor states: "Two patients dropped out." For example, if we arrange the patient numbers according to chronological order, then patient #5 should follow patient #9 and patients #16-20 should precede patient #10. However, I recommend the sponsor clarify this issue.

(c) This study contains some evidence supporting the applicant's claim of safety and efficacy with the reservation that further data is required before a decision can be made on accepting this study.

(i) The sponsor ignored the influence of pre-study analgesics. Tests need to be conducted to determine if the groups are comparable in regards to this variable. I recommend the data be stratified or adjustments be made in the analyses for the type of and elapsed time since the administration of pre-study analgesics.

(ii) In the pivotal studies using non morphine standards the quantification of sedation is less exact than in the 5 previous studies using morphine as the control. In this study, instead of collecting data at the same observation points as pain observations, the data is collected in terms of (a) onset of sedation, (b) duration of sedation, (c) degree of sedation. This is not nearly as precise as the method used in the 5 morphine control studies. At this point the study is completed and in so far as the design can not be changed, we recommend the sponsor defend the conclusions drawn from the data and how this set of conclusions compares to the studies using morphine as the control.

(iii) Methods of assessment for pain intensity and pain relief were not clearly specified when patients were asleep. A comparison of the individual patient's pain relief scores with sedation levels revealed that most of the patients who obtained complete pain relief were patients who were asleep. The sponsor failed to wake up the patient to complete the pain rating forms. Being asleep or awake does not relate to pain or lack of pain and the sponsor should explain why the conclusions are valid in regard to efficacy even with this design error. One would have to conclude that the firm needs to address the question raised in statistical review, p. 5, section iv.

(iv) Changes in vital signs due to morphine relate to baseline values and this is presumably true for buprenorphine. The sponsor did not adjust for baseline values in the analysis and the data should be reanalyzed.

(v) I recommend the statistics be recalculated considering the study a cross-over design (see statistical review.) The use of a two-way (patients and treatments) analysis of variance in this design is not appropriate. The applicant ought to provide a standard analysis for this design taking into account the treatment effect, period effect, treatment by period interaction, and residual effects uncontaminated by patient-to-patient (subjects within sequence) variability. A reference for the appropriate analysis is W. Federer Experimental Design, MacMillan, 1955.

(vi) Some patients participated in this analgesic trial within a few hours post-radiotherapy. The statistics need to be redone with this factor given consideration.

(vii) The side effect section of the data does not take into consideration that the natural course of events, i.e. progression of the disease causing the pain changes over time. Since this is a cross-over study, this issue is relevant to the side effect conclusions. An issue that needs to be addressed is the fact that 15 of the 20 patients completed the study within three days.

(d) I disagree with the sponsor's evaluation in that the conclusions are premature. Further analysis is required and if after that the conclusions still hold validity this study might support efficacy.

C. Conclusions

(1) Scientific - This submission contains some evidence supporting the sponsor's claim; however, the evidence as presented cannot be considered substantial since there are flaws in the design and serious omissions in the analysis of the data. The points to be addressed and the analysis to be performed are listed above.

(2) Deficiencies/Problems in this study as listed above.

II. a. Principal Investigator:

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Monitor: Dr. J. A. Buylla, Clinical Research Director, Reckitt and Colman

Title of Study:

Comparative Study of Buprenorphine, Pethidine and Pentazocine
Given Intramuscularly to Patients with Post-Operative Pain

(1) Objective of the Study

The purpose of this study was to assess the efficacy and determine the nature and incidence of unwanted effects of intramuscular buprenorphine in comparison with established intramuscular analgesics in patients experiencing moderate to severe post-operative pain.

This was a single-dose, double-blind, between patient study comparing buprenorphine (2 ug/kg and 4 ug/kg), pethidine (1 mg/kg) and pentazocine (0.6 mg/kg). Subsequently a further group of patients who received buprenorphine (8 ug/kg) were studied.

(6) Experimental Design

(1) Patient Population

(a) Demography

Since the treatment "buprenorphine (8 ug/kg)" was not included in the original protocol, the data were analyzed firstly excluding the buprenorphine (8 ug/kg) group and secondly including this group.

Comparability of the five treatment groups with respect to age and weight was examined using analysis of variance. Differences in sex distributions were investigated in the analysis. The sex distributions in each of the treatment groups were compared using the chi-square test.

The treatment groups were also analysed for comparability of pain intensity at baseline (both rest and move), using the chi-square test for homogeneity of pre-drug pain intensity.

The protocol did not contain any restrictions on age and weight in the admission criteria to the trial. However there were two patients with no age recorded, one each from the (2 ug/kg) and the (8 ug/kg) buprenorphine groups. There were also two patients with no weight recorded, one each from the (2 ug/kg) and (4 ug/kg) buprenorphine groups.

The demography data is contained in the NDA submission together with the surgical procedure for each patient.

Of the study population 55% were females and 45% were males and the sex distributions in the treatment groups were comparable. The chi-square value for testing the homogeneity of sex distributions was 2.05 (d.f. = 4, p = 0.73).

The submission presents the results of the GIM procedure of the Statistical Analysis System (SAS) for the analysis of age, and also the class and subclass arithmetic means. There was a sex difference ($p = 0.0046$), but after removing the effect due to sex, there was no significant difference between the mean ages among the treatment groups ($p = 0.23$). The sex difference was consistent across all groups, since the sex/treatment interaction was non-significant ($p = 0.15$).

After removing the effect of sex, the mean weights in the five treatment groups were significantly different ($p = 0.0535$). The differences in mean weights among the treatment groups were judged to have a negligible effect on the response to treatment and were therefore not considered in the subsequent analyses of efficacy variables. Plots of SPID and TOTPAR against weight were examined for the buprenorphine (4 ug/kg) group. Neither plots for the baseline pain subgroups, nor for the whole group showed a relationship between these efficacy measures and weight.

Repeating the analyses of age and weight, after removing the 18 excluded patients, gave the same pattern of results.

Baseline Pain Intensity Scores are given for each patient in the study together with all subsequent scores, calculated PID's and SPID's. Data refers to both "movement pain" and "rest pain."

Data shows the distribution of baseline pain intensity scores (rest and move) for each treatment group, together with mean pain scores. The patients excluded from the analysis of efficacy were omitted and chi-square tests of homogeneity were carried out. These showed that, regardless of whether the buprenorphine (8 ug/kg) group was included or not, that there was no significant difference between the treatment groups. This was true for both rest and movement pain. Consequently the treatment groups were regarded as comparable, but in the analysis of SPID's and TOTPAR's, the minor differences in baseline pain scores were controlled by using this score as the concomitant variable in an analysis of covariance.

(b) Clinical characteristics for inclusion:

The inclusion criteria are as listed:

"Any patient with pain may be admitted to the trial provided their own prior consent has been obtained, and their surgeon and anaesthetist are in agreement. Cases were chosen from among those with a moderate to severe degree of pain who might otherwise receive, for example, an injection of pethidine. Patients in poor condition or otherwise deemed to be bad risks will be excluded. Although essentially a single-dose study, patients requiring a further analgesic after a trial drug might participate in a second "round." These cases would be treated as a new patient while at the same time clearly marking the proforma "second round" and noting the code number of the previous trial treatment."

In this study the same basic criteria as in the previous study were applied.

(c) Exclusions: as listed in the previous review and similar in all eight pivotal studies.

(2) Procedures

(a) Specific formulation(s) used in study:

For the initial study the three test medications compared were buprenorphine, pethidine and pentazocine. Each patient was assigned one ampoule of test medication. The drugs were supplied in the following concentrations:

Buprenorphine	0.1 mg/ml	2 ml ampoule
Buprenorphine	0.2 mg/ml	2 ml ampoule
Pethidine	50.0 mg/ml	2 ml ampoule
Pentazocine	30.0 mg/ml	2 ml ampoule

The dose rate was 0.2 ml/10 kg body-weight, giving doses of 2 or 4 ug/kg buprenorphine, 1.0 mg/kg pethidine or 0.6 mg/kg pentazocine respectively. For the 134 patients assessed in the efficacy analysis the mean doses administered were 0.133 mg for the 34 patients in the 2 ug/kg buprenorphine group, 0.263 mg for the 34 patients in the 4 ug/kg buprenorphine group, 66.6 mg for the 37 patients in the pethidine group, and 36.2 mg for the 29 patients in the pentazocine group.

In the second phase of the study the drug was supplied in the following concentration:

Buprenorphine 0.4 mg/ml 2 ml ampoule

The dose rate was 0.2 ml/10 kg body-weight giving a dose of 8 ug/kg buprenorphine. The mean dose administered to the 34 patients in this group was 0.556 mg.

(b) Type of Experimental Controls:

This was a single-dose, double-blind, between patient study comparing buprenorphine (2 ug/kg, 4 ug/kg, 8 ug/kg), pethidine (1 mg/mk) and pentazocine (0.6 mg/kg) as a single intra-muscular injection. A total of one hundred and eighty six patients experiencing moderate to severe post-operative pain were admitted into the trial.

Initially it was proposed to compare buprenorphine (2 ug/kg and 4 ug/kg) with pethidine (1 mg/kg) and pentazocine (0.6 mg/kg) and only these four treatments were mentioned in the original protocol. These four treatments were randomly allocated to 152 patients with 38 patients receiving each of the treatments, both patient and observer being unaware of the nature and dose of the drug administered. It was subsequently decided to give injections of buprenorphine (8 ug/kg) to an additional 34 patients, again on a double-blind basis.

This procedure is not appropriate nor adequate for this study. See reviewer's comments.

(c) Dosage schedule: see Table 14 and 2(a) above.

(d) List desirable concomitant medication: none

(3) Safety considerations - observations prior to, during and after study:

a. Clinical studies: see introduction and Table 14.

b. Laboratory studies: see introduction of this section.

c. Indications for removing a patient from the study are listed in exclusion criteria above.

d. Study observations:

Vital signs including pulse rate, blood pressure and respiratory rate were recorded and are presented in the submission. For pulse rate, the pentazocine and buprenorphine (2 and 4 ug/kg) groups showed a significant fall from baseline for half to one hour, the levels then returning to baseline. For pethidine no changes from baseline were observed while the buprenorphine (8 ug/kg) group showed a gradual increase with a significantly higher level than baseline after four hours. For blood pressure (both systolic and diastolic) all treatments showed a similar initial fall over the first half hour followed by a gradual increase over the four hour period. Clinically the minor changes occurring with any of the treatments were not considered meaningful by the sponsor, especially in this relatively unstable post-operative period. For respiration rate, the pethidine, pentazocine and buprenorphine (4 ug/kg) groups showed no changes over the evaluation period. However, for the buprenorphine (2 and 8 ug/kg) groups the respiration rate was significantly lower than the baseline level from half an hour until the end of the evaluation period. Clinically a marked fall in respiration rate was observed in three patients who had received buprenorphine (8 ug/kg). In two of these, (treatment numbers 164 and 181) the temporary bradypnoea resolved spontaneously without additional treatment. In the third case (treatment number 178) whose respiratory rate dropped to 4 min^{-1} , Narcan (0.8 mg i.v.) was given with little effect, the patient's respiratory rate returning to normal some two hours later.

The most common side effect was sedation which was observed in over 80% of patients in each treatment group. While there were no significant differences between treatment groups in terms of incidence of sedation, based on degree of sedation, the pentazocine and buprenorphine (2 and 8 ug/kg) groups produced a significantly greater degree of sedation than the pethidine group ($p < 0.05$). There were no differences between the treatment groups with regard to the incidence of other side effects apart from sweating where the incidence in the buprenorphine (4 ug/kg) group was significantly higher than in the buprenorphine (2 ug/kg) group ($p < 0.05$). In only one case (treatment number 153) did side effects give rise to any clinical concern. This patient received 0.36 mg buprenorphine (8 ug/kg) and became very drowsy for a number of hours. Administration of Narcan (1.2 mg i.v.) after about four hours caused only slight improvement. However, the patient was fully conscious the following day. Subsequently his condition deteriorated and he died three days later. The investigator felt "it unlikely that the buprenorphine had materially contributed to his death although in retrospect he should probably not have been included in the study because of his poor physical condition." I agree with their evaluation and feel the death is not drug-related.

(4) Efficacy considerations:

(a) Clinical and laboratory measurements used to characterize efficacy or comparability:

Data as discussed in the prior review was obtained prior to therapy and at 0.25, 0.5, 1, 2, 3, and 4 hours following administration of the drug. Study design is summarized in Table 14.

Clinical evaluations following remedication were excluded from the analysis for those patients receiving additional analgesic medication before the end of the study period.

18 patients were excluded from the efficacy analysis as prior to and during the earlier part of the study, their ability to give reliable assessments of the subjective parameters of pain intensity and pain relief was considered questionable. Consequently these patients were excluded from the analysis of efficacy. However, objective measurements such as pulse rate and side effects could be measured satisfactorily and so the above patients were included in the analysis of vital signs and side effects.

In addition there were 10 patients with an initial pain intensity (rest) of 1 (mild pain), whereas the protocol specified moderate or severe pain. These patients were excluded from the analysis of pain intensity (rest).

The table below gives the number of patients exclusions for each treatment:

<u>Treat- ment</u>	<u>No. of Patients</u>	<u>Exclusions from pain (move) and pain relief</u>	<u>Reduced Total</u>	<u>Exclusions from Pain (rest)</u>	<u>Reduced Total</u>
Peth. (1 mg/kg)	38	1	37	3	35
Pent. (0.6 mg/kg)	38	9	29	12	26
Bupr. (2 ug/kg)	38	4	34	6	32
Bupr. (4 ug/kg)	38	4	34	7	31
Bupr. (8 ug/kg)	34	-	34	-	34
Total	186	18	168	28	158

Pain at rest was differentiated from pain with movement.

(b) $\alpha = .05$ is the degree of significance.

(c) The endpoints for efficacy evaluation are appropriate.

(5) Results of Statistical Consultation:

(i) There was no statement in the protocol as to whether patients were roused for evaluation of pain when they were sleeping. Upon examination of the case reports, it appeared that some patients were roused for evaluation when they were asleep (based on the comments in some of the case reports that the patient was rousable). However, in some other cases, the nurse observer commented that the patient (sleeping during the observation period) was not a good historian (patients #108, 109) which implied that evaluations were based on the patients' recollection. The applicant needs to clarify this, since in many cases, patients appeared to have good pain relief when they were sleeping.

(ii) The buprenorphine groups appeared to give greater pain relief than the pethidine group, but at the same time the sedation level of the buprenorphine groups was also significantly higher than that of the pethidine group.

(iii) No adjustment of the baseline values was made in the analyses of the changes in vital signs, although the applicant admitted that differences in treatment groups may be nominally affected by minor variations in the baseline values (p. 143, Vol. 1.11).

(iv) Pre-anesthetic medications appeared to be comparable among treatment groups. Some patients (30/186) had no records of anesthetics used and some patients (66/186) had no records of other drugs used during anesthesia. The applicant has not examined the comparability among treatment groups with regard to the missing records and explained how this would effect their analysis.

(v) The highest dose buprenorphine groups (8 ug/kg) was added later after the completion of the study of the first four groups. Thus, the patients in this group were not randomized. Results of the efficacy of this treatment group would be inconclusive.

(vi) One patient (#153) who received buprenorphine (8 ug/kg) became heavily sedated. He was conscious the next day but died three days later. Another patient (#104) who received buprenorphine (4 ug/kg) died one day post-treatment. Cause of death was cited as "bleeding from liver site."

(vii) Except for higher level of sedation of the buprenorphine groups, other side effects were generally not significantly different among treatment groups. However, side effects might be masked or complicated by anesthetic or other drugs used during anesthesia.

(viii) Comment (vi) of Study Number 1 also applies here.

(ix) Comment (v) of Study Number 1 also applies here. It should be noted that disagreement in patient entry numbers and their chronological sequence occurred only in the buprenorphine groups.

(6) Results of Study

(a) Sponsor's evaluation:

Pain relief was observed within 15 to 30 minutes for all treatment groups. Peak pain relief was achieved at one hour post dose for the pethidine (1 mg/kg) and pentazocine (0.6 mg/kg) and at about two hours for the buprenorphine groups. There was no significant difference between the times to peak PID for each of the groups. SPID (move, SPID (rest), and TOTPAR scores for both higher buprenorphine doses (4 and 8 ug/kg) were significantly greater than the corresponding scores for pethidine (1 mg/kg). During the first eight hours following drug administration fewer patients in the buprenorphine groups required remedication than in the pethidine (1 mg/kg) and pentazocine (0.6 mg/kg) groups.

Buprenorphine (2 and 4 ug/kg) and pentazocine (0.6 mg/kg) produced transient falls in pulse rate, lasting half to one hour while buprenorphine (8 ug/kg) produced a gradual increase lasting four hours. All treatments caused an initial transient fall in both systolic and diastolic blood pressures which lasted for about half an hour followed by a gradual rise. Only buprenorphine (2 and 8 ug/kg) produced a lowering of respiration rate. This was most marked in three patients who had received buprenorphine (8 ug/kg), but all returned to normal rates with no ill effects. Sedation was the most common side effect. Patients receiving buprenorphine (2 and 4 ug/kg) experienced a significantly greater level of sedation than patients receiving pethidine. All treatments produced a similar range and number of side effects. All treatments produced similar values for all parameters, the main differences being the longer duration of activity shown by buprenorphine (4 and 8 ug/kg) and the higher level of analgesia attained by buprenorphine (4 ug/kg) than by pethidine (1 mg/kg) without an increase in side effects.

(6) Reviewer's evaluation:

(i) The test and control groups were comparable by the statistical methods used in the analysis. Proper techniques were applied to assess baseline differences between groups, i.e., age, sex, number of patients per group, etc.

(ii) The documentation and analysis of results are sufficient to justify the conclusions.

(c) This study contains evidence supporting the applicant's claim of safety and efficacy. However, I have the following comments:

(i) The sponsor ignored the influence of pre-study analgesics in the statistical analysis. Tests need to be conducted to determine if the groups are comparable in regards to this variable. I recommend the data be stratified or adjustments be made in the analyses for the type of and elapsed time since the administration of pre-study analgesics. Some patients (30/186) had no records of anesthetics used and some patients (66/186) had no records of other drugs used during anesthesia. The applicant has not examined the comparability among treatment groups with regard to the missing records and explained how this would affect their analysis.

(ii) In all three of these pivotal studies using non-morphine standards the quantification of sedation is less exact than the 5 previous studies using morphine as the control. In this case instead of collecting data at the same observation points as pain observations, the data is collected in terms of (a) onset of sedation, (b) duration of sedation, and (c) degree of sedation. This is not nearly as precise as the method used in the first 5 studies. At this point the study is completed and in so far as the design cannot be changed I recommend the sponsor defend the conclusions drawn from the data and how does this set of conclusions compare to the earlier 5 studies.

(iii) Methods of assessment for pain intensity and pain relief were not clearly specified when patients were asleep. A comparison of the individual patient's pain relief scores with sedation levels revealed that most of the patients who obtained complete pain relief were patients who were asleep. The sponsor failed to wake up the patient to complete the pain rating forms. Upon examination of the case reports, it appeared that some patients were roused for evaluation when they were asleep (based on the comments in some of the case reports that the patient was rousable). However, in some other cases, the nurse observer commented that the patient (sleeping during the observation period) was not a good historian (patients #108, 109) which implied that evaluations were based on the patients' recollection. Being asleep or awake does not relate to pain or lack of pain and the sponsor should explain why the conclusions are valid in regard to efficacy even with this design error. One would have to conclude that the firm needs to address the question raised in statistical review p. 5 section iv. It is of interest to note that pethidine was associated with the lowest sedation ratings and was the least effective in producing analgesia. This leads one to again ask about the relationship of sedation to analgesia. It is important for the sponsor to separate sedation effects from analgesic effects of the test medications.

(iv) Changes in vital signs due to morphine relate to baseline values and this is presumably true for buprenorphine. The sponsor did not adjust for baseline values in the analysis and the data should be reanalyzed.

(d) I disagree with the sponsor's evaluation in that the conclusions are premature. Further analysis is required and if after that the conclusions still hold validity this study would support efficacy.

C. Conclusions

(1) Scientific - This submission contains some evidence supporting the sponsor's claim; however, the evidence as presented cannot be considered substantial since there are flaws in the design and serious omissions in the analyses of the data. The points to be addressed and the analysis to be performed are listed above.

(2) Deficiencies/Problems in this study as listed above.

III. Principal Investigator:

B.C. Hovell, M.B., Ch.B., F.F.A.R.C.S.
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Monitor: Dr. J.A. Buylla, Clinical Research Director, Reckitt and Colman

Title of Study:

Comparison of Buprenorphine and Omnopan as an Analgesic Agent for Post-Operative Pain

(1) Objective of the study:

The purpose of this study was to compare the analgesic efficacy, duration of action and side effects of buprenorphine and Omnopan, given by intramuscular injection for post-operative pain.

This trial was a double-dose, double-blind, between patient study comparing buprenorphine (0.3 mg) and Omnopan (20 mg).

(b) Experimental Design

(1) Patient Population

(a) Demography

This was a double-dose, double-blind, between patient study comparing buprenorphine (0.3 mg) and omnopon (20 mg). A total of 55 patients, experiencing moderate to severe post-operative pain following general surgical procedures, were admitted into the trial. However, only 45 patients completed the trial according to the protocol. One patient returned to theatre for further surgery before the end of the observation period, four patients failed to receive the second dose of test medication, and five patients were above the stipulated weight range.

Patients were allocated at random to one of the two treatment groups, both patient and observer being unaware of the nature of the drug administered.

Comparability of the two treatment groups with respect to age and weight was investigated using a two-way analysis of variance. Sex differences for each of these parameters were also examined in the analysis. The sex distributions in each of the treatment groups were compared using a chi-square test.

Treatment groups were analyzed for comparability of pain intensity at baseline, using a chi-square test for homogeneity of pre-drug pain intensity.

The mean ages and weights of patients in each of the treatment groups are submitted. Means in each of the treatment groups after removing the effect due to sex, show that the groups were comparable with respect to age and weight. In the analysis of weight, the effect due to sex was significant ($p < 0.01$).

There is therefore no evidence to suggest any imbalance in the distribution of demographic variables between the treatment groups.

The data shows the distribution of pre-drug (baseline) pain intensity scores for each treatment group prior to the first dose. A chi-square test for homogeneity showed no evidence of a difference in initial pain score between the treatment groups. Consequently the groups were regarded as comparable, but in the analysis of SPID's the minor differences in pre-drug pain scores were controlled by using this score as the concomitant variable in an analysis of covariance.

(b) Clinical characteristics for inclusion:

A total of 55 patients experiencing moderate to severe pain following general surgical procedures, who would normally require an injected analgesic for the relief of pain, were selected for participation in the study. The criteria are similar to the previous study.

(c) Exclusions:

- a. patients under 18 or over 70 years of age.
- b. patients weighing less than 50 kg or more than 80 kg.
- c. patients recently receiving regular therapy with narcotics.
- d. patients on mono amine oxidase inhibitor (MAOI) drugs.
- e. patients with severe respiratory disease or a significantly reduced respiratory reserve.
- f. patients unable to cooperate in the assessment procedure.

(2) Procedure

(a) Specific formulation(s) used in study:

The two test medications compared were buprenorphine and Omnopon. Each patient was assigned one test compound. The first dose of analgesic was administered by the anaesthetist and a second dose by the hospital nursing staff. The second dose was administered either when the patient indicated that pain relief was diminishing and the pain intensity score was noted to increase by one degree or six hours after the first injection. Both doses were of the same analgesic, the total contents of one ampoule being administered. The drugs were supplied in the following concentrations:

Buprenorphine	0.3 mg/ml	1 ml ampoule
Omnopon	20 mg/ml	1 ml ampoule

(b) Type of Experimental Controls:

This was a double-dose, double-blind between patient comparative study. Fifty-five patients commenced the study but it was subsequently decided to exclude 10 patients from the analysis. Five patients (treatment numbers 13, 30, 33, 40, and 53) were excluded because their weights were over 85 kg (see "Patient Population"); two patients (treatment numbers 10 and 23) were remedicated following the first administration by ward staff on an open basis when in the opinion of the observer there was no indication of increased pain, two patients (treatment numbers 35 and 41) did not receive the second test dose as in the opinion of the investigator administration was not warranted and one patient (treatment number 50) had to return to the theatre for examination of a wound haemorrhage prior to completion of the observation period.

This procedure is not appropriate nor adequate for this study. See reviewer's comments.

(c) Dosage schedule: see Table 14 and 2(a) above.

(d) List desirable concomitant medication: None

(3) Safety Considerations - Observations prior to, during, and after study

a. Clinical studies: see introduction and Table 12.

b. Laboratory studies: see introduction of this section.

c. Indications for removing a patient from the study are listed in exclusion criteria above.

d. Study observations:

An increase in pulse rate occurred with buprenorphine 0.3 mg after the first dose followed by a gradual return towards the baseline level after the second dose. With omnopon 20 mg a gradual decrease occurred after the first dose followed by a return to baseline subsequently. For systolic and diastolic blood pressure a significant fall over the first hour after administration was followed by a levelling off for buprenorphine 0.3 mg and a gradual trend towards baseline for omnopon 20 mg. After the second dose both drug groups showed evidence of an increase towards the baseline level over the 5 hour evaluation period. Respiratory rate decreased significantly over the 3 hour period following administration of the first dose, followed by a levelling off for omnopon 20 mg and an upward trend towards baseline for buprenorphine 0.3 mg. After administration of the second dose a further small decrease in respiratory rate was detected.

There were marginally more side effects reported for buprenorphine 0.3 mg than for omnopon 20 mg. A comparison of the treatment groups showed no evidence of a difference in the proportion of sedated patients between the groups (Fisher's exact chi-square test). However, there was a slight indication that the degree of sedation was greater with buprenorphine than with omnopon (single-sided $p = 0.086$).

The occurrence of all other side effects was small in both treatment groups and insufficient evidence was available to demonstrate a difference in proportion between the groups.

(4) Efficacy considerations:

(a) Clinical and laboratory measurements used to characterize efficacy or comparability:

Data obtained is described in Table 14 and was collected following the first dose (1, 2, 3, 4, 5, and 6 hours post-therapy) and following the second dose (1, 3, 5 hours post-therapy).

(b) $\alpha = .05$ is the degree of significance.

(c) The endpoints for efficacy evaluation are appropriate.

(5) Results of statistical consultation:

(i) The range of the weights of patients was specified as 50-80 kg in the protocol. However, the applicant decided to extend the range to 45-85 kg upon examination of the data and excluded 4 patients whose weights were over 85 kg. The reason for extending the range of weight and the cut-off point chosen after looking at the data was not clear. The applicant needs to explain this.

(ii) No distinction was made between pain at rest and pain on motion.

(iii) Comment (v) of Study Number 1 also applies here. Beginning with patient number 37, the chronological dates of subsequent patients jumped back and forth out of sequence. Also, patient number 55 was missing. The applicant needs to explain this.

(iv) Although there was no significant difference in SPID between treatment groups, the power of detecting a clinically meaningful difference was not provided by the applicant. The following table is prepared by this reviewer to illustrate the magnitude of the minimum differences in SPID that could be detected with the corresponding minimum acceptable powers. It must be emphasized that if the required minimum difference to be detected is smaller than the figures in the table, the power will be lowered to an unacceptable level.

	<u>Mean Min.</u>	<u>SPID Max.</u>	<u>Min. Difference to be detected</u>	<u>Power</u>
First dose	6.8	7.4	3.0	0.74
Second dose	8.7	9.3	2.0	0.74

(All power figures are approximate and are based on 2-sided t-tests with significance level .05).

(v) Analysis on the changes in vital signs was not adjusted for baseline values.

(vi) Comments (ii) and (iv) of Study Number 1 also apply here.

(vii) There appeared to be no significant difference in side effects between treatment groups.

(viii) The pulse rate behavior between treatment groups appeared to be different (see p. 341, Vol. 1.11).

(6) Results of Study:

(a) Sponsor's evaluation:

Pain relief was obtained following both treatments within one hour. Based on time to peak PID there was no significant difference in onset of activity between the two treatments. There was no significant difference between levels of analgesia produced by the treatments as shown by mean SPID and mean maximum PID, nor was there any significant difference between the duration of action of either treatment. No significant changes in pulse rate occurred with either treatment. Both drugs caused slight, transient decreases in both systolic and diastolic blood pressures. Respiratory rate was also transiently depressed following both drugs. Sedation was the most common side effect,

buprenorphine (0.3 mg) seeming to cause a greater degree of sedation than Omnopon (20 mg). Otherwise the drugs were very similar in side effect profile.

Both buprenorphine and Omnopon produced good levels of analgesia and showed similar properties of duration of activity and side effects.

(6) Reviewer's Evaluation

(i) The test and control groups were comparable by the statistical methods used in the analysis. Proper techniques were applied to assess baseline differences between groups, i.e., age, sex, number of patients per group, etc.

(ii) The documentation and analysis of results are not sufficient to justify the conclusions; however, the data does tend to substantiate the sponsor's claim. Further analysis is needed prior to accepting the study.

Beginning with patient number 37, the chronological dates of subsequent patients jumped back and forth out of sequence. Also, patient number 55 was missing. The applicant needs to explain this.

(c) This study contains some evidence supporting the applicant's claim of safety and efficacy. However, I have the following comments:

(i) The sponsor ignored the influence of pre-study analgesics in the statistical analysis. Tests need to be conducted to determine if the groups are comparable in regards to this variable.

I recommend the data be stratified or adjustments be made in the analyses for the type of and elapsed time since the administration of pre-study analgesics.

(ii) In all three of these pivotal studies using non-morphine standards, the quantification of sedation is less exact than the 5 previous studies using morphine as the control. In this case instead of collecting data at the same observation points as pain observations, the data is collected in terms of (a) onset of sedation, (b) duration of sedation, and (c) degree of sedation. This is not nearly as precise as the method used in the first five studies. At this point the study is completed and insofar as the design cannot be changed, I recommend the sponsor defend the conclusions drawn from the data and how does this set of conclusions compare to the earlier 5 studies.

Methods of assessments for pain intensity and pain relief were not clearly specified when patients were asleep. A comparison of the individual patient's pain relief scores with sedation levels revealed that most of the patients who obtained complete pain relief were patients who were asleep. The sponsor failed to wake up the patient to complete the pain rating forms. Being asleep or awake does not relate to pain or lack of pain and the sponsor should

explain why the conclusions are valid in regard to efficacy even with this design error. One would have to conclude that the firm needs to address the question raised in statistical review p. 5, section iv.

In practical terms the sedation levels were comparable in both groups so one can evaluate comparative analgesia.

(iii) Changes in vital signs due to morphine relate to baseline values and this is presumably true for buprenorphine. The sponsor did not adjust for baseline values in the analysis and the data should be reanalyzed.

(iv) The nature of side effects was comparable among treatment groups. It should be noted that side effects might be masked or complicated by the pre-study medications including type and amount of anesthetic. Reanalysis is needed.

(v) No distinction is made between pain at rest and with motion. As this distinction is made in two of the other seven studies, I recommend the sponsor explain the reason for this omission.

(vi) The reason for extending the range of cut-off points for weight and the inclusion of those patients whose weights were outside the range specified in the protocol are not clear.

(d) I disagree with the sponsor's evaluation in that the conclusions are premature. Further analysis is required and if after that the conclusions still hold validity this study would support efficacy.

C. Conclusions

(1) Scientific - This submission contains some evidence supporting the sponsor's claim; however, the evidence as presented cannot be considered substantial since there are flaws in the design and serious omissions in the analyses of the data. The points to be addressed and the analysis to be performed are listed below.

(2) Deficiencies/Problems in this study as listed above.

(3) Open label use studies

The third category includes nine open label studies. A total of 173 subjects experiencing moderate to severe pain due to a number of painful conditions were studied. Of these, 163 received buprenorphine. In addition, four other patients were given buprenorphine as part of a balanced anesthetic technique. Both single and multiple doses of buprenorphine were given, usually by the intravenous route (123 patients). An overview of the design of each study is presented in Table 16.

The intravenous administration of buprenorphine, 0.3 mg or 0.6 mg, produced some pain relief by 15 minutes. The peak pain relief occurred between 1 and 4 hours post-dose.

A comparison of 0.3 mg buprenorphine to 15 mg Omnopon, both administered intravenously, indicated that buprenorphine produced a greater degree of analgesia than Omnopon. However, attainment of peak pain relief was less rapid with buprenorphine. During the 6 hour study period, patients given Omnopon required more remedication than did the patients receiving buprenorphine.

Dobkin studied buprenorphine as an analgesic adjunct to a balanced anesthesia technique in four patients. He found it to be safe and acceptable when used for this purpose. However, the small patient population did not allow definite conclusions concerning this use.

In the Delooz study, patients given buprenorphine 0.2 mg intramuscularly for moderate to severe, acute traumatic pain, the onset of analgesia was noted within 15 to 30 minutes. Peak pain relief occurred between one and two hours. This dose of buprenorphine provided a good level of analgesia with few side effects, sedation and miosis being the most commonly reported.

In an open multiple dose study (Rees-Jones) of buprenorphine (0.3 mg intramuscular) to patients suffering post-operative pain, assessment prior to and at three hours after drug administration revealed that over half of the patients had complete pain relief after the first dose.

Open label studies administering buprenorphine intramuscularly revealed that with 0.2 mg, the onset of pain relief occurred within 15-30 minutes, and peak relief between 1-2 hours. With multiple doses of 0.3 mg, complete pain relief was obtained 3 hours after the first dose in 50% of the patients. In open-label intravenous studies with 0.3 - 0.6 mg, onset of pain relief occurred within 15 minutes, with peak relief noted at 1-4 hours and lasting up to 8 hours. Sedation was the most frequent side effect encountered.

High dose studies administered 10-20 times the therapeutic dose (0.4 to 7.0 mg) of buprenorphine intravenously producing few side effects. Pain relief occurred within 15 minutes and continued beyond 6 hours. The median remedication time after 3-6 mg doses was 12.5 hours. In these studies, 54 patients received intravenous buprenorphine in open label fashion in doses ranging from 0.4 mg to 7.0 mg. An overview of the experimental protocol for these studies is contained in Table 17.

In the first of these two studies conducted by Dr. Budd, forty-four patients were given intravenous buprenorphine, 0.4 to 7.0 mg. Pulse rate showed a slight, transient fall over the two hours immediately post dose. Both systolic and diastolic blood pressure decreased slightly after the higher doses of buprenorphine. No significant trends in vital signs were elicited.

Sedation was the most common side effect and was observed in nine patients. Vomiting occurred in two patients and nausea in one. None of the side effects required medical treatment. A total of thirty-three patients experienced no side effects.

In Budd's second study, ten patients received intravenous buprenorphine 3.0 mg to 6.0 mg while one patient received Omnopon. There was evidence of a slight, transient fall in pulse rate over the first hour but it returned to baseline levels six hours post dose. Both systolic and diastolic blood pressure decreased slightly over the first two hours, but these decreases were not maintained for the entire study period. Only one patient experienced side effects (dizziness and nausea). At no time during the study did any patient's condition require further medication apart from analgesics.

For the ten patients there was a fall in pH over the first 30 minutes post-dose. Seven of the patients who received buprenorphine showed pH values slightly below the normal range although in one case the value was low before administration of buprenorphine. All but one patient in the study exhibited occasional pCO₂ values below normal, but seven of these had low control values. One patient developed a pCO₂ value greater than normal at six hours. All of the patients showed an increase in pCO₂ at half or one hour after medication compared with control values. Subsequently, the values tended to fluctuate, but most were above those of control at three or six hours. These findings could suggest a mild respiratory acidosis. Serum bicarbonate was normal at control reading in only one patient. In two cases, values attained normality during the study, but in the others they remained below normal. These measurements are consistent with a respiratory acidosis. Similarly, seven patients had low control base excess values which in most cases remained abnormal up to two or three hours post-administration. Only one patient remained within the normal range at all observation times during the study. The other patients' values at various times suggested acid excess. On one occasion, one patient had a slightly low pO₂ value. These evaluations suggest some respiratory depression associated with the test medication and/or the anesthetic but this did not reach a level where medical intervention was necessary.

These remarkable data suggest that doses 10-20 times the recommended dose range (0.3 mg-0.6 mg) produce strikingly mild effects in post-surgical patients.

(4) "Other Clinical Studies"

The fourth category "Other Clinical Studies" contains summary reports concerning the worldwide use of buprenorphine in 684 individuals. In these studies, 313 patients were given buprenorphine for acute surgical pain, 103 for the pain of acute myocardial infarction, 159 for chronic or intractable pain, and 109 individuals were given buprenorphine for evaluation of its cardiorespiratory activity profile. The studies are described in Table 18.

The results from the studies carried out in post-operative pain support the claim that buprenorphine is a safe and effective long acting analgesic regardless of the surgical procedure or the location of the pain.

The two studies by Hampton *et al.* in myocardial infarction patients are particularly noteworthy because buprenorphine was found to be not only highly effective but also quite suitable by virtue of its minimal hemodynamic effects. This favorable cardiovascular profile was confirmed in the specific cardiorespiratory studies also included in this section. The studies undertaken in chronic or intractable pain produced similar results to those obtained in the other indications previously mentioned.

(5) Monitored post-marketing report from the U.K.

The sponsor has submitted a report based on data from 9,123 patients who received 17,120 injections of buprenorphine in general clinical use in the United Kingdom. The report did not reveal any unexpected safety or efficacy problems and in general supports the sponsor's claim. The report records the use of some 17,120 injections of buprenorphine given to 9,123 patients ranging in age from 3 to 99 years. This document did not report any new adverse experiences in widespread routine clinical usage, which were previously not recorded in clinical trials.

(6) Clinical literature review

A total of 63 manuscripts and/or abstracts have described the clinical effects of buprenorphine when administered by the parenteral route. The 63 items were comprised of 6 categories: (1) volunteer studies; (2) pre-operative use; (3) use as a narcotic antagonist; (4) post-operative use; (5) emergency pain; and (6) myocardial infarction.

The review of these 63 items did not reveal any unexpected safety or efficacy problems and in general supports the sponsor's claims.

It is desirable to critique one of these reports as it bears direct relevance to the questions of safety and efficacy.

Hampton, J.R. Management of the Pain of Myocardial Infarction. In Pain. New Perspectives in Measurement and Management, Edited by A.W. Harcus, R. Smith and B. Whittle, Churchill Livingstone, Edinburgh, 1977, p. 97-102. This article is located on page 229 in Vol. 128. Hampton summarized his findings on the use of buprenorphine in the pain of myocardial infarction. Ten patients received diamorphine (5 mg, i.v.) followed by buprenorphine (0.3 mg, i.v.) on recurrence of pain and five patients received only buprenorphine (0.3 mg, i.v.). In each case pain relief was rapid with only mild discomfort, at most, remaining 10 min after administration of buprenorphine. Thirteen patients fell asleep within 10 min of the injection, but could be easily

aroused. The duration of pain relief associated with buprenorphine was comparable to that of diamorphine. Hemodynamic measurements showed a mild significant fall in systemic blood pressure but it was concluded that buprenorphine, like diamorphine, seemed to have had no undesirable hemodynamic effects. Buprenorphine (0.3 mg, i.v.) had approximately the same analgesic effects as diamorphine (5 mg, i.v.).

5) Safety:

The issues of safety have also been discussed for each study or groups of studies in the clinical efficacy section above.

The NDA submission discussed safety within the following framework: adverse experiences were classified and discussed according to the following body systems: central nervous system, special senses, cardiovascular system, and respiratory system. Patients described under controlled studies represent all those in Phase II and III double-blind clinical trials. Patients described in open studies consist of all uncontrolled Phase II and III trial patients as well as those described in Budd's report of high dose administration 10-20 times the therapeutic dose (0.4 to 7.0 mg) of buprenorphine i.v. Data is summarized in Appendix II and III from the NDA submission.

I will present the data and my comments in the same framework both for ease of discussion and meaningful comparisons.

Central Nervous System:

The incidence of adverse experiences related to the central nervous system is presented in Table 19.

Table 19
Incidence of Nervous System
Adverse Experiences After Buprenorphine

<u>Adverse Reaction</u>	<u>(N=561)</u>		<u>(N=387)</u>	
	<u>Controlled Studies</u>	<u>#</u>	<u>Open Studies</u>	<u>%</u>
Ner/CNS/B				
Coma	1	0.2	0	-
Confusion	7	1.2	2	0.5
Depersonalization	1	0.2	0	-
Depression	1	0.2	2	0.5
Dizziness/Vertigo	24	4.3	27	7.0
Dream Abnormal	3	0.5	0	-
Euphoria	3	0.5	4	1.0
Hallucinations	1	0.2	0	-
Headache	4	0.7	11	2.8
Nervousness	1	0.2	1	0.3
Somnolence	374	66.7	232	59.9
Speech Disorder	2	0.4	0	-
Tremor	0	-	1	0.3
Withdrawal	2	0.4	1	0.3
Ner/PNS				
Paresthesia	1	0.2	0	-
Ner/PNS/CN				
Diplopia	1	0.2	1	0.3

It is of interest that the rate of sedation reported in the United Kingdom monitored release survey is less (about 6%) than the somnolence ratings of 66.7% for the controlled studies and the 59.9% reported in the open studies. The sponsor believes that "as drowsiness was anticipated with the use of an effective potent analgesic by the clinicians and is often considered beneficial as in post-surgical pain, it was not considered an undesirable side effect. Therefore it was not reported as a side effect by the clinicians." The data indicate that the incidence of sedation in patients given morphine or other potent analgesics in the controlled studies are, as expected, similar for buprenorphine. (See Table 20).

Table 20
Incidence of Somnolence in Patients Given Either Buprenorphine,
Morphine, Pethidine, Pentazocine or Omnopon in
Controlled Clinical Studies

<u>Agent</u>	<u>Somnolence</u>	<u>Total # of Patients</u>	<u>%</u>
Buprenorphine	374	561	66.7
Morphine	197	417	47.0
Pentazocine	49	58	84.5
Pethidine	32	38	84.2
Omnopon	23	29	79.3

Table 21 presents the incidence of selected CNS drug effects for the several potent analgesics given in controlled clinical studies.

Table 21

Incidence of Selected Nervous System Related Side Effects for Buprenorphine and Other Potent Analgesics When Given in Controlled Clinical Studies

Adv. Reac.	N=561		N=417		Percentages		N=38	N=29
	#	%	#	%	#	%		
Ner/CNS/B								
Anxiety	0	-	0	-	1	1.7	0	-
Ataxia	0	-	0	-	1	1.7	0	-
Coma	1	0.2	0	-	0	-	0	-
Confusion	7	1.2	2	0.5	4	6.9	1	2.6
Depersonalization	1	0.2	1	0.2	0	-	0	-
Depression	1	0.2	0	-	1	1.7	0	-
Dizziness/Vertigo	24	4.3	12	2.9	4	6.9	1	2.6
Dream Abnor.	3	0.5	0	-	0	-	0	-
Euphoria	3	0.5	3	0.7	0	-	0	-
Hallucination	1	0.2	3	0.7	1	1.7	0	-
Headache	4	0.7	1	0.2	1	1.7	1	2.6
Hysteria	0	-	2	0.5	0	-	0	-
Nervousness	1	0.2	1	0.2	0	-	0	-
Somnolence	374	66.7	196	47.0	49	84.5	32	84.2
Speech							23	79.3
Disorder	2	0.4	0	-	0	-	0	-
Tremor	0	-	0	-	0	-	0	-
Withdrawal								
Syndrome	2	0.4	0	-	0	-	0	-
Ner/PNS								
Paresthesia	1	0.2	0	-	0	-	0	-
Ner/PNS/CN								
Diplopia	1	0.2	0	-	0	-	0	-

Of note is the low incidence of CNS reactions such as hallucinations, euphoria, depersonalization and confusion in the patients studied. This low rate is supported by the infrequent occurrences reported in the United Kingdom monitored release survey (post-marketin). This data, however, bears little resemblance to the data collected in Dr. Jasinski's physical dependence

studies previously reviewed. What these two section of the submission do share is data to indicate the individual given buprenorphine or morphine can not easily distinguish between the two and that CNS effects noted when the drug is given to patients with moderate to severe pain or to pain-free patients given the drugs to evaluate the "high" are different.

In three cancer patients who had been on maintenance therapy with narcotic analgesics, the administration of buprenorphine precipitated abstinence. Two instances occurred in a controlled trial (Houde - cases #323 and #426) while the other instance was reported in an open study (Robbie - case #015). This is not surprising in view of the antagonist activity of buprenorphine which in animals has been shown to be comparable to that of naloxone in potency (ratio 1:1).

Gastrointestinal Tract

The incidence of side effects related to the gastrointestinal tract after buprenorphine administration is presented in Table 22.

Table 22

Incidence of Gastrointestinal Tract Adverse Experiences After Buprenorphine Related

Adverse Experience	N=561		N=387	
	Controlled Studies #	Controlled Studies %	Open Studies #	Open Studies %
Dry mouth	3	0.5	2	0.5
Constipation	0	-	2	0.5
Diarrhea	1	0.2	1	0.3
Dyspepsia	1	0.2	0	-
Dysphagia	0	-	1	0.3
Nausea	44	7.8	39	10.1
Nausea/Vomiting	2	0.3	8	2.1
Vomiting	17	3.0	20	5.2

The incidence of these side effects is low, with nausea being the most frequent.

A comparison of the gastrointestinal side effects of the several potent analgesics given in controlled trials is made in Table 23.

The incidence of side effects was found to be very similar among these 5 drugs with the exception of Omnopon which produced a noticeably higher rate of nausea and vomiting.

Table 23
Incidence of Selected Gastrointestinal Adverse Experiences for
Buprenorphine and Other Potent Analgesics When Given in
Controlled Clinical Trials

Adv. Exper.	N=561		N=417		N=58		N=38		N=29	
	Buprenorphine #	Buprenorphine %	Morphine #	Morphine %	Pentazocine #	Pentazocine %	Pethidine #	Pethidine %	Omnopon #	Omnopon %
Dry mouth	3	0.5	2	0.5	1	1.8	0	-	0	-
Diarrhea	1	0.2	0	0	0	-	0	-	0	-
Dyspepsia	1	0.2	0	0	0	-	0	-	0	-
Nausea	44	7.8	30	7.2	7	12.1	3	7.9	7	24.1
Nausea/ Vomiting	2	0.3	2	0.5	0	-	0	-	1	3.5
Vomiting	17	3.0	6	1.4	2	3.4	1	2.6	3	10.3

Integumentary System

A number of reactions involving the integumentary system were reported in this submission. Reactions related to the skin were recorded with about equal frequency in controlled and open studies. As could be expected, sweating was the most prevalent reaction. Flushing occurred twice during the controlled open studies and is coded as vasodilation in the tables. Data is presented in Table 24.

Table 24
Incidence of Integumentary Adverse Experiences
After Buprenorphine

Adverse Experience	N=561		N=387	
	Controlled Studies #	Controlled Studies %	Open Studies #	Open Studies %
Vasodilation	2	0.4	0	-
Inject. Site Reaction	0	-	2	0.5
Pain Inject. Site	3	0.5	0	-
Rash	1	0.2	0	-
Pruritis	2	0.3	0	-
Sweat	30	5.3	12	3.1

A comparison of buprenorphine to other potent analgesics for side effects related to the skin is presented in Table 25.

Table 25

Incidence of Selected Integumentary Adverse Experiences for
 Buprenorphine and Other Potent Analgesics When Given in
 Controlled Clinical Trials

Adver. Exp.	N=561		N=417		N=58		N=38		N=29	
	#	%	#	%	#	%	#	%	#	%
Vasodilation	2	0.4	0	-	0	-	0	-	0	-
Inject Site Reaction	0	-	5	1.2	0	-	0	-	0	-
Pain Inject- tion Site	3	0.5	4	1.0	0	-	0	-	0	-
Rash	1	0.2	0	-	0	-	1	2.6	0	-
Pruritis	2	0.3	1	0.2	0	-	0	-	0	-
Sweat	30	5.3	4	1.0	5	8.6	4	10.5	4	13.8

The rate of occurrence of these reactions is alike for buprenorphine and the other potent analgesics and none of these were severe and most consisted of transient pain at the site.

Reactions relative to the special senses

These reactions were, for the most part, anticipated and can be considered to be common to the pharmacological profile of potent analgesics. The data is presented in Table 26. Also, it is probably also true that the incidence of miosis is vastly underreported. It probably occurs to some degree in most patients given buprenorphine. Nine of the 10 reactions coded as amblyopia were described by the various investigators as blurred vision; the remaining reaction was recorded as amblyopia.

Table 26
 Incidence of Special Senses Adverse
 Experiences After Buprenorphine

Adverse Reaction	N=561		N=387	
	#	%	#	%
Miosis	2	0.4	15	3.9
Pupil Disorder	0	-	1	0.3
Amblyopia	9	1.6	1	0.3
Vision Abnormality	0	-	1	0.3
Tinnitus	1	0.2	0	-

Cardiovascular System

The incidence of side effects referable to the cardiovascular system is shown in Table 27.

Table 27

Incidence of Cardiovascular System
After Buprenorphine

<u>Adverse Experience</u>	N=561 Controlled		N=387 Open	
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>
Bradycardia	2	0.4	1	0.3
Tachycardia	0	-	3	0.8
Palpitation	0	-	-	-
Hypertension	4	0.7	3	0.8
Hypotension	35	6.2	9	2.3

Hypotension was the most common reported cardiovascular effect. The sponsor states: "This side effect is often considered to be an effect secondary to sedation." I recommend the sponsor go back to the data on the relationship between hypotension and sedation and perform the proper statistical analysis to substantiate this statement.

The sponsor also states: "Peripheral vasodilation may also be contributory. All of these reports were obtained from post-surgical patients. Since hypovolemia may very well enhance susceptibility to hypotension after potent analgesics, one could expect its incidence to be much more frequent in post-surgical patients." I recommend the frequency of cardiovascular side effects be presented for the other major analgesics given for comparison in the NDA. This type of comparison is presented for other systems involved, such as CNS and is noticeably absent from the NDA. This is a simple matter, as all patient data from the controlled (N=561) and open (N=387) are on computer file with the sponsor.

As seen from Table 27, hypotension was reported in 44 cases. The majority of the reported cases (30) were not considered to require medical intervention by the clinical investigator. Most often these represented blood pressure decreases to the 80-90/40-50 range. The remaining 14 patients were felt to require medical treatment. This consisted of elevating the patient's bed and/or starting or increasing the flow of either parenteral fluids or blood. Of the 14 cases, three cases (Hovell - Case 104, Dobkin - Case 207, Dobkin - Case 43) were considered to be secondary to surgical blood loss. Of these

patients, #104 was a 59 year old male whose past history included chronic bronchitis and cor pulmonale. He underwent cholecystectomy. Prior to buprenorphine administration he was noted to be breathless with blood pressure of 140/60. After 0.32 mg intramuscular buprenorphine his pressure decreased to 60/40 and respirations were described as labored. Intravenous fluids and eventually whole blood were given. The next day the surgical site was explored for bleeding sites. A short time later he experienced a cardiac arrest and was pronounced dead approximately one hour later. Death was attributed to "bleeding from liver site." There was no evidence presented that buprenorphine was contributory. I agree with this evaluation.

Of interest was the discussion of the occurrence of hypotension in those patients described in the United Kingdom Monitored release Program. It was noted that "the association of tachycardia with hypotension is more important than either alone." Only 11 patients of 9,123 were reported to have a pulse rate of more than 120 and a systolic blood pressure of less than 100 mm Hg. Six of these had similar recordings prior to buprenorphine.

This data does present evidence of safety relative to morphine in regards to the cardiovascular system.

Respiratory System:

The number and frequency of respiratory side effects after buprenorphine administration are presented in Table 28.

Table 28

Incidence of Respiratory System Adverse Experiences After Buprenorphine

Adverse Experience	N=561		N=387	
	Controlled N	%	Open N	%
Anoxia	0	-	1	0.3
Apnea	1	0.1	0	-
Cyanosis	2	0.4	0	-
Dyspnea	3	0.4	4	1.0
Hypoventilation	11	2.0	0	-
Respiratory Disorder	0	-	2	0.5

There were 17 side effects listed for the respiratory system in individuals given buprenorphine. For classification purposes, all reactions originally recorded as "respiratory disorder" or "anoxia" as well as 4 of 7 reactions

recorded as "dyspnea" were termed "hypoventilation" (11), dyspnea (3), cyanosis (2), and apnea (1). Of these, one dyspnea (Case 17) and one anoxia (Case 11) reported by Dr. Robbie occurred in patients with malignant disease involving the lungs. Further, a case of respiratory distress (Case 164) reported by Dr. Hovell occurred in a patient who had undergone partial thyroidectomy, and a cyanotic attack (Case 170) occurred in a patient reported to have blood loss of at least 1200 ml. These effects appear non-drug related.

The remaining patients (13) experienced respiratory function changes from which the causative effects of anesthetics and post-operative analgesics cannot be excluded. Of these, eight required no ventilatory assistance, including the rather dramatic report of Hovell (Case 27) in which respiratory rate fell from 20 to 5 after 0.3 mg buprenorphine. This investigator noted that although respiratory rate decreased, the depth of respiration increased. Two of the remainder were given ventilatory assistance. One of these (Hovell - Case 23) became apneic after an intramuscular dose of 0.3 mg. One (Potter - Case 6) of the three cases treated pharmacologically with doxapram showed prompt response to the agents administered. In the other two (Potter - Case 14 and Hovell - Case 178), the response was not as evident. "It appears that, should a clinically significant decrease in respiratory activity occur after buprenorphine, ventilation and doxapram will be effective". I agree with the sponsors' conclusion in this regard; however, more experience is required to show the efficacy of doxapram in buprenorphine induced respiratory depression.

Dr. Orwin's work, which was previously discussed, suggested that some decrease in respiratory function occurs with buprenorphine, just as with any clinically potent analgesic. The United Kingdom monitored release survey notes, however, that the incidence of decreased respiratory activity is 1.2%. Naloxone was given to seven patients with satisfactory reversal in three cases, no further comment was made in two cases and an unsatisfactory effect was seen in one case. The dose of naloxone was 0.4 mg in four cases and was not specified in the others. Doxapram at various doses was given to 23 patients to stimulate respiration. A satisfactory response was reported in nine patients and no further comments were made regarding the others.

Consideration of the respiratory effects of buprenorphine should include the results of two clinical studies performed by Investigator Keith Budd using high dose buprenorphine administration (See previous section on "high dose studies").

(6) Accounting for Investigators - It appears that all investigators listed in the IND are submitting clinical reports for evaluation in support of this NDA.

(7) Need for Post-Marketing Clinical Studies

Defer until I review the forthcoming response to deficiency letter.

(8) Labeling Review - Defer until I review the forthcoming response to our deficiency letter.

(9) Overall Evaluations and Conclusions:

As therapeutic agents, morphine and morphinelike drugs are indispensable, but these same agents are liable to nontherapeutic self-ingestion by segments of the population. Society has condemned this self-ingestion and its associated behaviors and has invoked stringent legal mechanisms controlling the manufacture and distribution of morphinelike drugs. In an attempt to develop analgesics, antitussives, and antidiarrheals that were devoid of those properties of morphine leading to abuse, a large number of drugs have been synthesized and studied

A new class of synthetic drugs known as antagonist-analgesic opiates have significantly improved the treatment of chronic and severe pain. The new synthetics represent 25 years of drug development and combine the analgesic potency of conventional narcotics with reduced side effects and a reduced potential for abuse, although they do have psychological side effects.

Two of the drugs in this class have been approved by the Food and Drug Administration. Butorphanol (marketed as Stadol by Bristol Laboratories) and nalbuphine (marketed as Nubain by Endo Laboratories) are currently marketed as injectable forms. The oral dosage forms of both butorphanol and nalbuphine are being studied under the IND process.

Buprenorphine is a ring-C-bridged opioid derived from thebaine. As a partial agonist on the opiate receptor it produces analgesia and antagonist effects. Its analgesic potency is approximately 30 times that of morphine, but its partial agonist profile and particularly its slow receptor kinetics impart pharmacological properties that are distinct from morphine on the one hand and butorphanol and nalbuphine on the other hand.

The clinical development of buprenorphine was carried out in the U.S.A., Britain, Continental Europe, New Zealand, and South Africa. This submission contained the results of a wide variety of clinical trials involving 1,022 subjects. These subjects were administered buprenorphine either intramuscularly or intravenously in open or double-blind fashion. The drug is currently marketed in the United Kingdom, and the data obtained from a monitored post-marketing report on more than 17,000 administrations is also included in this submission (9123 subjects).

The clinical section of this submission contains seventy-four clinical studies performed and described by fifty-five physicians and included clinical pharmacology studies to evaluate safety and tolerance, including evaluation of the respiratory effects of buprenorphine (74 subjects), pharmacokinetic studies in both healthy volunteers and in patients (21 subjects). The dose

range studies to establish a clinically useful dose range involved 310 subjects. The pivotal efficacy comparisons were obtained with morphine, pentazocine, pethadine, and Omnopon (a trade name for a drug marketed in the United Kingdom) (417 subjects). A series of open trials were also undertaken to broaden the clinical experiences with the drug by the intramuscular and intravenous routes of administration (221 subjects). Case record forms are included for the patients who received buprenorphine and the 388 subjects who received other drugs in these studies.

Physical dependence liability in man has been assessed and the data submitted for review.

The purpose of this submission was to demonstrate that buprenorphine in the dosage range of 0.3 mg to 0.6 mg is an effective and safe potent analgesic agent. Among the eight controlled double-blind clinical trials comparing buprenorphine with morphine and other potent analgesics, seven studies involved patients with moderate to severe post-surgical pain and one study involved patients with pain associated with cancer.

Five of these eight "pivotal studies" compared buprenorphine with morphine in the post-surgical pain model using similar study protocols. These randomized, parallel, double-blind studies included 479 patients who experienced moderate to severe pain. Buprenorphine and morphine were given in single dose administrations by the intramuscular route. The study doses ranged from 0.15 mg to 6 mg in buprenorphine and 5 mg to 15 mg in morphine. Patients were evaluated for pain intensity, pain relief, time to remedication, vital signs and side effects. Side effects were similar for both drugs. The most frequently reported adverse experience was somnolence. Respiratory changes of clinical significance were rarely observed. In addition, nausea, vomiting, dizziness/vertigo and sweating were seen.

Based on these five studies, the applicant concluded that buprenorphine was either equal or superior to morphine in relieving moderate to severe post-surgical pain at the various test dose levels. The applicant further claimed that both test drugs were equally safe.

It is my opinion that this submission contains some evidence supporting the applicant's claims of the efficacy and safety of buprenorphine as a general analgesic agent. However, the evidence as presented cannot be considered substantial since there are some flaws in the design of most of the applicant's studies and some potentially serious omissions in the analyses of the data. Adequate arrangements (such as rousing a sleeping patient for evaluation of pain level) were not made in the experimental designs for separating out fully a sedation response from a pain relief response. In addition, in all but one study no distinction was made between pain on motion and pain at rest.

While the flaws are problematic they are not fatal from a clinical point of view. They do, however, limit the statistical inferences one can draw from these data to ones in terms of sedation and pain relief considered jointly and sedation and total pain intensity differences considered jointly. One cannot, however, make the analogous inferences for the efficacy variables singly because of the correlation structure of the data and the experimental design. This issue will need to be addressed by the sponsor if they wish to claim administration of buprenorphine is associated with analgesia properties separate from the sedation properties.

Additional reservations in accepting any of these five pivotal studies are that in the statistical analyses of the data no adjustments were made for the influence of pre-study analgesics and anesthetics; no adjustments in the analyses of vital signs were made for baseline values; and some data gathered after remedication were included in the analyses, contrary to the protocol. It should be noted that not all of the above deficiencies apply to all studies. Where no significant differences ($p > 0.05$) were found, the sensitivity of the statistical procedures is marginally acceptable (power=0.74 to 0.80).

In the case where there were no significant differences in the analyses of efficacy and safety variables, one must also be able to estimate the probability of detecting clinically meaningful differences between treatments at given levels of significance. This probability is referred to as the power of the statistical procedure. The applicant did not provide any power analysis for such cases. I recommend this information is required when the safety and efficacy data is resubmitted to FDA.

The remaining three of the eight "pivotal studies" compare buprenorphine with other potent injectable analgesics. Depending on the study, the standard drugs were pethidine, pentazocine, or Omnopon. The three studies contain some evidence that buprenorphine is more efficacious and at the same time more sedative than pethidine. There is also some evidence that buprenorphine provides comparable levels of analgesia when compared with pentazocine and Omnopon. There appeared to be no significant difference in side effects among the test drugs.

In all three studies, no statement was made as to how patients were evaluated for pain when they were sleeping during the evaluation periods. Provisions for recording site and nature of pain were made in the protocols of two studies but none of these items was available either in the case reports or in the summary. Patients' sequential entry number did not agree with their chronological orders raising the question as to the ways patients were selected for the studies.

Statistical analysis in Dr. Robbie's crossover study was inappropriate. A standard analysis of the crossover design should have been provided but was not. In all three studies, no adjustment was made for baseline values in the analyses of the changes in vital signs. Buprenorphine appeared to give higher sedation levels than pethidine. Two patients in the buprenorphine groups in Dr. Hovell's first study died. The cause of death in one patient was attributed to liver bleeding, and the other died in a "non-drug related" episode. Other side effects appeared to be comparable among treatment groups.

In addition to the eight pivotal studies described above, the submission contains clinical data of relevance to the issue of safety and efficacy. These included studies in the following classes: (1) open label studies; (2) "other clinical studies"; (3) monitored post-marketing report from the United Kingdom and (4) a review of the clinical literature on buprenorphine. Nothing remarkable or unexpected was observed in my review of this part of the NDA submission. The review of the proposed labeling will be deferred at this time.

b(4)

(10) Recommendation: I recommend the NDA not be approved, and the clinical deficiencies that are relevant to place the application in an approvable status that are listed below be conveyed to the sponsor.

The eight "pivotal studies" were reviewed in two parts by the Division of Biometrics. The reviews by Hoi M. Leung, Ph.D. are dated February 12, 1980 and April 22, 1980 and contain sections "Conclusions that should be conveyed to the sponsor." These comments should be combined with my comments and forwarded to the sponsor along with the comments from the other reviewers.

Bioavailability Studies

- 1) Formal bioavailability studies as required for NDA approval have not been submitted.
- 2) Controlled clinical trials (double-blind comparisons with morphine) (N=5).

I. Principal Investigator:

a. Robert Ouellette, M.D.
St. Vincent Hospital
Worcester, Massachusetts

Harriet Kiltie, M.D. - Monitor
Lederle Laboratories

Title of Study:

Comparison of the Analgesic Activity of Buprenorphine with Morphine Given as a Single Intramuscular Injection to Post-Operative Patients Experiencing Moderate to Severe Pain

1. The sponsor ignored the influence of pre-study analgesics in the statistical analysis. Ten patients received pre-study analgesics as late as 2 to 3 hours prior to the study drugs (pages 38-44, Volume 1.8). I recommend the data be stratified or adjustments made in the analyses for the type of pre-study analgesics and elapsed time since the administration of drug.

2. Methods of assessments for pain intensity and pain relief were not clearly specified when patients were asleep. The buprenorphine groups appeared to have higher mean sedation levels than the 5 mg morphine group although this difference was not statistically significant. A comparison of the individual patient's pain relief scores with sedation levels revealed that most of the patients who obtained complete pain relief were patients who were asleep. The sponsor failed to wake up the patients to complete the pain rating forms. Being asleep or awake does not relate to pain or lack of pain and the sponsor should explain why the conclusions are void in regard to efficacy even with this design error.

3. Changes in vital signs due to morphine relate to baseline values and this is presumably true for buprenorphine. The sponsor did not adjust for baseline values in the analysis and the data should be reanalyzed.

4. The nature of side effects was comparable among treatment groups with slightly higher occurrences in the morphine groups. However, it should be noted that side effects might be masked or complicated by the pre-study medications including type and amount of anesthetic. Reanalysis is needed.

5. In this study there was no distinction made between pain at rest and pain on motion. This distinction was made in study number 5 discussed later in this review and the results of some of the analyses were different between pain at rest and pain on motion. The applicant should demonstrate the role this distinction plays in all of these studies.

II. Principal Investigator:

Robert Ouellette, M.D.
Department of Anesthesiology
St. Vincent's Hospital
Worcester, Massachusetts

Harriet Kiltie, M.D. - Monitor
Lederle Laboratories

Title of Study:

Comparison of Analgesic Activity of 0.2 mg and 0.4 mg of Buprenorphine
Against 5 and 10 mg of Morphine as Intramuscular Injection in Post-
Surgical Patients with Moderate to Severe Pain

(i) The sponsor ignored the influence of pre-study analgesics in the statistical analysis. I recommend the data be stratified or made adjustments in the analyses for the type of and elapsed time since the administration of pre-study analgesics.

(ii) Methods of assessments for pain intensity and pain relief were not adequate when patients were asleep. The sponsor failed to wake up the patient to complete the pain rating forms. Being asleep or awake does not relate to pain or lack of pain and the sponsor should explain why the conclusions are void in regard to efficacy even with this design error. One would have to conclude that the firm needs to address the question raised in statistical review p. 5 section iv.

(iii) Changes in vital signs due to morphine relate to baseline values and this is presumably true for buprenorphine. The sponsor did not adjust for baseline values in the analysis and the data should be reanalyzed.

(iv) Side effects might be masked or complicated by the pre-study medications including type and amount of anesthetic. Reanalysis is needed.

(v) In this study there was no distinction made between pain at rest and pain on motion. this distinction was made in study number 5 discussed later in this review and the results of some of the analyses were different between pain at rest and pain on motion. The applicant should demonstrate the role this distinction plays in all of these studies.

III. a. Principal Investigator:

Allen B. Dobkin, M.D.
Department of Anesthesiology
State University of New York
Upstate Medical Center
Syracuse, New York

Harriet Kiltie, M.D.
Monitor - Lederle Laboratories

Title of Study:

Comparison of the Analgesic Activity of Two Doses of Buprenorphine Against Two Doses of Morphine Each Given as a Single Intramuscular Injection to Patients Experiencing Post-Surgical Pain.

(i) The sponsor ignored the influence of pre-study analgesics in the statistical analysis. I recommend the data be stratified or made adjustments in the analyses for the type of and elapsed time since the administration of pre-study analgesics.

(ii) Methods of assessments for pain intensity and pain relief were not clearly specified when patients were asleep. The sponsor failed to wake up the patient to complete the pain rating forms. Being asleep or awake does not relate to pain or lack of pain and the sponsor should explain why the conclusions are void in regard to efficacy even with this design error. One would have to conclude that the firm needs to address the question raised in statistical review of page 5, section iv.

(iii) Changes in vital signs due to morphine relate to baseline values and this is presumably true for buprenorphine. The sponsor did not adjust for baseline values in the analysis and the data should be reanalyzed.

(iv) The nature of side effects was comparable among treatment groups with slightly higher occurrences in the morphine groups. However, it should be noted that side effects might be masked or complicated by the pre-study medications including type and amount of anesthetic. Reanalysis is needed.

(v) In this study there was no distinction made between pain at rest and pain on motion. This distinction was made in study number 5 discussed later in this review and the results of some of the analyses were different between pain at rest and pain on motion. The applicant should demonstrate the role this distinction plays in all of these studies.

IV. a. Principal Investigator:

J.W. Downing MB BCH FFARCS,
Professor of Anaesthetics,
University of Natal
Durban
South Africa

Monitor: R.C. Hoare, Clinical Research Director, Reckitt and Colman

Title of Study:

A Double-Blind Study of Buprenorphine and Morphine for the Treatment of Patients with Post-Operative Pain

(i) SPID was significantly higher for the buprenorphine group with or without the six additional patients in the open study. TOTPAR also favored the buprenorphine group ($p = 0.07$) in both instances. Maximum PID was compared using a Mann-Whitney U-test. The buprenorphine group was favored ($p = 0.02$) in the double-blind study. Inclusion of the six additional patients reduced the significance level to 0.12. Time to maximum PID indicated that maximum pain relief occurred at a significantly later time in the buprenorphine group than in the morphine group ($p = 0.0001$) whether the six patients were included or not.

(ii) The number of patients suffering from sedation (mostly mild) was comparable between treatment groups. Over the 4 hour evaluation period, pulse rate, systolic and diastolic blood pressure decreased significantly below baseline while vital capacity and peak flow rose significantly in both treatment groups. Nausea and vomiting were observed in only one patient.

The applicant concluded that "0.6 mg buprenorphine gave a higher level of analgesia, with a longer duration of activity than 15 mg morphine with no increase in unwanted effects." I feel this is not acceptable since it was based on the significant later time to maximum PID of buprenorphine than morphine and also on the assessment of the 8 hour open study of buprenorphine alone. Only direct comparison of time to remedication over an extended period of time could substantiate this claim.

The proportion of patients who suffered from sedation was small (6 patients in the buprenorphine group and 4 in the morphine group) and these 10 patients had only mild to moderate sedation. Thus, the effects of sedation in this study would not be expected to affect the analyses seriously as in the previous studies.

(iii) Comparisons of changes in vital signs should have been adjusted for baseline values but were not. I recommend the sponsor supply this information.

V. Principal Investigator

B.C. Hovell, M.B., Ch.B., F.F.A.R.C.S.
Consultant Anesthetist
Hull Royal Infirmary
Kingston-Upon-Hull
United Kingdom

Monitor: Dr. J.A. Buylla, Clinical Research Director, Reckitt and Colman

Title of Study:

Comparative Study of Buprenorphine and Morphine Given Intramuscularly to Patients Suffering Acute Post-Operative Pain

(i) Missing data is a major problem in this study, leading one to question the level of clinical control exercised by the investigator and the reliability of the remaining data. For example, 40% of the patients had no record of anesthetic and/or other drugs used during anesthesia. Five patients had missing pain scores at some observation periods. Estimated values were used in these cases. Nearly half of the patients had missing observations in their signs at some period of observation. Thus, analyses of changes in vital signs would not be reliable.

(ii) Buprenorphine (0.3 mg) appeared to have a higher sedative effect than did morphine (10 mg). As I have illustrated above in study number 1 pain relief and sedation could not fully be separated when comparing the treatment groups. Those comments would also be appropriate for this study.

(iii) Since side effects due to the test drugs might be confounded with those induced by anesthetic or other drugs used during anesthesia, and 40% of the patients had no such records, it is not possible to draw any conclusions regarding the comparability of side effects.

3) Controlled clinical trials (double-blind comparisons with other potent analgesics)

I. Principal Investigator:

D.S. Robbie, M.B., Ch.B., F.F.A.R.C.S.
Consultant Anaesthetist
The Royal Marsden Hospital
London
United Kingdom

Clinical Monitor: Dr. J.A. Buylla, Clinical Research Director, Reckitt and Colman

Title of Study:

Comparative Study of Buprenorphine and Pentazocine Given Intramuscularly to Patients with Cancer Pain

(i) The sponsor ignored the influence of pre-study analgesics. Tests need to be conducted to determine if the groups are comparable in regards to

this variable. I recommend the data be stratified or adjustments be made in the analyses for the type of and elapsed time since the administration of pre-study analgesics.

(ii) In the pivotal studies using non morphine standards the quantification of sedation is less exact than in the 5 previous studies using morphine as the control. In this study instead of collecting data at the same observation points as pain observations, the data is collected in terms of (a) onset of sedation, (b) duration of sedation, (c) degree of sedation. This is not nearly as precise as the method used in the 5 morphine control studies. At this point the study is completed and in so far as the design can not be changed, we recommend the sponsor defend the conclusions drawn from the data and how this set of conclusions compares to the studies using morphine as the control.

(iii) Methods of assessment for pain intensity and pain relief were not clearly specified when patients were asleep. A comparison of the individual patient's pain relief scores with sedation levels revealed that most of the patients who obtained complete pain relief were patients who were asleep. The sponsor failed to wake up the patient to complete the pain rating forms. Being asleep or awake does not relate to pain or lack of pain and the sponsor should explain why the conclusions are valid in regard to efficacy even with this design error. One would have to conclude that the firm needs to address the question raised in statistical review, p. 5, section iv.

(iv) Changes in vital signs due to morphine relate to baseline values and this is presumably true for buprenorphine. The sponsor did not adjust for baseline values in the analysis and the data should be reanalyzed.

(v) I recommend the statistics be recalculated considering the study a cross-over design (see statistical review.) The use of a two-way (patients and treatments) analysis of variance in this design is not appropriate. The applicant ought to provide a standard analysis for this design taking into account the treatment effect, period effect, treatment by period interaction, and residual effects uncontaminated by patient-to-patient (subjects within sequence) variability. A reference for the appropriate analysis is W. Federer Experimental Design, MacMillan, 1955.

(vi) Some patients participated in this analgesic trial within a few hours post-radiotherapy. The statistics need to be redone with this factor given consideration.

(vii) The side effect section of the data does not take into consideration that the natural course of events, i.e. progression of the disease causing the pain changes over time. Since this is a cross-over study, this issue is relevant to the side effect conclusions. An issue that needs to be addressed is the fact that 15 of the 20 patients completed the study within three days.

II. a. Principal Investigator:

B.C. Hovell, M.B., Ch.B., F.F.A.R.C.S.
Consultant Anaesthetist
Hull Royal Infirmary
Kingston-Upon-Hull
United Kingdom

Monitor: Dr. J. A. Buylla, Clinical Research Director, Reckitt and Colman

Title of Study:

Comparative Study of Buprenorphine, Pethidine and Pentazocine
Given Intramuscularly to Patients with Post-Operative Pain

(i) The sponsor ignored the influence of pre-study analgesics in the statistical analysis. Tests need to be conducted to determine if the groups are comparable in regards to this variable. I recommend the data be stratified or adjustments be made in the analyses for the type of and elapsed time since the administration of pre-study analgesics. Some patients (30/186) had no records of anesthetics used and some patients (66/186) had no records of other drugs used during anesthesia. The applicant has not examined the comparability among treatment groups with regard to the missing records and explained how this would affect their analysis.

(ii) In all three of these pivotal studies using non-morphine standards the quantification of sedation is less exact than the 5 previous studies using morphine as the control. In this case instead of collecting data at the same observation points as pain observations, the data is collected in terms of (a) onset of sedation, (b) duration of sedation, and (c) degree of sedation. This is not nearly as precise as the method used in the first 5 studies. At this point the study is completed and in so far as the design cannot be changed I recommend the sponsor defend the conclusions drawn from the data and how does this set of conclusions compare to the earlier 5 studies.

(iii) Methods of assessment for pain intensity and pain relief were not clearly specified when patients were asleep. A comparison of the individual patient's pain relief scores with sedation levels revealed that most of the patients who obtained complete pain relief were patients who were asleep. The sponsor failed to wake up the patient to complete the pain rating forms. Upon examination of the case reports, it appeared that some patients were roused for evaluation when they were asleep (based on the comments in some of the case reports that the patient was rousable). However, in some other cases, the nurse observer commented that the patient (sleeping during the observation period) was not a good historian (patients #108, 109) which implied that evaluations were based on the patients' recollection. Being asleep or awake does not relate to pain or lack of pain and the sponsor should explain why the conclusions are valid in regard to efficacy even with this design error. One

would have to conclude that the firm needs to address the question raised in statistical review p. 5 section iv. It is of interest to note that pethidine was associated with the lowest sedation ratings and was the least effective in producing analgesia. This leads one to again ask about the relationship of sedation to analgesia. It is important for the sponsor to separate sedation effects from analgesic effects of the test medications.

(iv) Changes in vital signs due to morphine relate to baseline values and this is presumably true for buprenorphine. The sponsor did not adjust for baseline values in the analysis and the data should be reanalyzed.

III. Principal Investigator:

B.C. Hovell, M.B., Ch.B., F.F.A.R.C.S.
Consultant Anaesthetist
Hull Royal Infirmary
Kingston-Upon-Hull
United Kingdom

Monitor: Dr. J.A. Buylla, Clinical Research Director, Reckitt and Colman

Title of Study:

Comparison of Buprenorphine and Omnopan as an Analgesic Agent for Post-Operative Pain

(i) The sponsor ignored the influence of pre-study analgesics in the statistical analysis. Tests need to be conducted to determine if the groups are comparable in regards to this variable.

I recommend the data be stratified or adjustments be made in the analyses for the type of and elapsed time since the administration of pre-study analgesics.

(ii) In all three of these pivotal studies using non-morphine standards, the quantification of sedation is less exact than the 5 previous studies using morphine as the control. In this case instead of collecting data at the same observation points as pain observations, the data is collected in terms of (a) onset of sedation, (b) duration of sedation, and (c) degree of sedation. This is not nearly as precise as the method used in the first five studies. At this point the study is completed and insofar as the design cannot be changed, I recommend the sponsor defend the conclusions drawn from the data and how does this set of conclusions compare to the earlier 5 studies.

Methods of assessments for pain intensity and pain relief were not clearly specified when patients were asleep. A comparison of the individual patient's pain relief scores with sedation levels revealed that most of the patients who

obtained complete pain relief were patients who were asleep. The sponsor failed to wake up the patient to complete the pain rating forms. Being asleep or awake does not relate to pain or lack of pain and the sponsor should explain why the conclusions are valid in regard to efficacy even with this design error. One would have to conclude that the firm needs to address the question raised in statistical review p. 5, section iv.

In practical terms the sedation levels were comparable in both groups so one can evaluate comparative analgesia.

(iii) Changes in vital signs due to morphine relate to baseline values and this is presumably true for buprenorphine. The sponsor did not adjust for baseline values in the analysis and the data should be reanalyzed.

(iv) The nature of side effects was comparable among treatment groups. It should be noted that side effects might be masked or complicated by the pre-study medications including type and amount of anesthetic. Reanalysis is needed.

(v) No distinction is made between pain at rest and with motion. As this distinction is made in two of the other seven studies, I recommend the sponsor explain the reason for this omission.

(vi) The reason for extending the range of cut-off points for weight and the inclusion of those patients whose weights were outside the range specified in the protocol are not clear.

NDA Orig
HFD-120
HFD-120/HAGross/4/22/80
FT:klt/5/19/80
DOC#1571A

Ed Gross
6-12-80

Howard A. Gross, M.D. 5/22/80

Appendix I

Tables

Table 6: Safety and Tolerance Studies

Number of Subjects	Route of Reference	Description		
Number of Receiving Subjects in Study	Administered Buprenorphine	Vol.	Page	
24	16	im	1.2	7
Henry W. Elliott, M.D., Ph.D. Salano Institute of Medical and Psychiatric Research Vacaville, California				
Ronald Okun, M.D. Dept. of Medical Pharmacology and Therapeutics Orange County Medical Center Orange, California				
John P. Morgan, M.D. Dept. of Pharmacology & Toxicology University of Rochester School of Medicine & Dentistry Rochester, New York	18	im	1.2	96
3. Eugene R. Jolly, M.D., Ph.D. President Biometric Testing, Inc. Englewood Cliffs, New Jersey	6	im	1.2	239

Figure 6: cont'd

In a multiple dose intramuscular study with nine male subjects, Day 1 and 6 were the single blind placebo phase. Days 2 through 5 were the double blind phase, in which 1 ml doses of buprenorphine 0.2 mg three times per day, 0.4 mg three times per day, or placebo three times per day were given. Observations before and 2 hours post-dose were made on respiration rate, pulse rate and blood pressure, pupil diameter, behavioral, effective autonomic, emergent symptoms, ECG, and local tissue tolerance.

Joseph R. Bianchine, M.D., Ph.D.
Dept. of Pharmacology
Ohio State University
Columbus, Ohio

Table 7

Number of Subjects in Study	Number of Receiving Subjects	Route of Reference in Study	Buprenorphine	Ch.B., FFARCS, D.A.	Ch.B., Dept. of Clinical Pharmacology Reckitt & Colman Kingston-upon-Hull, United Kingdom	im	1.4	1	1.4	34	im	1.4	67	im	1.4	6	6	im	1.4	5	im	1.4	131
5	5	im	1.4	J. M. Orwin, M.B., Ch.B., FFARCS, D.A. Dept. of Clinical Pharmacology Reckitt & Colman Kingston-upon-Hull, United Kingdom	J. M. Orwin, M.B., Ch.B., FFARCS, D.A. Dept. of Clinical Pharmacology Reckitt & Colman Kingston-upon-Hull, United Kingdom	im	1.4	1	1.4	34	im	1.4	67	im	1.4	6	6	im	1.4	5	im	1.4	131
5	5	im	1.4	In a single blind crossover study, five subjects received 0.3 mg buprenorphine intravenously followed in 30 minutes by either naloxone (doses varied for each patient) or saline (in equivalent volume to the naloxone). Observations included respiration parameters, pulse rate, blood pressure, and subjective effects.	In a single blind, crossover study, six subjects received buprenorphine 0.3 mg or morphine 12.5 mg intramuscularly in random order. Observations were made before and for 7 hours after medication. These included pulse rate, blood pressure, pupil size, respiration parameters, subjective, and unwanted effects were recorded.	In an open, single dose study, buprenorphine 1.2 mg dose was given intramuscularly. Observations included respiratory parameters (minute volume, tidal volume, end tidal PCO_2 and respiration rate) with subjects (5 normal males) breathing air. Blood pressure, pupil size, and pulse rate were also recorded.																	
5	5	im	1.4	J. M. Orwin, M.B., Ch.B., FFARCS, D.A. Dept. of Clinical Pharmacology Reckitt & Colman Kingston-upon-Hull, United Kingdom	J. M. Orwin, M.B., Ch.B., FFARCS, D.A. Dept. of Clinical Pharmacology Reckitt & Colman Kingston-upon-Hull, United Kingdom	im	1.4	1	1.4	34	im	1.4	67	im	1.4	6	6	im	1.4	5	im	1.4	131

Table 7: con't

J. M. Orton, M.B., Ch.B.,
FFARS, D.A.
Dept. of Clinical Pharmacology
Reckitt & Colman
Kingston-upon-Hull,
United Kingdom

6 6 1.4 iv

Part I: Double blind, crossover study with 0.3 mg buprenorphine given intravenously on 3 different occasions. One hour later all subjects received doxapram 0.5 mg/kg, 1.0 mg/kg or placebo (normal saline) intravenously in a randomized crossover double-blind manner. All subjects received all the reversal treatments with at least 5 days between each experiment. Respiration parameters, pulse rate, blood pressure, pupil size and emergent symptoms were recorded prior to doxapram dosing and at 1/4, 1/2, 1, 2, 3, 4, and 5 hours post-doxapram.

Part II: In Part II of this double-blind, crossover, multiple dose (iv) study, 5 of the 6 patients in Part I received 0.3 mg buprenorphine intravenously and then doxapram at one hour after the dose. Doxapram was given at 1.5 mg/min for 30 minutes and at 2.0 mg/min for 1.5 hours more. Clinical and respiratory parameter were determined prior to doxapram dosing and at 1/4, 1/2, 1, 2, 3, 4, and 5 hours post-doxapram.

Pharmacokinetic Studies

Number of Subjects in Study	Number of Receiving Subjects in Study	Route of Reference Administered Buprenorphine	Vol.	Page
1. B. C. Hovell, M.B., Ch.B., FFARCS Consultant Anesthetist Hull Royal Infirmary Kingston-upon-Hull, United Kingdom	2	oral	1.13	231 im
2. B. C. Hovell, M.B., Ch.B., FFARCS Consultant Anesthetist Hull Royal Infirmary Kingston-upon-Hull, United Kingdom	2	oral	1.13	236
3. B. C. Hovell, M.B., Ch.B., FFARCS Consultant Anesthetist Hull Royal Infirmary Kingston-upon-Hull, United Kingdom	5	iv im sublingual	1.13	278

Number of Subjects in Study	Route of Reference Administered Buprenorphine	Vol.	Page	Description
1. B. C. Hovell, M.B., Ch.B., FFARCS Consultant Anesthetist Hull Royal Infirmary Kingston-upon-Hull, United Kingdom	oral	1.13	231 im	This is an open label, single-dose (oral and oral) tritiated buprenorphine study. To determine plasma levels 2 μ g/ kg buprenorphine (^3H) was given intramuscularly to 1 volunteer and 1 capsule, 15 μ g buprenorphine was given orally to another. Blood (10 ml) was drawn at various post-dose for 24 hours for analysis. Urine and feces samples were collected for 14 days after dosing.
2. B. C. Hovell, M.B., Ch.B., FFARCS Consultant Anesthetist Hull Royal Infirmary Kingston-upon-Hull, United Kingdom	oral	1.13	236	This is an open label, single-dose (oral) tritiated buprenorphine study. In this excretion study ^3H labeled buprenorphine 20 $\mu\text{g}/\text{kg}$ was given orally to two volunteers with blood (10 ml) drawn at 1/4, 1/2, 3/4, 1, 2, 3, 4, 6, and 24 hours and urine and feces collected daily for 7 days and again at 2 weeks after dosing. Samples were analyzed for radioactivity.
3. B. C. Hovell, M.B., Ch.B., FFARCS Consultant Anesthetist Hull Royal Infirmary Kingston-upon-Hull, United Kingdom	iv im sublingual	1.13	278	This is an open label single dose (iv, im, or sublingual) buprenorphine study to investigate the relationship between pain relief and plasma concentration of buprenorphine using radioimmunoassay techniques. Doses of buprenorphine given to 5 volunteers were 0.3 mg iv, 0.3 mg im, and 0.3 mg by the sublingual routes. Pain relief was assessed before dosing and at observation times. Plasma concentrations were determined at 15, 30, 60, 120, or 240 minutes post-dose.

Physical Dependence Studies

Number of Subjects Receiving Buprenorphine in Study	Route of Reference	Administrator	Description
9	subcutaneous	1.13 295	This is a single dose, double blind, CRC 7603 study. Subcutaneous buprenorphine 0.2, 0.4, and 0.8 mg, morphine 15 and 30 mg and placebo were compared for effects, with observations made 0.5, 1, 2, 3, 4, 5, 12, and 24 hours dosing. The drug effects were measured on size change, subjects' and observers' size, dose opiate questionnaires and a subject drug effects questionnaire.
9	subcutaneous	1.13 295	This is a single dose study. Subcutaneous buprenorphine 0.6 and 1.2 mg and subcutaneous morphine 20 and 40 mg were assessed as study 1.
9	subcutaneous	1.13 295	This is a single dose, double blind, CRC 7603 study. Buprenorphine, 1.0 mg; morphine, 30 mg; methadone, 30 mg; and placebo were given subcutaneously at weekly intervals with observations made at 0.5, 1, 2, 3, 4, 5, 6, 12, 24, 30, 36, 48, 54, 60, and 72 hours after administration. The assessments were listed in study 1.

2. Donald R. Jasinski, M.D.
Director
NIDA Addiction Research Center
Lexington, Kentucky

Donald R. Jasinski, M.D.
Director
NIDA Addiction Research Center
Lexington, Kentucky

Table 9: con't

4. Ronald R. Jasinski, M.D. *

Director

N.Y.A. Addiction Research Center

Lexington, Kentucky

5 5 1.13 295

subcu-
taneous

A direct addiction study was conducted with subcutaneous buprenorphine. Once daily the volunteers received a single subcutaneous injection. For 2 weeks the injection was saline, then buprenorphine 0.5 mg was substituted for the saline. The dose was progressively doubled until the 15th day when buprenorphine 8.0 mg was administered. This dose was continued to the end of the study. Naloxone (as subcutaneously) was given to precipitate dependence and withdrawal symptoms. Morphine was administered during this period to test the degree of antagonist blockade. At the end of the buprenorphine period subjects were switched to saline. The subjects were observed for withdrawal symptoms through 17 days.

DOSE RANGE STUDIES

Number of Subjects	Number of Receiving Subjects in Study	Route of Reference Adminis- tration	Vol.	Page	Description
1. Robert Guerlette, M.D. St. Vincent Hospital Worcester, Massachusetts	41	41	im	1.5	This is an open label, single dose, intramuscular injection study. Four groups of approximately 10 patients each experiencing moderate to severe post-operative pain within 48 hours from the time of major surgery received intramuscular doses buprenorphine of 0.1, 0.2, 0.4 mg or 0.6 mg. Observations were made before and 0.5, 1, 2, 3, 4, 5, 6 hours post-dose for pain intensity, pain relief (post-dose only), sedation, vital (blood pressure, pulse and respiration rate) and side effects.
2. Allen B. Doblin, M.D. Dept. of Anesthesiology State University of New York Upstate Medical Center Syracuse, New York	65	65	im	1.5	This is an open label, single dose, intramuscular injection study. Patients experiencing post-surgical pain received single doses of buprenorphine from 0.1 to 0.6 mg. Observations of pain intensity, pain relief, sedation, vital signs (blood pressure, pulse and respiratory rate) and side effects were made before and at 0.5, 1, 2, 3, 4, 5, and 6 hours post-medication.
3. Abraham Sunshine, M.D. Arthur C. Logan Memorial Hosp. New York, New York	24	24	im	1.6	This is an open label, single dose, intramuscular injection study. Patients suffering from severe pain from surgery, fracture or musculoskeletal disorders received one or more doses of buprenorphine intramuscularly of 0.1, 0.2, 0.4, or 0.6 mg and were evaluated before and after dose for pain intensity.

Table 10: con't

4. Thomas G. Kantor, M.D. New York University School of Medicine New York, New York	16	16	1.6	127	im			
5. D. S. Robbie, M.B., Ch.B., FFRCS Consultant Anesthetist The Royal Marsden Hospital London, United Kingdom	20	20	1.6	188	im			
6. Raymond W. Heede, M.D. Sloan-Kettering Institute for Cancer Research New York, New York	162	162	1.7	1	im	1.44	1.7	1

This is an open label, single dose, intramuscular injection study. Patients with moderate to severe post-surgical pain received intramuscular buprenorphine in doses of 0.2 or 0.4 mg. Pain intensity, pain relief (post-dose only) and vital signs were evaluated before and at 0.5, 1, 2, 3, 4, and 5 hours post-dose. Side effects were evaluated at each time interval.

This is an open, single-dose, intramuscular injection study. Patients suffering moderate to severe cancer pain received buprenorphine in doses ranging from 0.5 to 16 μ g/kg. A number of patients received additional doses because at least 24 hours between administrations. Each patient was evaluated before and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, and 7 hours post-treatment for the following parameters: pain intensity, pain relief (post-dose only), pulse rate, blood pressure, respiratory rate, and side effects.

This is a double-blind twin crossover study. Patients with pain due to cancer, post-operative, traumatic, or intolerant to narcotics were given morphine or morphine intramuscularly in a double-blind fashion. Each patient received a lower dose of one agent and a higher dose of the other, in a series of 7 twin C-557 over comparisons. Doses of morphine were 0.1, 0.2, 0.4, 0.8, and 1.6 mg. Pain intensity and pain relief (post-dose only) were evaluated before and at hourly intervals (for 6 hours).

**Summarization of the Experimental Design
for Double-Blind Controlled Comparisons of Buprenorphine to Morphine**

Number of Subjects in Study	Number of Receiving Subjects Buprenorphine in Study	Route of Reference Administration	Vol.	Page
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1. Robert Quellette, M.D.
St. Vincent Hospital
Worcester, Massachusetts
- 69 38 im 1.8 1
- In a double blind, parallel group study, two groups of patients with moderate to severe post-operative pain were given 0.15 mg buprenorphine or 5 or 10 mg morphine as a single intramuscular injection for relief of pain. Pain intensity, pain relief (post-dose only), sedation, vital signs (blood pressure, pulse and respiratory rate) and side effects were assessed before medication and at 1/3, 1/2, 1, 2, 3, 4, 5, and 6 hours post-therapy.
2. Robert Quellette, M.D.
St. Vincent Hospital
Worcester, Massachusetts
- 133 77 im 1.8 184
- In a double blind, parallel group study, two groups of patients with moderate to severe post-operative pain received 0.2 or 0.4 mg buprenorphine or 10 mg morphine sulfate, as a single intramuscular injection for relief of pain. Pain intensity, pain relief (post-dose only), sedation, vital signs (blood pressure, pulse and respiratory rate) and side effects were assessed before medication and at 1/2, 1, 2, 3, 4, 5, and 6 hours post-dose.
3. Allen B. Dotkin, M.D.
Dept. of Anesthesiology
State University of New York
Upstate Medical Center
Syracuse, New York
- 160 80 im 1.9 1
- In a double blind, parallel group study, two groups of patients with moderate to severe post-operative pain received 0.2 or 0.4 mg buprenorphine or 5 or 10 mg morphine sulfate, as a single intramuscular injection for relief of pain. Pain intensity, pain relief (post-dose only), sedation, vital signs (blood pressure, pulse and respiratory rate) and side effects were assessed before medication and at 1/2, 1, 2, 3, 4, 5, and 6 hours post-dose.

Table 12: cont'd

J. W. Downing, M.B., Ch.B., FRANZ Professor of Anaesthetics University of Natal Durban, South Africa	66	37	im	1.9	210	In a double blind, parallel group study, two groups of patients (58) with moderate to severe pain after elective caesarean section received 0.6 mg buprenorphine or 15 mg morphine intramuscularly. Pain intensity, pain relief (post-dose only), pulse rate, blood pressure, vital capacity and peak flow and side effects were assessed before and at 1/4, 1, 2, 3, and 4 hours post-dose. Nine of these patients were evaluated at 5, 6, 7, and 8 hours post-therapy in an open fashion. Two patients were given 0.3 mg in double-blind fashion. An additional 6 patients were given 0.6 mg buprenorphine in open label fashion.
B. C. Hovell, M.B., Ch.B. FFARCS Consultant Anaesthetist Royal Infirmary Kingston upon Hull, United Kingdom	51	26	im	1.10	1.	In a double blind parallel group study, two groups of patients with moderate to severe pain after general surgical procedures received 0.3 mg buprenorphine or 10 mg morphine. Pain intensity (more than 5 on a 10 point scale), pain relief (post-dose only), pulse rate, blood pressure, respiratory rate, degree of sedation, and side effects were assessed before medication and at 0.25, 0.5, 1, 2, 3, 4, 5, or 6 hours post-therapy.

Summary of Efficacy Data for Buprenorphine and Morphine
in Controlled Double-Blind Comparisons

Investigator/Dose	Onset of Analgesia	Time to Peak	SPID*	TOTPAR*	Duration of Action
Dr. R. Ouellette					
0.15 mg Bupr.	10 min	0.5-1.0 hr	10.5	14.0	4-6 hr
0.3 mg Bupr.	10 min	0.5-1.0 hr	11.9	15.3	4-6 hr
5 mg Morphine	10 min	0.5-1.0 hr	11.9	14.6	4-6 hr
10 mg Morphine	10 min	0.5-1.0 hr	8.0	10.6	4-6 hr
Dr. R. Ouellette					
0.2 mg Bupr.	within 0.5 hr	0.5-2 hr	11.0	13.7	6 hr
0.4 mg Bupr.	within 0.5 hr	0.5-2 hr	12.5	13.6	>6 hr
5 mg Morphine	within 0.5 hr	0.5-2 hr	8.2	10.6	6 hr
10 mg Morphine	within 0.5 hr	0.5-2 hr	9.5	12.8	>6 hr
Dr. A.B. Dobkin					
0.2 mg Bupr.	0.5-1.0 hr	within 1 hr	6.0	8.3	4 hr
0.4 mg Bupr.	0.5-1.0 hr	within 1 hr	6.6	9.1	4.5 hr
5 mg Morphine	0.5-1.0 hr	within 1 hr	3.2	4.6	3 hr
10 mg Morphine	0.5-1.0 hr	within 1 hr	5.0	6.6	3.5 hr
Dr. J.W. Downing					
0.6 mg Bupr.	0.25-1.0 hr	4-5 hr	5.9	8.9	5-6 hr
15 mg Morphine	0.25-1.0 hr	1-3 hr	4.3	7.5	4 hr
Dr. B.C. Hovell					
0.3 mg Bupr.	by 0.25 hr	2-4 hr	10.5	17.7	>6 hr
10 mg Morphine	by 0.25 hr	2-4 hr	7.9	13.8	>6 hr

Double-Blind Comparison of Buprenorphine with Other Potent Analgesics
 (Pentazocine, Pethidine and Omnopon)

Number of Subjects	Number of Receiving Subjects in Study	Route of Reference	Adminis-tration	Vol.	Page	Description
22	22	im	1.10	135		Patients with cancer pain received single intramuscular doses of buprenorphine 2 and 4 μ g/kg and pentazocine 0.6 mg/kg body weight in a randomized double-blind Latin Square design. Parameters assessed before and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, and 7 hours post-dose included pain intensity (grave and rest), pain relief (post-dose only), pulse rate, blood pressure, respiratory rate and side effects.

22	im	1.10	135			
22	im	1.11	1			
186	110	im	1.11	1		

Four groups of patients with moderate to severe post-operative pain received either buprenorphine 2 or 4 μ g/kg, pethidine 1.0 mg/kg or pentazocine 0.6 mg/kg body weights as a single intramuscular injection to relieve pain. Patients were assigned to treatment groups in a randomized double-blind fashion. Each patient had P.I.N. intensity (move), pain intensity (rest), pain relief (post-dose only), pulse rate, blood pressure, respiration rate, and side effects assessed before and at 1/4, 1/2, 1, 2, 3, and 4 hours post-dose. Time to remedication was recorded and observations continued after re-dosing. Subsequently 34 patients received 8 μ g/kg buprenorphine and were studied in a similar manner.

3. B. C. Rovell, M.B., Ch.B.,
FRAN
Consultant Anaesthetist
Hall Royal Infirmary
Kingston upon Hull,
United Kingdom

55 27 im 1.11 256

Two groups of post-surgical patients with moderate to severe pain received buprenorphine 0.3 mg or Ondansetron 20 mg intramuscularly twice in a randomized double dose double-blind study. Pain intensity, pulse rate, blood pressure, respiration rate, and side effects were assessed before drug and at 1, 3, 4, 5, and 6 hours after the first dose and at 1, 3, and 5 hours after the second dose.

Summary of Efficacy Data for Buprenorphine and Various Potent Analgesic Agents in Controlled Double-Blind Trials

<u>Investigator</u>	<u>Onset of Analgesia</u>	<u>Time to Peak</u>	<u>SPID*</u>	<u>TOTPAM*</u>	<u>Duration**</u>
Dr. Robbie					
2 μ g/kg Bupr.	0.5 hr	2-3 hr	6.5	13.5	7.0 hr
4 μ g/kg Bupr.	0.5 hr	2-3 hr	6.0	13.1	6.5 hr
0.6 mg/kg Pentazocine	0.5 hr	1 hr	6.3	12.5	6.2 hr
Dr. B. Novell					
2 μ g/kg Bupr.	0.25-.30 hr	1-2 hr	5.9	10.4	11.7 hr
4 μ g/kg Bupr.	0.25-.30 hr	1-2 hr	7.1	12.2	12.2 hr
0.5 μ g/kg Pentazocine	0.25-.30 hr	1-2 hr	5.7	10.5	12.5 hr
1 mg/kg Pethidine	0.25-.30 hr	1-2 hr	4.9	9.6	11.7 hr
Dr. B. Novell					
0.3 mg Bupr.	0-1 hr	2-4 hr	7.4	Not Recorded	6 hr
20 mg Unanon	0-1 hr	2-4 hr	6.8	Recorded	6 hr

* Values connected by brackets are significantly different using Hartley's Test on means adjusted for baseline pain ($p < 0.05$).

**Duration is expressed as the median time to administration of additional analgesic.

Table 16

Open Studies -
Intravenous or Intramuscular Administration of Buprenorphine

Number of Subjects		Route of Reference		Description	
Number of Receiving Subjects Buprenorphine in Study	Adminis-tration	Vol.	Page		
OPEN, INTRAVENOUS ADMINISTRATION STUDIES					
1. J. L. Ranty, M.B., B.S., FRCRCS Consultant Anesthetist Chelmsford Group Hospitals Essex, United Kingdom	iv	28	1	1.12	1
2. D. Mehta, M.B., FRCRCS, DA Consultant Anesthetist Norfolk and Norwich Hospital Norwich, United Kingdom	iv	10	84	1.12	84
<p>Post-surgical patients with moderate to severe pain were given either 0.3 mg or 0.6 mg buprenorphine intravenously on an open, single dose basis. Pain intensity, pulse rate, blood pressure, respiration rate, and side effects were assessed at each observation period - pre-therapy, and 1/4, 1/2, 1, 2, 3, 4, 5, 6, and 7 hours post-therapy. Remedication time was recorded.</p> <p>Two groups of 10 post-operative patients with moderate to severe pain were given buprenorphine, 0.3 mg, or Omnopon, 15 mg, intravenously on an open, non-randomized basis. Pain intensity, pulse rate, blood pressure, respiratory rate, and side effects were assessed at each observation period - pre-therapy, and at 1/4, 1/2, 1, 2, 3, 4, 5, and 6 hours post-therapy. Remedication time was recorded.</p>					

Table 16: cont'

I. C. Gaffes, M.D., FFARCS, DA Reader in Anaesthesia University of Liverpool Liverpool, United Kingdom	30	30	iv	1.12	170							
G. W. Stephen, M.D., Ch.B., FFARCS Consultant Anaesthetist Queen Charlotte's Maternity Hospital London, United Kingdom	31	31	iv	1.12	243							
P. Edmund, M.D., M.B., Ch.B., FFARCS Consultant Urological Surgeon Royal Infirmary Edinburgh, United Kingdom	7	7	im/iv	1.12	330							

Female patients experiencing pain after gynaecological surgery were given buprenorphine 5 µg/kg doses intravenous on an open basis. Pain intensity, pulse rate, blood pressure, respiration rate, and side effects were assessed at each observation time - pre-therapy and at 1/4, 1/2, 1, 2, 3, 4, 5, and 6 hours post-therapy. Remedication times were recorded.

Patients experiencing moderate to severe pain after Caesarean section or abdominal hysterectomy were given either 0.3 mg or 0.6 mg buprenorphine intravenous in an open fashion. Patients were assessed prior to and at 1/4, 1/2, and 1 hour intervals up to 6 hours after drug administration for pain intensity, pulse rate, blood pressure, respiratory rate, and side effects. Remedication times were recorded.

Patients with proven ureteral obstruction and ureteral colic (milderate to severe pain) were given 0.6 mg buprenorphine intravenous (im) or intramuscular (1) in an open fashion. Pain intensity, pulse, rate, blood pressure, and side effects were assessed at each observation time - pre-therapy or at 1/4, 1/2, 1, 2, and 4 hours post-therapy.

Table 16: cont

R. Potter, M.B., B.S., MRCS, FRCP, FRCRCS Consultant Anesthetist King's College Hospital London, United Kingdom	14	14	1.13	iv	1.13	4	4	1.13	67	im	1.13	99
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Post-surgical patients were given buprenorphine 0.3 or 0.6 mg in an open single dose fast oral. Pain intensity, pulse rate, blood pressure, respiratory rate, and side effects were assessed pre-therapy and at 1/4, 1/2, 1, 2, 3, 4, 5, and 6 hours post-therapy.

Patients scheduled for major abdominal surgery were given intravenous buprenorphine 0.2 mg/70 kg as an induction dose prior to anesthesia followed with supplemental doses of 0.3 mg as necessary. (From 2 to 13 supplemental doses were given). Blood pressure, pulse rate, respiratory rate, and minute volume were recorded before pre-medication, before anesthesia, during, and at end of anesthesia at 1/2, 1, 2, 3, 4, 2 hours post-anesthetic (2.5 hours post-operative extubation). Subjective evaluation of buprenorphine sedation was also obtained.

OPEN, INTRAMUSCULAR ADMINISTRATION STUDIES

I. H. Delooy, M.D., Ph.D.
Professor of Anesthesiology
Academisch Ziekenhuis
Leuven, Belgium

In an open study patients with moderate to severe acute pain of various etiologies were given 0.2 mg buprenorphine intramuscularly as a single dose. Pain intensity, heart rate, blood pressure, respiration rate, and side effects were assessed at each observation time - pre-therapy and at 1/4, 1/2, 3/4, 1, 1.5, 2, 3, and 6 hours post-therapy. Time to relief was assessed after medication. Time to remanifestation was recorded.

Table 16: con't

In an open study patients with moderate to severe pain after general gynaecological or orthopaedic surgery were given 0.3 mg buprenorphine intramuscularly at 6-hour intervals or sooner if required for up to 4 doses. Pain intensity, pulse rate, blood pressure, respiratory rate, and side effects were assessed before medication and at 3 hours after i/o. If pain relief was assessed post-therapy. Generalization times were recorded.

2. E.G. Rees-Jones, M.B., Ch.B., 23

im 1.13 163

DA

Consultant Anaesthetist

Park Hospital

Manchester, United Kingdom

Appendix II d

TOTAL NUMBER OF REPORTS OF EACH LISTED ADVERSE EXPERIENCE

STUDY TYPE: SPECIAL

OPEN

BODY SYSTEM	ADVERSE EXPERIENCE	BUPRENNORPHINE			OMNIPON			TOTAL
		WILD	MILD	SEV	TOTAL	MILD	MOD	
DIGESTIVE	NAUSEA	50%	50%	0%	2	0%	0%	0
	VERTIGO	100%	0%	0%	2	0%	0%	0
	DRIZZINESS	100%	0%	0%	1	0%	0%	0
NERV/CNS/H	SOMNOLENCE	55%	44%	0%	9	0%	0%	0

NUMBER OF SUBJECTS REPORTING EACH LISTED ADVERSE EXPERIENCE

Appendix III

PHASE I

STUDY TYPE: CLOSLD

BODY SYSTEM	ADVERSE EXPERIENCE	BUPRENORPHINE						PLACEBO						PENTAZOCINE					
		MILD	MOD	SEV	TOTAL	MILD	MOD	SEV	TOTAL	MILD	MOD	SEV	TOTAL	MILD	MOD	SEV	TOTAL		
BODY/ABD	PAIN ABD	752	25%	0%	4	100%	0%	0%	1	0%	0%	0%	0	0%	0%	0%	0		
	ASTHENIA	29%	50%	21%	14	50%	50%	0%	4	0%	0%	0%	0	0%	0%	0%	0		
	CHILLS	66%	13%	0%	15	0%	0%	0%	0	0%	100%	0%	1	0%	0%	0%	1		
C	FEVER	50%	0%	50%	2	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	REACT UNSPEC	62%	5%	33%	21	67%	0%	33%	3	0%	0%	0%	0	0%	0%	0%	1		
	HEADACHE	74%	10%	7%	27	33%	33%	33%	3	0%	100%	0%	1	0%	0%	0%	1		
C	REACT UNSPEC	0%	0%	100%	1	0%	0%	0%	0	0%	100%	0%	1	0%	0%	0%	1		
	RADICULAR	100%	0%	0%	1	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	RADYCARDIA	100%	0%	0%	1	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	TACHYCARDIA	100%	0%	0%	1	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	HYPERTENS	0%	0%	0%	0	0%	0%	0%	0	0%	100%	0%	0	0%	0%	0%	0		
	HYPOTENS	100%	0%	0%	1	100%	0%	0%	1	0%	0%	0%	0	0%	0%	0%	0		
	PALLOR	52%	39%	9%	21	0%	0%	0%	0	0%	100%	0%	1	0%	0%	0%	1		
	VASODILAT	48%	33%	19%	21	60%	49%	0%	5	50%	50%	0%	5	50%	50%	0%	2		
	DRY MOUTH	37%	43%	19%	37	37%	25%	37%	3	0%	100%	0%	4	0%	0%	0%	4		
	CONSTIP	20%	89%	0%	5	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	DIARRHEA	0%	100%	0%	1	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	1		
	ANOREXIA	17%	33%	50%	6	0%	100%	0%	2	0%	0%	0%	0	0%	0%	0%	0		
	APPETITE DEC	0%	100%	0%	1	0%	100%	0%	1	0%	0%	0%	0	0%	0%	0%	0		
	DYSPEPSIA	0%	100%	0%	1	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	NAUSEA	48%	35%	17%	52	40%	60%	0%	5	75%	25%	0%	4	0%	0%	0%	4		
	NAUSEA VOMIT	100%	0%	0%	1	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	VOMIT	32%	50%	17%	46	25%	25%	50%	4	0%	100%	0%	1	0%	0%	0%	1		
	INJECT SITE REACT	75%	12%	12%	16	50%	25%	25%	4	0%	0%	0%	0	0%	0%	0%	0		
	ARTHRITIS	0%	0%	100%	1	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	SPASM GENERAL	100%	0%	0%	1	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	URIN ABNORM	100%	0%	0%	1	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	URIN RETENT	25%	75%	0%	12	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	ANXIETY	66%	9%	11%	6	0%	0%	0%	0	0%	100%	0%	1	0%	0%	0%	0		
	GENIT	75%	25%	0%	12	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	DEPRESSENAL	91%	0%	0%	12	9%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	DEPRESSILIN	71%	28%	9%	7	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	DIZZINESS	57%	39%	4%	56	25%	50%	25%	4	40%	60%	0%	5	0%	0%	0%	5		
	DREAM ABNORM	33%	33%	13%	3	100%	0%	0%	1	0%	0%	0%	0	0%	0%	0%	0		
	FACI LCN LABIL	100%	0%	0%	1	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	EUPHORIA	55%	35%	10%	20	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	1		
	HALLUCIN	67%	33%	0%	3	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	NAURO SNESS	67%	12%	0%	8	0%	0%	0%	0	0%	100%	0%	0	0%	0%	0%	0		
	SLUMMOLENCE	24%	52%	24%	4	0%	0%	0%	0	0%	100%	0%	6	0%	100%	0%	6		
	SPECIFIC DIS	75%	25%	0%	1	100%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	2		
	STUPOR	100%	0%	0%	1	100%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	THUNKING ARRHY	66%	33%	14%	3	0%	0%	0%	0	0%	100%	0%	1	0%	100%	0%	1		
	TR-FAUR	100%	0%	0%	1	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	VERPIIGO	100%	0%	0%	1	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	HYPERSENSITIA	100%	0%	0%	1	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	PARESISMSIA	66%	33%	0%	1	0%	100%	0%	1	0%	100%	0%	2	0%	100%	0%	2		
	UICCUP	69%	20%	0%	5	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		
	PSIPIAL DIS	100%	0%	0%	1	0%	0%	0%	0	0%	0%	0%	0	0%	0%	0%	0		

NUMBER OF SUBJECTS REPORTING EACH LISTED ADVERSE EXPERIENCE

Appendix III a

STUDY TYPE: CLOSED

PHASE I

ADVERSE EXPERIENCE	ACTV SYSTEM	BUPRENORPHINE			PLACEBO			PENIHAZOCINE		
		MILD	MID	SEV	MILD	MID	SEV	MILD	MID	SEV
RES/ANSL	RHINITIS	33%	33%	3	0%	0%	0%	0%	0%	0
SKIN/GEN	PRURITUS	31%	69%	0%	16	31%	66%	0%	3	0%
SKIN/SORL	SWEAT	59%	26%	15%	27	50%	25%	4	25%	4
SS/EPARHER	DEA/ TRANS	100%	0%	0%	1	0%	0%	0%	0%	0
SS/EPERCOM	CORJUNCTIVITIS	50%	50%	0%	2	0%	0%	0	0%	0
SS/VERGLN	EYE DIS	0%	100%	0%	1	0%	0%	0%	0%	0
SS/EYEVIS	AMBLYOPIA	66%	33%	0%	12	0%	0%	0%	0%	1
	PHOTOPICHLA	100%	0%	0%	2	0%	0%	0%	0%	0
	VISUAL ANORM	60%	40%	0%	5	0%	100%	0%	1	0%
SS/SML	PAROSOMIA	100%	0%	0%	3	0%	0%	0%	0%	0
SS/TSI	TASIE PERVERS	100%	0%	0%	1	0%	0%	0%	0%	0
UG/UT/UR/F	INCUNAT IN URIN	100%	0%	0%	1	0%	0%	0%	0%	0
UG/UT/UR/N	URIN ANORM	100%	0%	0%	1	0%	0%	0%	0%	0

NUMBER OF PATIENTS REPORTING EACH LISTED ADVERSE EXPERIENCE
 PHASES II & III
 STUDY TYPE: CLOSED

Appendix III b

BODY SYSTEM	ADVERSE EXPERIENCE	REPRENORPHINE			MORPHINE			PENTAZOCINE			TOTAL
		WILD MOD	SEV	TOTAL	MILD	MOD	SEV	TOTAL	MILD	MOD	
BODY/GEN	ASTHENIA	0%	0%	100%	2	66%	0%	33%	3	0%	0%
	CHILLS	100%	0%	1	0%	100%	0%	100%	2	100%	0%
	FEVER	0%	0%	0	0%	0%	0%	0%	1	0%	1
	REACT UNSPEC	33%	0%	66%	3	66%	0%	33%	3	0%	0%
BODY/HEAD	HEADACHE	25%	75%	100%	4	100%	0%	0%	1	100%	0%
BODY/MULT	WITHDRAW SYND	50%	50%	0%	2	0%	0%	0%	0	0%	0
CV/CARD/ARR	BRADYCARDIA	100%	0%	0%	2	0%	100%	0%	1	100%	0%
CV/VASC/RP	HYPERTENS HYPOTENS	25%	75%	0%	4	100%	0%	0%	1	100%	0%
CV/VASC/CAP	PALE	0%	100%	0%	1	0%	0%	0%	0	100%	0%
CV/VASC/GEN	SYNCOPE	0%	0%	0%	0	0%	0%	100%	1	0%	0%
DIG/BIOC	VASODILAT	0%	100%	0%	2	0%	0%	0%	0	100%	0%
DIG/EC	DRY MOUTH	0%	0%	100%	3	0%	50%	50%	2	100%	0%
DIG/GEN	DIARRHEA	100%	0%	0%	1	0%	0%	0%	0	0%	0
DIG/GEN	DYSPEPSIA	100%	0%	0%	1	0%	0%	0%	0	0%	0
	NAUSEA	61%	34%	52	44	63%	27%	10%	30	65%	14%
	NAUSEA VOMIT	100%	0%	0%	2	100%	0%	0%	2	100%	0%
	VOMIT	76%	10%	62	17	50%	33%	16%	6	100%	0%
EYE	REACT UNSPEC	100%	0%	0%	1	0%	0%	0%	0	0%	0
HL/RAC/IGR	CYANOSIS	100%	0%	0%	2	0%	0%	0%	0	0%	0
I-JCN	INJECT SITE REACT	0%	0%	0%	0	60%	20%	20%	5	0%	0%
	PAIN INJECT SITE	33%	33%	33%	3	25%	50%	25%	4	0%	0%
MC/MIS	SPASM GENERL	100%	0%	0%	1	0%	0%	0%	0	0%	0
NER/CNS/D	ANXIETY	0%	0%	0%	0	0%	0%	0%	0	100%	0%
	ATAxia	0%	0%	0%	0	0%	0%	0%	0	100%	0%
	COMA	0%	0%	100%	1	0%	0%	0%	0	0%	0
	CONFUS	100%	0%	0%	7	100%	0%	0%	2	50%	0%
	DEPENSONAL	100%	0%	0%	1	100%	0%	0%	1	0%	0%
	DEPRESSION	100%	0%	0%	1	0%	0%	0%	0	100%	0%
	DIZZNESS	50%	25%	25	24	42%	25%	33%	12	25%	75%
	DIZZNESS	66%	0%	33%	3	0%	0%	0%	0	0%	0
	DREAM ABNORM	100%	0%	0%	3	100%	0%	0%	1	100%	0%
	EUPHORIA	100%	0%	0%	1	0%	0%	0%	0	100%	0%
	HALUCIN	0%	100%	0%	1	66%	33%	0%	3	100%	0%
	HYSTERICIA	0%	0%	0%	0	100%	0%	0%	0	100%	0%

NUMBER OF PATIENTS REPORTING EACH LISTED ADVERSE EXPERIENCE
 PHASES II & III
 STUDY TYPE: CLOSED

Appendix III b

BODY SYSTEM	ADVERSE EXPERIENCE	BUPRENORPHINE			MORPHINE			PENTAZOCINE		
		MILD MOD	SEV	TOTAL	MILD MOD	SEV	TOTAL	MILD MOD	SEV	TOTAL
	NERVOUSNESS	0%	0%	100%	0%	0%	100%	1	0%	0%
	SOMNOLENCE	27%	46%	27%	374	33%	36%	196	34%	55%
	SPEECH DIS	100%	0%	0%	2	0%	0%	0	0%	0%
	PARESTHESIA	0%	0%	100%	1	0%	0%	0	0%	0%
	DIPLOPIA	100%	0%	0%	1	0%	0%	0	0%	0%
	APNEA	0%	0%	100%	1	0%	0%	0	0%	0%
	DYSPNEA	66%	0%	33%	3	100%	0%	1	0%	0%
	HYPOTENTIL	0%	0%	0%	0	50%	50%	2	0%	0%
	RESPIRAT DIS	50%	50%	0%	4	0%	0%	0	0%	0%
	RASH	100%	0%	0%	1	0%	0%	0	0%	0%
	PRURITUS	0%	50%	50%	2	0%	100%	0%	1	0%
	SKIN/GEN	67%	23%	10%	30	50%	25%	4	80%	20%
	SKIN/SINGL									5
	SS/EAR/NER	100%	0%	0%	1	0%	0%	0	0%	0%
	SS/EYE/NOSE	50%	0%	50%	2	50%	50%	4	0%	0%
	SS/EYE/VIS	66%	22%	11%	9	100%	0%	1	0%	0%
	UG/UT/BLF	50%	50%	0%	2	0%	0%	0	0%	0%
	UG/UT/URIN	0%	0%	0%	0	100%	0%	1	0%	0%

NUMBER OF PATIENTS REPORTING EACH LISTED ADVERSE EXPERIENCE

Appendix III

PHASES II & III
STUDY TYPE: CLOSED

BODY SYSTEM	ADVERSE EXPERIENCE	PETHIDINE			DHEMPON			TOTAL
		0%	MOD	SEV	0%	MILD	MOD	
BODY/GEN	ASTHENIA	0%	0%	0%	0%	0%	0%	0
	CHILLS	0%	0%	0%	0%	0%	0%	0
	FEVER	0%	0%	0%	0%	0%	0%	0
BODY/HEAD	REACT UNSPEC	0%	0%	0%	0%	0%	0%	0
	HEADACHE	100%	0%	0%	1	0%	0%	0
	WITHDRAW SYND	0%	0%	0%	0	0%	0%	0
BODY/MULT	BRADYCARDIA	0%	0%	0%	0	0%	0%	0
	CV/VASC/BP	0%	50%	50%	2	0%	0%	0
	HYPERTENS	77%	22%	0%	9	80%	20%	5
CV/VASC/CAP	HYPOTENS	100%	0%	0%	1	0%	0%	0
	PALLOR	0%	0%	0%	0	0%	0%	0
	SYNCOPE	0%	0%	0%	0	0%	0%	0
CV/VASC/GEN	VA SOOTILAT	0%	0%	0%	0	0%	0%	0
	DRY MOUTH	0%	0%	0%	0	0%	0%	0
	DIG/BUC	0%	0%	0%	0	0%	0%	0
DIG/EC	DIG/EC	0%	0%	0%	0	0%	0%	0
	DIARRHEA	0%	0%	0%	0	0%	0%	0
	DYSPEPSIA	0%	0%	0%	0	0%	0%	0
DIG/GEN	NALSEA	100%	0%	0%	3	85%	14%	7
	NAUSEA	0%	0%	0%	0	100%	0%	1
	VOMIT	100%	0%	0%	1	100%	0%	3
EYE	REACT UNSPEC	0%	0%	0%	0	0%	0%	0
	CYANOSIS	0%	0%	0%	0	0%	0%	0
	INJECT SITE REACT	0%	0%	0%	0	0%	0%	0
HAL/RBC/HGB	PAIN INJECT SITE	0%	0%	0%	0	0%	0%	0
	SPASM GENERAL	0%	0%	0%	0	0%	0%	0
	SPASM	0%	0%	0%	0	0%	0%	0
IJCN	ANXIETY	0%	0%	0%	0	0%	0%	0
	ATAXIA	0%	0%	0%	0	0%	0%	0
	COPA	0%	0%	0%	0	0%	0%	0
MS/MUS	CONFUS	100%	0%	0%	1	0%	0%	0
	DEPERSONAL	0%	0%	0%	0	0%	0%	0
	DEPRESSION	0%	0%	0%	0	0%	0%	0
NER/CNS/B	DIIZZNESS	100%	0%	0%	0	0%	0%	0
	DREAM ANORM	0%	0%	0%	0	0%	0%	0
	EUPHORIA	0%	0%	0%	0	0%	0%	0
SCPNLENCE	HALLUCIN	0%	0%	0%	0	0%	0%	0
	HISTERIA	0%	0%	0%	0	0%	0%	0
	NERVOL SNESS	0%	0%	0%	0	0%	0%	0
SPEECH/01S	SCPNLENCE	43%	56%	0%	32	30%	56%	23
	SPEECH/01S	0%	0%	0%	0	0%	0%	0
	DIPTOPIA	0%	0%	0%	0	0%	0%	0
NER/PNS	PARES/NESTIA	0%	0%	0%	0	0%	0%	0
	NER/PNS/CN	0%	0%	0%	0	0%	0%	0

NUMBER OF PATIENTS REPORTING EACH LISTED ADVERSE EXPERIENCE

Appendix IIIb

PHASES III & IIII

STUDY TYPE: CLOSED

BODY SYSTEM	ADVERSE EXPERIENCE	PETHIDINE			OMNOPON			TOTAL
		MILD	MOD	SEV	MILD	MOD	SEV	
RES/GEN	APNEA	0%	0%	0%	0%	0%	0%	0
	OYSPNEA	0%	0%	0%	0%	100%	0%	1
	HYPVENTIL	0%	0%	0%	0	0%	0%	0
	RESPIRAT DIS	0%	0%	0%	0	0%	0%	0
SKIN/DERM/ERY	RASH	100%	0%	0%	1	0%	0%	0
SKIN/GEN	PRURITUS	0%	0%	0%	0	0%	0%	0
SKIN/SHGL	SWEAT	100%	0%	0%	4	50%	25%	4
SS/EAR/HER	TITANITUS	0%	0%	0%	0	0%	0%	0
SS/EYE/UVE	MIOSIS	0%	0%	0%	0	0%	0%	0
SS/EYE/VIS	AMBL YCPIA	100%	0%	0%	1	0%	0%	0
UG/UT/B/F	URIN RETENT	0%	0%	0%	0	100%	0%	1
UG/UT/URN	URIN ABNORM	0%	0%	0%	0	0%	0%	0

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CJA

NUMBER OF PATIENTS REPORTING EACH LISTED ADVERSE EXPERIENCE
 PHASES II & III
 STUDY TYPE: OPEN

Appendix III C

BODY SYSTEM	ADVERSE EXPERIENCE	BUPRENORPHINE			OMNIPRIN			TOTAL
		MILD	MED	SEV	MILD	MED	SEV	
POCY/GEN	ASTHENIA	0%	100%	0%	1	0%	0%	0
	CHILLS	0%	100%	0%	1	0%	0%	1
	FEVER	100%	0%	0%	2	0%	0%	0
BODY/HEAD	HEADACHE	72%	18%	9%	11	0%	0%	0
ECGV/PULF	WITHDRAW SYND	0%	100%	0%	1	0%	0%	0
CV/ CARD/ARR	SYSTOCARDIA	100%	0%	0%	1	0%	0%	0
CV/VASC/BP	TACHYCARDIA	66%	33%	0%	3	0%	0%	0
	HYPERTENS	66%	0%	33%	3	0%	0%	0
DIG/GEN	HYPOTENS	89%	11%	0%	9	0%	0%	0
DIG/EC	DRY MOUTH	100%	0%	0%	2	0%	0%	0
	CONSTIP	100%	0%	0%	2	0%	0%	0
DIG/FSOPH	DIARRHEA	100%	0%	0%	1	0%	0%	0
DIG/GEN	DYSPHAGIA	100%	0%	0%	1	0%	0%	0
IJCN	NAUSEA	70%	18%	2%	37	66%	33%	3
NFR/CNS/R	NAUSEA/VOMIT	75%	25%	0%	6	100%	0%	1
	VOMIT	72%	27%	0%	18	100%	0%	2
INJECT SITE/REACT	INJECT SITE/REACT	50%	0%	2	2	0%	0%	0
CONFUS	CONFUS	50%	0%	50%	2	0%	0%	0
DEPRESSION	DEPRESSION	100%	0%	0%	2	0%	0%	0
DIZZINESS	DIZZINESS	86%	4%	0%	23	100%	0%	2
EUPHORIA	EUPHORIA	75%	25%	0%	4	0%	0%	0
NERVOUSNESS	NERVOUSNESS	100%	0%	0%	1	0%	0%	0
SCIATULLENCE	SCIATULLENCE	41%	49%	0%	22	66%	33%	3
VERTIGO	VERTIGO	66%	33%	0%	3	0%	0%	0
TREMOR	TREMOR	0%	0%	100%	1	0%	0%	0
DIPLOPIA	DIPLOPIA	0%	100%	0%	1	0%	0%	0
ANOXIA	ANOXIA	0%	100%	0%	1	0%	0%	0
DYSPNEA	DYSPNEA	50%	50%	0%	4	0%	0%	0
RESPIRAT DIS	RESPIRAT DIS	100%	0%	0%	2	0%	0%	0
SKIN/DERMATRY	RASH	0%	0%	0%	0	100%	0%	0
SKIN/SWGL	SWEAT	75%	25%	0%	12	0%	0%	0
SS/EYF/UVF	MICROSIS	73%	26%	0%	15	0%	0%	0
SS/EYE/VIS	PUPIL DIS	0%	100%	0%	1	0%	0%	0
	AMBYLOPIA	100%	0%	0%	1	0%	0%	0
	VISICK ABNORM	100%	0%	0%	1	0%	0%	0

100%

NUMBER OF PATIENTS REPORTING EACH LISTED ADVERSE EXPERIENCE

Appendix III d

SPECIAL

STUDY TYPE: OPEN

STUDY SYSTEM	ADVERSE EXPERIENCE	BUPRENORPHINE			IMIDURON			TOTAL					
		WILD	MILD	MOD	SEV	WILD	MILD	MOD	SEV	WILD	MILD	MOD	SEV
DIG/GEN	NAUSEA	50%	50%	0%	0%	2	0%	0%	0%	0	0	0	0
	VOMIT	1.00%	0%	0%	0%	2	0%	0%	0%	0	0	0	0
NER/CNS/H	ORIZINESS	1.00%	0%	0%	0%	1	0%	0%	0%	0	0	0	0
	SOMNOLENCE	55%	44%	0%	0%	9	0%	0%	0%	0	0	0	0

Table 17

Special Studies - High Dose Experience

Open Studies: Intravenous or Intramuscular Administration of Buprenorphine

							Description
1. K. Budd, M.B., Ch.B. FFRCS Consultant Anaesthetist The Royal Infirmary Bradford, United Kingdom	44	44	iv	1.14	1		This is a single dose, open study. Patients experiencing moderate to severe post-operative pain received buprenorphine in 0.2 mg increments until the patient was pain free. The starting dose was 0.4 mg. Pain intensity, pulse rate, blood pressure and side effects were assessed before and immediately after injection and at intervals (invest at own discretion) up to 6 hours. Pain relief was assessed after dosing. Remedication time was recorded and observations cont day 4.
2. K. Budd, M.B., Ch.B. FFRCS Consultant Anaesthetist The Royal Infirmary Bradford, United Kingdom	11	10	iv	1.14	79		This is a single dose, open study. Patients suffering moderate to severe post-operative pain were given buprenorphine (3-6 mg intravenously, one patient was given 0.6 mg for comparative purposes). Immediately prior to and at intervals (no definite regimen) after drug administration patients were assessed for pain intensity, pulse rate, blood pressure and side effects. Samples of arterial blood were taken for blood gas analysis (pH, PaCO_2 , and PaO_2), base excess and standard bicarbonate, at 0.25, 0.5, 1.5, 2, 3, and 6 hours after therapy. Pain relief was recorded on a drug.

Table 18

" OTHER CLINICAL STUDIES "

	Number of Subjects in Study	Number of Subjects Receiving Suprenor- phine	Route of Reference	Administration	Vol.	Page
1. Dr. M. E. Dodson Manchester Royal Infirmary Manchester, United Kingdom	8	8	iv	1.15	65	
2. Dr. D. B. Scott Edinburgh Royal Infirmary Edinburgh, United Kingdom	25	13	iv	1.15	68	
3. Dr. J. R. Hampton Nottingham General Hospital Nottingham, United Kingdom	35	35	iv	1.15	71	
4. Prof. B. R. Simpson and Dr. F. P. Buckley The London Hospital London, United Kingdom	21	21	iv	1.15	74	
5. Dr. H. J. Wust Institute of Anaesthesiology Dusseldorf, Germany	13	13	iv	1.15	79	
6. Dr. L. Beyerle University of Essen Essen, Germany	50	25	im	1.15	87	
7. Dr. Hans J. Braun University of Tübingen Tübingen, Germany	13	10	im	1.15	102	
8. Dr. F. P. Buckley The London Hospital London, United Kingdom	32	30	im	1.15	110	

Table 18: cont

9. Professor J. Cambier Beaujon à Clichy Hospital Paris, France	37	20	im	1.15	114
10. Dr. D. Campbell Glasgow Royal Infirmary Glasgow, United Kingdom	17	17	im	1.15	117
11. Professor P. Cernea LaPitié-Salpêtrière Hospital Paris, France	24	16	im	1.15	120
12. Dr. A. Delal University of Salford Salford, United Kingdom	20	20	im	1.15	123
13. Dr. Ellul University Hospital of Nijmegen Nijmegen, Holland	24	24	im	1.15	126
14. Professor P. Gauthier-Lafaye Regional Center Hospital Strasbourg, France	10	10	im	1.15	129
15. Dr. B.C. Hovell Hull Royal Infirmary Kingston-upon-Hull, United Kingdom	16	16	im	1.15	131
16. Dr. A. H. B. Masson Chalmers Hospital Chalmers, United Kingdom	19	19	im	1.15	134
17. Professor A. Ryckewaert Lariboisière Hospital Paris, France	22	22	im	1.15	137
18. Professor B. R. Simpson and Dr. F. P. Buckley The London Hospital London, United Kingdom	21	21	im	1.15	140
19. Professor J. Spierdijk	40	20	im	1.15	143

Table 18: cont'd

- | | | | | | | |
|-----|--|-----|----|----|------|-----|
| 20. | Professor P. Viars and
Professor P. Cernea
LaPitié-Salpétrière
Paris, France | 90 | 30 | im | 1.15 | 157 |
| 21. | Dr. J. R. Hampton
Nottingham General Hospital
Nottingham, United Kingdom | 118 | 59 | iv | 1.15 | 160 |
| 22. | Dr. H. J. Stahl and
Dr. Klaus Huse
University of Dusseldorf
Dusseldorf, Germany | 12 | 12 | im | 1.15 | 164 |

Table 18: co.

23. Dr. M. Laurent	9	9	iv	1.15	188
Hospitalier de Tivoli					
La Louviere, Belgium					
24. Dr. B. C. Hovell	20	20	iv	1.15	191
Hull Royal Infirmary					
Kingston-upon-Hull,					
United Kingdom					
25. Dr. D. Humphrey	9	9	iv	1.15	194
Bradford Royal Infirmary					
Bradford,					
United Kingdom					
26. Dr. P.G.M. Wallace	15	15	im	1.15	197
Glasgow Royal Infirmary					
Glasgow, United Kingdom					
27. Dr. G. Rolly and	80	80	im	1.15	200
Dr. L. Verschellen					
Academisch Ziekenhuis					
Ghent, Belgium					
28. Dr. D. A. McQuillan	60	30	iv/s.l.	1.15	206
National Woman's Hospital					
Auckland, New Zealand					
29. Drs. C. Devaux, M. D. Besse,	40	40	im	1.15	217
D. Tricard, R. Zimmer, and					
P. Gauthier-Lafaye					
Regional Center Hospital					
Strasbourg, France					
30. Dr. J. Quack	37	20	im	1.15	231
, University of Kiel					
Kiel, Germany					
31. Dr. W.H. Forrest, Jr.	96	*	im	1.15	236
Associate Professor of Anesthesia					
Stanford School of Medicine					
Palo Alto, California					

Appendix II and III are the Total Number of Reports of Each Adverse Experience

II a - Phase I (Study Type: closed)

II b - Phases II and III (Study Type: closed)

II c - Phases II and III (Study Type: open)

II d - Special Studies (Study Type: open)

III a - Phase I (Study Type: closed)

III b - Phases II and III (Study Type: closed)

III c - Phases II and III (Study Type: open)

III d - Special Studies (Study Type: open)

TOTAL NUMBER OF REPORTS OF EACH LISTED ADVERSE EXPERIENCE
PHASE I
STUDY TYPE: CLUSED

Appendix IIa

ACDY SYSTEM	ADVERSE EXPERIENCE	AUPHENOPHINE			PLACEBO			PENTAZOCINE			
		MILD	MOD	TOTAL	MILD	MOD	SEV	TOTAL	MILD	MOD	SEV
		1	0	1	0	0	0	1	0	0	0

TOTAL NUMBER OF REPORTS OF EACH LISTED ADVERSE EXPERIENCE

Appendix II a
PHASE I
STUDY TYPE: CLOSTO

BODY SYSTEM	ADVERSE EXPERIENCE	BUPREX/ARPHAINE			PLACEBO			PENIAZOCINE		
		MILD	MED	TOTAL	MILD	MED	TOTAL	MILD	MED	TOTAL
RES/MST	RHINITIS	31%	31%	62%	3	0	3	0	0	0
SKIN/GEN	PRURITUS	35%	65%	0%	17	33%	66%	0%	0%	0%
SKIN/SAGL	SWEAT	51%	37%	11%	36	50%	25%	4	25%	50%
SS/EAR/HER	OCULAR TRAHS TOTAL	100%	0%	0%	1	0%	0%	0	0%	0
SS/EYE/CON	CONJUNCTIVITIS	50%	50%	0%	2	0%	0%	0%	0%	0
SS/EYE/GEN	EYE DIS	0%	100%	0%	1	0%	100%	0%	0%	0
SS/EYE/VIS	ANALYCEPIA	66%	33%	0%	12	0%	0%	0%	0%	0
	PIGMENTATION	100%	0%	0%	2	0%	0%	0%	0%	0
	VISION ABNORM	42%	57%	0%	7	0%	100%	0%	0%	0
	PAROSOMIA	100%	0%	0%	3	0%	0%	0%	0%	0
SS/SNL	TASTE PERVERS	100%	0%	0%	1	0%	0%	0%	0%	0
UG/UT/0/F	INCINNIN URIN	100%	0%	0%	1	0%	0%	0%	0%	0
UG/UT/URN	URIN ABNORM	100%	0%	0%	1	0%	0%	0%	0%	0

TOTAL NUMBER OF REPORTS OF EACH LISTED ADVERSE EXPERIENCE
PHASES II & III
STUDY TYPE: CLOSED

Appendix III b

BODY SYSTEM	ADVERSE EXPERIENCE	BUPRENORPHINE		MORPHINE		PENTAZOCINE		TOTAL
		MILD	MOD	SEV	TOTAL	MILD	MOD	
BODY/GEN	ASTHENIA	0%	100%	0%	2	67%	0%	33%
	CHILLS	0%	100%	0%	1	0%	100%	2
	FEVER	0%	0%	0%	0	100%	0%	0%
	REACT UNSPEC	33%	0%	67%	3	67%	0%	33%
BODY/HEAD	HEADACHE	25%	75%	0%	4	100%	0%	0%
	WITHDRAW SYND	50%	50%	0%	2	0%	0%	0%
	BRADYGARDIA	100%	0%	0%	2	0%	100%	0%
	HYPERTENS	25%	75%	0%	4	100%	0%	0%
CV/CARD/ARR	HYPOTENS	82%	14%	2%	35	87%	13%	0%
	PALLOR	0%	100%	0%	1	0%	0%	0%
	SYNCOPE	0%	0%	0%	0	0%	100%	1
	VASDILAT	0%	100%	0%	2	0%	0%	0%
CV/VASC/GEN	DRY MOUTH	0%	0%	100%	3	0%	50%	50%
	DIARRHEA	100%	0%	0%	1	0%	0%	0%
	DYSPESSIA	100%	0%	0%	1	0%	0%	0%
	NAUSEA	58%	33%	8%	45	63%	27%	10%
DIG/EC	NAUSEA/VOMIT	100%	0%	0%	2	100%	0%	0%
	VOMIT	78%	17%	5%	18	50%	33%	16%
	REACT UNSPEC	100%	0%	0%	1	0%	0%	0%
	CYANOSIS	100%	0%	0%	2	0%	0%	0%
HAL/RBC/HGB	INJECT SITE REACT	0%	0%	0%	0	60%	20%	5
	PAIN INJECT SITE	33%	33%	33%	3	25%	50%	25%
	IJCN	100%	0%	0%	1	0%	0%	0%
	SPASM GENERAL	100%	0%	0%	1	0%	0%	0%
MS/MUS	ANXIETY	0%	0%	0%	0	0%	0%	0%
	ATAXIA	0%	0%	0%	0	0%	0%	0%
	COMA	0%	0%	100%	1	0%	0%	0%
	CONFUS	100%	0%	0%	7	100%	0%	0%
	DEPERSONAL	100%	0%	0%	1	100%	0%	0%
	DEPRESSION	100%	0%	0%	1	0%	0%	0%
	DIZZINESS	46%	31%	23%	26	42%	25%	33%
	DREAM ABNORM	66%	0%	33%	3	0%	0%	0%
	EUPHORIA	100%	0%	0%	3	100%	0%	0%
	HALLUCIN	0%	100%	0%	1	80%	20%	5
	HYSTERIA	0%	0%	0%	0	100%	0%	2

TOTAL NUMBER OF REPORTS OF EACH LISTED ADVERSE EXPERIENCE
PHASES II & III
STUDY TYPE: CLOSED

Appendix II b

BODY SYSTEM	ADVERSE EXPERIENCE	BUPRENORPHINE			MORPHINE			PENTAZOCINE			TOTAL
		MILD	MOD	SEV	TOTAL	MILD	MOD	SEV	MILD	MOD	
NER/PNS	NERVOSNESS	0%	0%	100%	1	0%	100%	100%	0%	0%	0
	SOMNOLENCE	29%	46%	26%	384	33%	31%	37%	196	34%	55%
	SPEECH DIS	100%	0%	0%	2	0%	0%	0%	0	0%	0%
NER/PNS	PARESTHESIA	0%	0%	100%	1	0%	0%	0%	0%	0%	0
NER/PNS/CN	DIPLOPIA	100%	0%	0%	1	0%	0%	0%	0	0%	0
RES/GEN	APNEA	0%	0%	100%	1	0%	0%	0%	0%	0%	0
	DYSPNEA	66%	0%	33%	3	100%	0%	0%	0	0%	0
	HYPVENTIL	0%	0%	0%	0	50%	50%	0%	1	0%	0
	RESP DIS	50%	50%	0%	4	0%	0%	0%	0	0%	0
SKIN/DERM/ERY	RASH	100%	0%	0%	1	0%	0%	0%	0	0%	0
SKIN/GEN	PRURITUS	0%	50%	50%	2	0%	100%	0%	1	0%	0
SKIN/SMGL	SWEAT	67%	23%	10%	30	50%	25%	25%	4	80%	20%
SS/EAR/HER	TINNITUS	100%	0%	0%	1	0%	0%	0%	0	0%	0
SS/EYE/UVE	MIOSIS	50%	0%	50%	2	50%	50%	0%	4	0%	0
SS/EYE/VIS	AMBYLOPIA	66%	22%	11%	9	100%	0%	0%	1	0%	0
UG/UT/B/F	URIN RETENT	50%	50%	0%	2	0%	0%	0%	0	0%	0
UG/UT/URN	URIN ABNORM	0%	0%	0%	0	100%	0%	0%	1	0%	0

**TOTAL NUMBER OF REPORTS OF EACH LISTED ADVERSE EXPERIENCE
PHASES II & III
STUDY TYPE: CLOSED**

Appendix IIb

BODY SYSTEM	ADVERSE EXPERIENCE	PETHIDINE			CMNDOPON			TOTAL
		MILD	MOD	SEV	TOTAL	MILD	MOD	
BODY/GEN	ASTHMA	0%	0%	0%	0%	0%	0%	0
	CHILLS	0%	0%	0%	0%	0%	0%	0
	FEVER	0%	0%	0%	0%	0%	0%	0
BODY/HEAD	REACT UNSPEC	0%	0%	0%	0%	0%	0%	0
BODY/FUL	HEADACHE	100%	0%	0%	1	0%	0%	0
	WITHDRAW SYND	0%	0%	0%	0	0%	0%	0
CV/CARD/ARR	BRADYCARDIA	0%	0%	0%	0	0%	0%	0
CV/VASC/BP	HYPERTENS	0%	50%	50%	2	0%	0%	0
	PALLOR	77%	22%	0%	9	80%	20%	0%
	SYNCOPE	100%	0%	0%	1	0%	0%	5
	VASODILAT	0%	0%	0%	0	0%	0%	0
	DRY MOUTH	0%	0%	0%	0	0%	0%	0
DIG/BLC	DIARRHEA	0%	0%	0%	0	0%	0%	0
DIG/EC	DYSPEPSIA	0%	0%	0%	0	0%	0%	0
DIG/GEN	NAUSEA	100%	0%	0%	3	85%	14%	7
	NAUSEA VOMIT	0%	0%	0%	0	100%	0%	1
	VOMIT	100%	0%	0%	1	100%	0%	3
EYE	REACT UNSPEC	0%	0%	0%	0	0%	0%	0
HAL/RBC/HGB	CYANOSIS	0%	0%	0%	0	0%	0%	0
IJCN	INJECT SITE REACT	0%	0%	0%	0	0%	0%	0
	PAIN INJECT SITE	0%	0%	0%	0	0%	0%	0
MS/MUS	SPASM GENERAL	0%	0%	0%	0	0%	0%	0
NER/CNS/B	ANXIETY	0%	0%	0%	0	0%	0%	0
	ATAXIA	0%	0%	0%	0	0%	0%	0
	COMA	0%	0%	0%	0	0%	0%	0
	CONFUS	100%	0%	0%	1	0%	0%	0
	DEPERSONAL	0%	0%	0%	0	0%	0%	0
	DEPRESSION	0%	0%	0%	0	0%	0%	0
	DIIZZNESS	100%	0%	0%	1	0%	0%	0
	DREAM ABNORM	0%	0%	0%	0	0%	0%	0
	EUPHORIA	0%	0%	0%	0	0%	0%	0
	HALLUCIN	0%	0%	0%	0	0%	0%	0
	HISTERIA	0%	0%	0%	0	0%	0%	0
	NERVOLNESS	0%	0%	0%	0	0%	0%	0
	SCMNOLENCE	43%	56%	0%	32	30%	56%	23
	SPEECH DIS	0%	0%	0%	0	0%	0%	0
NER/PNS	PARESIS/A	0%	0%	0%	0	0%	0%	0
NER/PNS/CN	DIPLOPIA	6%	0%	0%	0	0%	0%	0

TOTAL NUMBER OF REPORTS OF EACH LISTED ADVERSE EXPERIENCE
PHASES II & III
STUDY TYPE: CLOSED

Appendix IIb

BODY SYSTEM	ADVERSE EXPERIENCE	PETHIDINE			OMNIDON			TOTAL
		MILD	MOD	SEV	TOTAL	MILD	MOD	
RES/GEN	APNEA DYSPNEA	0%	0%	0%	0	0%	0%	0
		0%	0%	0%	0	0%	100%	0
								1
	HYPVENTIL RESPIRAT DIS	0%	0%	0%	0	0%	0%	0
		0%	0%	0%	0	0%	0%	0
								0
SKIN/DERM/ERY	RASH	100%	0%	0%	1	0%	0%	0
SKIN/GEN	PRURITITUS	0%	0%	0%	0	0%	0%	0
SKIN/SNGL	SWEAT	100%	0%	0%	4	50%	25%	4
SS/EAR/HER	TINNITUS	0%	0%	0%	0	0%	0%	0
SS/EYE/UVUE	WIOSES	0%	0%	0%	0	0%	0%	0
SS/EYE/VIS	AMBL VCPIA	100%	0%	0%	1	0%	0%	0
UG/UT/B/F	URIN RETENT	0%	0%	0%	0	100%	0%	1
UG/UT/URN	URIN ABNORM	0%	0%	0%	0	0%	0%	0

TOTAL NUMBER OF REPORTS OF EACH LISTED ADVERSE EXPERIENCE

Appendix II C

STUDY SYSTEM	ADVERSE EXPERIENCE	BUPROPION/PIPERLINE			CHIROPON			TOTAL
		MILD	MED	SEV	MILD	MED	SEV	
BLVY/GEN	ASTHENIA	0%	100%	0%	1	0%	0%	0
	CHILLS	0%	100%	0%	1	100%	0%	1
	FEVER	100%	0%	0%	2	0%	0%	0
	HEADACHE	72%	16%	7%	11	0%	0%	0
	WATHERMGRN SYND	0%	100%	0%	1	0%	0%	0
BLVY/HEAD	ORADYCARDIA	100%	0%	0%	1	0%	0%	0
BLVY/PIR/P	CVT CARD/AIR	66%	33%	0%	3	0%	0%	0
BLVY/PIR/P	TAHYCARDIA	66%	33%	0%	3	0%	0%	0
BLVY/PIR/P	HYPERTENS	60%	33%	0%	3	0%	0%	0
BLVY/PIR/P	HYPOTENS	60%	33%	0%	3	0%	0%	0
BLVY/PIR/P	DRY MOUTH	60%	33%	0%	2	0%	0%	0
BLVY/PIR/P	CCKSTIP	60%	33%	0%	2	0%	0%	0
BLVY/PIR/P	DIARRHEA	100%	0%	0%	1	0%	0%	0
BLVY/ESOPH	DYSPHAGIA	100%	0%	0%	1	0%	0%	0
BLVY/GIN	NAUSEA	70%	10%	2%	37	66%	33%	3
BLVY/GIN	NAUSEA VOMIT	75%	0%	0%	6	100%	0%	1
BLVY/GIN	VOMIT	73%	26%	0%	19	100%	0%	2
BLVY/GIN	INJEC 1 SITE REACT	50%	50%	0%	2	0%	0%	0
BLVY/GIN	CONFUS	50%	50%	0%	2	0%	0%	0
BLVY/GIN	DEPRESSION	100%	0%	0%	2	0%	0%	0
BLVY/GIN	DIIZZINESS	67%	42%	0%	24	100%	0%	2
BLVY/GIN	EUPHORIA	75%	25%	0%	4	0%	0%	0
BLVY/GIN	NEVOUSNESS	100%	0%	0%	1	0%	0%	0
BLVY/GIN	SOMNOLENCE	43%	47%	0%	233	66%	33%	9
BLVY/GIN	VERIGC	66%	33%	0%	3	0%	0%	0
BLVY/GIN	TREMOR	0%	0%	100%	1	0%	0%	0
BLVY/GIN	ANXIETIA	0%	100%	0%	1	0%	0%	0
BLVY/GIN	DYSPNEA	50%	100%	0%	1	0%	0%	0
BLVY/GIN	RESPIRAT DIS	100%	0%	0%	4	0%	0%	0
BLVY/GIN	RASH	0%	0%	0%	2	0%	0%	0
BLVY/GIN	SWEAT	75%	25%	0%	12	0%	0%	0
BLVY/GIN	NICROS	75%	25%	0%	16	0%	0%	0
BLVY/GIN	PURPL DIS	0%	100%	0%	1	0%	0%	0
BLVY/GIN	ANALYCPA	100%	0%	0%	1	0%	0%	0
BLVY/GIN	VISION ABNORM	100%	0%	0%	1	0%	0%	0

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-401

CHEMISTRY REVIEW(S)

MAY 8 1980

NDA 18-401 REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

Division: DNDP
Chemist Review #1
Reviewing Chemist: C. Lockett

Applicant: Eaton-Reccol, Inc.

Address: Norwich, New York 13815

Product Name(s):

Proprietary: Buprenorphine Hydrochloride Injectable

Non-Proprietary: Buprenorphine hydrochloride

Code Name/number: RX-6029-M HC1; EU-4764

Dosage Form(s) and Route(s) of Administration: Refer to following page

Pharmacological Category and/or Principal Indication: Indicated for the relief of moderate to severe pain

Structural Formula and Chemical Name:

[5 α , 7 α (S)]-17-(cyclopropylmethymethyl)- α -(1,1-dimethyl-ethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy- α -methyl-6,14-ethenomorphinan-7-methanol hydrochloride

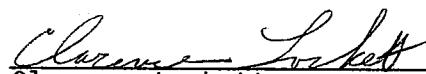
Alternate name: N-cyclopropylmethyl-7 α -(1-(S)-hydroxy-1,2,2-trimethyl-propyl-6,14-endoethano-6,7,8,14-tetrahydronororipavine

Initial Submission: October 31, 1979; received Bureau of Drugs November 1, 1979.

Related Documents: See following page

Conclusions and Recommendations:

This NDA is satisfactory to proceed with Sample Validation.


Clarence Lockett
April 17, 1980

cc

NDA Orig

HFD-102/Kumkumian

HFD-120

HFD-120/CLockett/4/17/80

RD init. RSchultz/4/22/80

FT:klt/4/23/80

DOC#1681A

LOJ 5-8-80

Dosage Form and Route of Administration:

1 or 2 ml of an aqueous 0.3 mg/ml solution of buprenorphine in the form of its hydrochloride salt.

Intravenous injectable

Related Documents:

Dosage Form

IND

[] }

b(4)

Drug Master Files

[] }

b(4)

Structural Formula and Chemical Name:

molecular Formula: C₂₉H₄₁NO₄HC1

28 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Chemistry- 19

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-401

PHARMACOLOGY REVIEW(S)

Review and Evaluation of Clinical Data
Resubmission

Sponsor: Norwich-Eaton Pharmaceuticals
P.O. Box 191
Norwich, New York 13815

JUL 8 1981

Drug: Buprenorphine Hydrochloride Injectable

Category: Mixed agonist-antagonist analgesic for the relief of moderate-to-severe pain

Document Reviewed: Volumes 3.1 - 3.5 dated January 16, 1981 and Volumes 2.1 - 2.49 dated August 6, 1980.

Date of Review: May 21, 1981

The submission of January 16, 1981 contains the sponsor's response to a nonapprovable letter dated July 15, 1980 from Marion J. Finkel, M.D., HFD-100. This submission responds to all the deficiencies noted in our letter of July 15, 1980. It also contains a draft package insert which contains a revision of the Dosage and Administration section to include adolescents (13 years of age and over). This change is based on information derived from the "Report on the Monitored Release of Temgesic Injection" which was submitted in the original NDA (Volume 1.15, page 1). Also enclosed are reports of four additional animal safety studies which confirm the results of similar previously submitted investigations. Additional pharmacology studies are enclosed dealing with the effect of buprenorphine on drug metabolizing enzymes and investigation of the mechanism of buprenorphine-induced respiratory depression and possible antagonist reversal.

The Vol. 2.1 - 2.49 submission dated August 6, 1980 provides the following additional information:

1. Three animal safety studies.
2. A pharmacokinetic clinical study.
3. The final report on the multicenter clinical study comparing buprenorphine to morphine.
4. A revised package insert.

The data from the multicenter study were submitted before the sponsor received the 7/15/80 regulatory letter with the result that the analysis of the data suffer the same flaws as did those of the original eight studies.

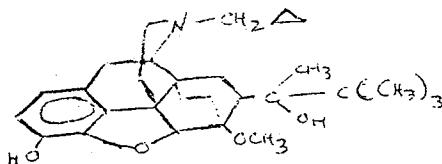
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Review and Evaluation of
Pharmacology and Toxicology Data of
NDA-18-401

Sponsor: Eaton-Reccol, Inc.
Norwich-Eaton
Box 191
Norwich, New York 13815

Drug: Buprenorphine hydrochloride injectable

N-cyclopropylmethyl-7-alpha-(1-(s)-hydroxy-1,2,2,-trimethylpropyl)-
-6,14-endo-ethano-6,7,8,14-tetrahydronororipavine hydrochloride



Category: Narcotic agonist-antagonist analgesic

Related Drug(s): pentazocine, butorphanol, nalbuphine

Previous Pharmacology Reviews: H. Sorer 1/31/75
H. Sorer 6/25/75
W.D. Brown 10/3/77
W.D. Brown 12/28/78

Related INDs/NDAs

IND 11-142 Buprenorphine Parenteral
IND 12-831 Buprenorphine Sublingual
IND 12-978 Buprenorphine Oral
IND 13-951 Buprenorphine Oral

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Most of the pharmacology and toxicology data has been submitted to INDs 11-109, 11-142, 12-831, 12-978, and 13-951 and has been previously reviewed by H. Sorer (IND 11-109 on 1/31/75 and 6/25/75) and W.D. Brown (IND 12-831 on 9/16/76, IND 12-978 on 11/15/76, and IND 11-142 on 11/17/78). However, for the sake of completeness and in order to perform a correlative review, previously reported and reviewed data will be incorporated into this review. In addition, a table will be made of data generated in foreign countries and submitted to this NDA.

The initial pharmacological analysis of buprenorphine was submitted to IND 11-109 and was tabulated by H. Sorer.

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Physical dependence studies and substitution in opiate-dependent animals

Species: Mouse

Test: Straub tail index

Drug	Straub ED ₅₀ (Mg/kg, i.v.)	LD ₅₀ mg/kg. i.v.)	Straub Index
Buprenorphine	0.19 (0.095-0.38)	28 (26-31)	147
Morphine SO ₄	3.7 (3.0-4.5)	221 (188-260)	60
Codeine PO ₄	56 (30-104)	86 (67-111)	1.5

Test - Nalorphine or Naloxone precipitated jumping
 (method of Saelens, et al., Arch Int. Pharmacodyn. 190: 213, 1971)
 7 injections challenge

Drug	Dose range <u>s.c.</u>	Nalorphine jumps/mouse	No. of mice jumping more than 5X	Naloxone jumps/mouse	No. of mice jumping more than 5X
Bupren- orphine 3.5-14		0	0/10	2.0	1/10
Penta- zocine 40-60		0	0/10	3.6	1/10
Codeine 50-150		0.3	0/10	51.1	7/8
Morphine 35-140		30.4	7/10	73.3	6/8

13 Injections Challenge

Bupren- orphine 3.5-56	0	0.10	0	0/10
Penta- zocine 40-60	0	0/10	32.3	5/7
Codeine PO ₄ 50-150	65	7/8	71.5	3/6
Morphine SO ₄ 35-560	244	10/10		

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Species - Rat

Test - Abrupt withdrawal after 6 days of continuous i.p. infusion

<u>Drug</u>	<u>% weight gain or loss</u>
Buprenorphine	+ 2-3%
Morphine	-22%

Species - Dog (chronic spinalized beagles)

Test - Abrupt withdrawal after 3 weeks of 0.1 mg/kg/day of buprenorphine in divided doses (0.025 mg/kg q. 6 h, i.v.)

Reference - Martin et al. J. Pharmacol. Exp. Ther. 197: 517-532, 1976.

(1) mild abstinence which was present at 8 hours after last dose and peaked at 25th hour of abstinence

Test - Precipitated abstinence with naloxone (0.2 mg/kg, i.v.)

(1) precipitated mild abstinence score = 10 mg/kg/day of morphine

(2) took 20X as much naloxone to precipitate buprenorphine withdrawal as opposed to morphine withdrawal

Species - monkey (Rhesus)

Test - Abrupt and precipitated withdrawal with nalorphine and naloxone after

(1) Buprenorphine administered for 30-32 days - initial and final doses were

3.0 and 12.5 mg/kg, respectively.

(2) abrupt withdrawal - no withdrawal syndrome

(3) days 14 - 16 and 28-29 nalorphine (2 mg/kg) or naloxone (2 mg/kg) - no precipitated withdrawal

(a) codeine treated animals as positive control=severe precipitated withdrawal and severe abrupt withdrawal

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(4) Results verified in University of Michigan study

- (a) abrupt withdrawal and nalorphine and naloxone challenges after 3 days dosing with 0.32 (initial) to 5.12 mg/kg (final dose) given to 3 monkeys.
- (b) no withdrawal syndrome observed with abrupt or antagonist challenges

Species - monkey (Patas)

Test - abrupt and precipitated withdrawal (naloxone 2 mg/kg, s.c.)

a) 30 day buprenorphine treatment

b) no withdrawal upon abrupt or naloxone challenge

c) cyclazocine treated animals - moderately severe abstinence upon naloxone challenge (cyclazocine 0.5-1.0 mg/kg, s.c., 30 days)

Substitution and Precipitation Studies

Species - Dog (chronic spinalized beagles)

Tests - Precipitated abstinence and substitution

a) buprenorphine (0.024 to 0.096 mg/kg, i.v.) precipitated abstinence with a lesser slope than naloxone

b) buprenorphine substituted for morphine in morphine dependent withdrawn animals i.v. buprenorphine (0.001 to 0.016 mg/kg)

Species - Rat - morphine dependent - continuous morphine infusion

a) morphine (50-200 mg/kg/day for 6 days continuously, i.p.) then withdrawn

b) buprenorphine - day 7-8 10 mg/kg - did not substitute

c) morphine - day 7-8 - suppressed abstinence

Species - Rat - morphine dependent by 2X daily injections (10-100 mg/kg, s.c.)

(1) Naloxone - severe abstinence precipitated

(2) buprenorphine - (0.3-30 mg/kg) - did not precipitate

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Species - Monkey (Rhesus)

(1) morphine dependent (3.0 mg/kg, s.c. q 6 h.) given buprenorphine 12 hours after last dose of morphine

a) 0.32 mg/kg precipitated severe abstinence for 12 hours

b) 0.02-0.16 mg/kg - abstinence signs were mixed with those of mild, morphine-like depression

Species - Monkey (Patas)

(1) morphine dependent (6 mg/kg, s.c.) animals administered buprenorphine 2 hr. after last dose of morphine

a) 0.1 mg/kg - moderate abstinence precipitated - shaking, yawning, fighting

b) 10 mg/kg - severe abstinence precipitated

(2) cyclazocine-dependent monkeys - buprenorphine (0.5 mg/kg, s.c.) precipitated moderate abstinence syndrome - scratching, yawning, shaking

(3) single dose suppression test - buprenorphine neither suppressed nor exacerbated the morphine withdrawal syndrome in Patas monkeys

Effects on respiration -

No new studies submitted. Data reviewed here was previously submitted to INDs 11-109 and 11-142 and reviewed.

Species - mice

(1) buprenorphine (0.001-1 mg/kg) - some respiratory depression, not dose-related.

morphine (1-10 mg/kg) - dose-related respiratory depression

pentazocine (10-100 mg/kg) - start of a dose-related response at higher dose

Species - Rat

- (1) 0.001-0.1 mg/kg, s.c. and i.a.) - respiratory depression characterized by decreased respiratory rate, rise in pCO_2 although the response was not dose-related.

Species - rabbits

- (1) buprenorphine (0.1-40 mg/kg, s.c.) failed to alter pO_2 , pCO_2 , and pH
- (2) pentazocine and morphine produced dose-related decreases in pO_2 , increased pCO_2 , and pH which paralleled their analgesic potency.
- (3) 10 mg/kg i.v. buprenorphine = decreased pO_2 to 60% of control value

Species - dogs (beagle) - pentobarbital-anesthetized

- (1) buprenorphine (0.1-1.0 mg/kg, i.v.) produced respiratory depression characterized by decreased respiratory rate and rise in pCO_2 , although the response was not dose-related. Tidal volume was decreased by buprenorphine.
- (2) Death from respiratory failure could be induced by buprenorphine.
- (3) Respiratory failure was not reversible by naloxone - a 1 mg/kg dose of buprenorphine was not reversed by 1 or 10 mg/kg of naloxone.
- (4) morphine - (0.1, 1.0, 3.0 mg/kg) was administered intravenously in a second study in pentobarbital anesthetized dogs.

At doses up to 1 mg/kg, morphine had little effect on respiration.

At 3 mg/kg, morphine depressed respiratory rate but tidal volume was markedly increased. pO_2 was significantly reduced after 3 mg/kg although pCO_2 was not significantly elevated. Blood pH was reduced at both 1 and 3 mg/kg morphine sulfate.

Naloxone (0.1 mg/kg) reversed respiratory depression; i.e., pCO_2 and tidal volume were reduced and blood pH increased.

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Species - Rat - artificially respiration versus unrespired

(1) pentobarbital anesthetized (60 mg/kg, i.p.) rats were infused with buprenorphine (3 or 6 mg/kg/min) until respiratory depression ensued. Artificial respiration reversed respiratory and cardiovascular depression. Vital signs were maintained with artificial respiration even during continued infusion (6 mg/kg/min).

(2) lightly anesthetized rats (30 mg/kg, i.p. pentobarbital), buprenorphine was infused at 3, 6, 9, and 12 mg/kg/min in unrespired, artificially respiration and naloxone pre-treated rats.

Group	Lethal dose of buprenorphine infused at	6 mg/kg/min	9 mg/kg/min	12 mg/kg/min
unrespired	180		106 \pm 29	72 \pm 23
artificially respiration	-		270	300 \pm 17
naloxone pre-treated (1 mg/kg, i.v., 3 min. prior to infusion)	-		189 \pm 20	168 \pm 17

With established respiratory depression, higher doses of naloxone (23 mg/kg, i.v.) were required to reverse depression. Morphine-induced respiratory depression was readily reversed with naloxone (0.5 mg/kg, i.v.). However, hypotension and bradycardia were exacerbated by the 23 mg/kg naloxone dose.

Cardiovascular studies

All data previously submitted to INDs 11-109 and 11-142 and reviewed. Data will be included here for the sake of completeness.

Species - Rat

(1) buprenorphine, 1 mg/kg, i.v. - decreased H.R. without decreased BP

Species - guinea pig

(1) anesthetized artificially respiration received buprenorphine, morphine, or pentazocine, i.v.

a) buprenorphine (1, 2, or 5 mg/kg) and pentazocine (3, 5, or 10 mg/kg) produced marked bradycardia accompanied by occasional arrhythmias

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- b) Isoproterenol (6.25 to 50 $\mu\text{g}/\text{kg}$) reversed bradycardias without producing arrhythmias
- c) Atropine (0.05-0.2 mg/kg) or naloxone (0.05-0.8 mg/kg) produced some reversal of the bradycardia, although not dose-related
- d) bilateral vagotomy, nalorphine, and phentolamine were ineffective

Species - cats

- (1) pentobarbitalized animals given i.v. buprenorphine (0.01, 0.03, 1 and 3 mg/kg)
 - a) produced bradycardia and respiratory depression but failed to alter the postural reflex

Species - Dog

- (1) Pentobarbitalized dogs were administered buprenorphine, morphine, or pentazocine
 - a) buprenorphine, 0.1 to 10 mg/kg , marked bradycardia and slight hypotension
 - b) morphine, 0.3 to 30 mg/kg , dose-related hypotension and respiratory depression and slight bradycardia
 - c) pentazocine, 3 or 10 mg/kg , slight bradycardia, slight hypotension, and respiratory depression

EKG records in dogs

- (1) buprenorphine (0.01 to 3 mg/kg , i.v.) in 4 dogs, pentazocine 0.03 and 3 mg/kg in another dog
 - (2) buprenorphine - no marked hypotension at 3 mg/kg (unlike morphine)
 - a) bradycardia potentiated by administration of 1 mg/kg epinephrine or 5 mg/kg norepinephrine led to arrhythmias
 - b) morphine did not produce this effect
 - c) pentazocine produced slight arrhythmias

Behavioral responses to buprenorphine:

Species - rat - buprenorphine, s.c. (0.3-1.0 mg/kg) - initial sedation with stereotypy followed by motor stimulation - antagonized by naloxone (10-100 mg/kg)

Species - guinea pig

- (1) catalepsy following buprenorphine - $ED_{50}=0.96$ (0.34-2.7) mg/kg
@ 16X as potent as morphine in this respect

Species - cat

- (1) 0.5, 1, 2, 5, and 10 mg/kg, s.c. buprenorphine - non-morphine-like actions
- a) 0.5-1.0 mg/kg - mydriasis
 - b) 2.0 mg/kg - slight behavioral depression - no morphine-like "mania"
 - c) 5 and 10 mg/kg - analgesia and darting movements at 10 mg/kg

Species - dog

- (1) Two dogs - rising dose tolerance study 0.05 to 10 mg/kg for 10 days dosing
- a) no consistent effects on body temperature, heart rate, or pulse rate noted
 - b) slight behavioral depression above 0.05 mg/kg with hind limb weakness
- (2) no "sham rage" observed in dogs
- (3) 30 day subacute study - some vomiting during first 6 days of study

Species - Monkey -

- (1) slightly dazed after buprenorphine (10 mg/kg, s.c.)

b(4)

Monkey -

- (1) dependence study with buprenorphine - tolerance developed to depressant effect of buprenorphine; at initially higher dose levels, CNS depressant effects would reemerge and then fade over several days of administration.

Species - Rat

(1) discriminative stimulus generalization paradigm

a) animals trained to discriminate fentanyl from saline

1. drugs that generalized to fentanyl cue

- a. codeine, 10-40 mg/kg, p.o.
- b. morphine, 10-40 mg/kg, p.o.
- c. diphenoxylate, 5-20 mg/kg, p.o.

2. buprenorphine - equipotent with fentanyl at level of 50% effect, only 1/2 as potent at level of 100% effect (0.08mg/kg)

3. fentanyl and buprenorphine cues were antagonized by naloxone (0.02-0.31 mg/kg, s.c.); i.e., lowest dose of drug producing 100% effect

Species - Monkey ()**b(4)**

(1) trained to self-administer morphine, i.v.

(2) buprenorphine (3 to 300 ug/kg) pretreatment had no effect on morphine response rates

(3) Continuous infusions of buprenorphine 20 and 40 ug/kg/hr

a) low morphine doses - decreased by buprenorphine infusion

b) high morphine doses - increased by both infusion rates of buprenorphine

Miscellaneous Pharmacology:

G.I. Propulsion in rats

(1) buprenorphine 0.01 to 1 mg/kg. s.c. inhibited meal transit (charcoal)

a) above 1 mg/kg - buprenorphine facilitated charcoal transit

b) thus, the buprenorphine dose-response curve lines were curvilinear - i.e., an inverted "U" shape

Effects of buprenorphine on isolated tissue preparations

(1) Tissues - rat phrenic nerve diaphragm, rat vas deferens, rat anococcygeus muscle, pregnant rat uterus, hamster fundus, guinea pig ileum, rat ileum and duodenum.

(2) Buprenorphine possessed smooth muscle depressant properties in a concentration of 1-10 ug/ml, depending on the tissue being tested.

(3) No evidence was obtained for specific antagonism or potentiation of acetylcholine, noradrenaline, histamine, prostaglandin or 5-HT and no effect on B₁ or B₂ receptors.

(4) In all experiments, buprenorphine inhibition was non-competitive.

(5) Buprenorphine had no effect on the neuromuscular junction (rat phrenic nerve diaphragm).

(6) Buprenorphine had no adrenergic neuron blocking activity in the rat vas deferens preparation.

(7) Buprenorphine had a slight (25% reduction in contractions) in 1/3 rat uteri at 3 ug/ml.

Effects on Blood Sugar:

rats - buprenorphine produced hypoglycemia; morphine produced hyperglycemia

man - buprenorphine - 3 human volunteers: no effect on blood glucose

Anti-diuretic effect - rat

(1) at equianalgesic doses, buprenorphine had a greater antidiuretic effect than morphine.

(2) a 20 fold increase in dose - morphine now had a greater antidiuretic effect than buprenorphine.

(3) dog - buprenorphine (0.01-0.1 mg/kg, i.v.) - no suppression of urine output over a 2 hr. period.

Drug interactions - dog

(1) Buprenorphine was substituted for meperidine as a premedication for surgical anesthesia - no adverse effects were observed on cardiovascular or

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respiratory parameters or general behavior, although salivation took longer to dry up after atropine in combination with buprenorphine.

Abuse Potential - Presentation by J.W. Lewis of Reckitt and Colman to FDA Controlled Substances Advisory Committee

(1) Chemistry - difficult to exchange cyclopropylmethyl group for methyl which would increase potency or change agonist/antagonist characteristics

(2) abuse potential relative to narcotic agonists and agonist/antagonists in animals and man

a) single dose effects

b) substitution/precipitation studies in morphine dependence

c) abrupt or nalorphine or naloxone withdrawal

Buprenorphine is most like propiram in its profile of effects but has little intrinsic physical dependence capacity. Psychomimetic effects seen with pentazocine have not been observed. Buprenorphine has less intrinsic agonistic activity than propiram.

The narcotic antagonist effects of buprenorphine have been observed in narcotic tolerant cancer patients and in reversing fentanyl used in anesthesia.

Buprenorphine has been characterized as a partial agonist of the μ -receptor by Martin et al. J. Pharmacol. Exp. Ther. 197: 517, 1976.

(3) Acute toxicity

In rodents, buprenorphine LD₅₀ are similar to those observed for propoxyphene, pentazocine and propiram. However, buprenorphine is 300X as potent as propoxyphene, 200X as potent as propiram, and 100X as potent as pentazocine.

In humans, buprenorphine in therapeutic doses has at least as much if not more respiratory depressant capacity than therapeutic doses of morphine. At supra therapeutic doses, the antagonist component of buprenorphine becomes apparent and there is a flattening of the dose-response curve for respiratory depression. Up to 7 mg, i.v. buprenorphine have been given without clinical evidence of significant respiratory depression.

Buprenorphine is only partially reversed by naloxone. Nevertheless, the drug has excellent safety relative to other narcotics.

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Drug Interactions (rat)

(1) Buprenorphine (0.016-100 mg/kg) with either alphaxolone (6 mg/kg, i.v.) or halothane/oxygen for surgical anesthesia.

(2) Animals were observed for 7 days. There were no difference in weight gain across saline or buprenorphine-treated groups.

Absorption, Distribution, Metabolism, and Excretion (ADME)

The majority of the ADME studies on buprenorphine have been previously reviewed under IND 11-109 and 11-142. Previously submitted data will be included for the sake of completeness.

Species: Rat

Dose schedule: 100 ug/kg, p.o. or 20 ug/kg, i.m.

Objective: Comparison of ADME OF 3 H-buprenorphine by oral vs. intramuscular routes.

After i.m. dosing, blood levels of 3 H-buprenorphine + (metabolites?) peaked in 10 minutes and then declined markedly to a low level 2-3 hours after treatment. A second peak occurred at 8 hours and then declined to a low level at 24 hours after treatment. The second peak suggests a possible enterohepatic circulation of buprenorphine.

After oral administration, blood radioactivity levels peaked in 10 minutes and declined to a lower level 40 minutes after dosing. Peak plasma radioactivity levels were comparable between oral and intramuscular routes of administration.

The major excretory route for buprenorphine by either route of administration was the bile. About 80% of the total radioactivity was recovered from bile, urine, and feces of rats within 24 hours of dosing with buprenorphine.

In terms of organ distribution, well-defined peaks were observed in liver distribution of 3 H-buprenorphine following either intramuscular or oral administration. Levels of 3 H-buprenorphine (+ metabolites?) were very low at 24 hours post-administration. Except for liver tissue, levels of radioactivity were lower after oral than intramuscular administration by a factor of 5. Peak brain levels were 2-3 times greater after i.m. administration. Little or no residual radioactivity was found 7 days after oral or i.m. administration.

Species: Rat

Dose schedule: 3 H-buprenorphine, 20 ug/kg, sublingual or intramuscular

Objective: comparison of blood and tissue levels of 3 H-buprenorphine by sublingual vs. intramuscular administration

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In animals given buprenorphine sublingually, the esophagus was ligated. Peak blood levels were obtained within 0.5 to 2 hours after the i.m. dose and 2 to 4 hours after the sublingual dosing. Peak brain levels were about 3 times higher by the i.m. route. This study suggests that sublingual administration of buprenorphine may yield higher blood levels of drug on a mg for mg oral vs. sublingual basis.

Species: Rat
Dose: 5 ug/kg, i.m. to biliary cannulated rats

Biliary excretion accounted for 65% of the administered radioactivity after 24 hours. Urine and biliary excretion accounted for 68 to 91% of the administered radioactivity after 24 hours. Some radioactivity was found in the stomach, suggesting gastric secretion may occur. The data further suggest that buprenorphine undergoes entero-hepatic circulation.

Species: Rat
Dose: 20ug/kg, i.m. 3 H-buprenorphine

The objective was to study 3 H-buprenorphine and its nor-metabolites' distribution in rats. Plasma to brain ratio of free drug was about 0.25. Only traces of the nor metabolite were present in plasma and brain while significant amounts were found in the kidney.

Species: Rat
Study: metabolic pattern of buprenorphine

About 30% of the total radioactivity was excreted in the bile in 24 hours mainly as glucuronides of buprenorphine and N-dealkyl buprenorphine. Unchanged buprenorphine was detected in small amounts. In rats, a larger portion of the radioactivity excreted in bile was associated with N-dealkyl buprenorphine than in other species studied.

The site of glucuronide conjugation has not been determined but in the case of buprenorphine, it is probably the free phenolic hydroxy group. The N-dealkylated product may have been present as an O or N-glucuronide or both.

Species: Rat
Study: pharmacokinetic profile of buprenorphine in pregnant and nonpregnant rats

After i.m. injection, the pharmacokinetic profile of buprenorphine was similar in both groups. Additionally, kinetic parameters in maternal plasma and the fetus were similar at day 11 of gestation.

On day 21, clearance from the fetus appeared to be much slower than clearance from the plasma. It was subsequently determined that in the mature rat fetus there is a high degree of conjugation and localization in the fetal gastro-intestinal tract. This observation suggested the existence of a pathway for biliary excretion of the conjugated drug in the mature fetus.

Species: Rat

Dose schedule: 5 mg/kg, i.m. buprenorphine for 7 days.
80 mg/kg, p.o.

In treated rats, oral buprenorphine increased zoxazolamine paralysis time by 60%, whereas i.m. treated animals showed a 36% increase in paralysis time. The activities of p-nitroanisole-0-demethylase and biphenyl 2-and 4-hydrolase and the levels of cytochrome P450 and b₅ were significantly reduced.

It could not be determined whether the effect on zoxazolamine was due to a change in hepatic enzyme activity or residual buprenorphine acting as a competitive substrate.

In Vitro Studies:

Protein binding of buprenorphine - equilibrium dialysis against human plasma and plasma proteins

Buprenorphine was about 96% bound to plasma. L and B globulins bound a higher proportion than α -globulins or albumin. Binding to albumin was increased by defatting, indicating a competitive interaction between buprenorphine and lipids.

Gut metabolism of buprenorphine - in vivo and in vitro

Three preparations were used: isolated, everted gut strips from rats to study transfer of ³H-buprenorphine, etorphine and dihydromorphine, in vivo intestinal studies of isolated small intestine in rats, and intestinal mucosa analyzed for UDP-glucuronyl transferase.

The rate of mucosal to serosal membrane transfer was higher for buprenorphine at concentrations of 5 and 10 ug/ml when drug and metabolite were compared to dihydromorphine. However, a significantly higher percentage of free dihydromorphine (85-91%) was absorbed. At the lower concentrations (1 and 5 ug/ml), the majority of etorphine (93-94%) or buprenorphine (85-97%) was present as the glucuronide conjugate.

The UDP-glucuronyl transferase activity of the intestinal mucosa was of a similar order for buprenorphine and etorphine, being 25-50% of the liver activity. The intestinal activity for dihydromorphine was only 10% that of liver. Intestinal absorption of ³H-buprenorphine demonstrated a biexponential loss from the intestinal contents, indicating that more than one process may be involved.

The partition coefficients (heptane:pH 7.4 buffer) were also measured. Buprenorphine was 10 times as lipophilic as etorphine and 10⁶ times as lipophilic as dihydromorphine.

Species: Rabbit (female)

Dose schedule - single dose 5 mg/kg, i.m. ³H-buprenorphine (@ 300 uCi/rabbit)

Objective - to obtain data on the absorption, distribution, metabolism and

excretion of ³H-buprenorphine in the rabbit

Site -

The dose used in this study, 5 mg/kg, was the high dose level used in teratology studies. After i.m. injection, maximal plasma equivalents of buprenorphine (170-270 ug equivalents/gm) were observed within 15 minutes. By 8 hours, the concentrations in plasma declined to 40-90 ug equivalents/gm and then declined more slowly thereafter. Additional studies demonstrated values near 50 ug/g present 4 days after dosing.

The presence of polar metabolites in the plasma increased dramatically from 24 to 82% of the total radioactivity in plasma at 4 hours post-administration. The majority of drug in the urine was in the form of a glucuronide conjugate with lesser amounts (<10%) as the N-dealkyl metabolite and buprenorphine. Upon hydrolysis, the conjugate metabolites were observed to have the same chromatographic properties as buprenorphine and N-dealkyl buprenorphine. In the feces, the majority of the recovered radioactivity was identified as buprenorphine (44-86%) with the remaining radioactivity being present as free N-dealkyl buprenorphine.

At 7 days after dosing, the bile contained from 0.07 to 0.9% of the administered dose. This indicated an enterohepatic circulation of buprenorphine and would explain why 3/4 rabbits demonstrated a rise in plasma radioactivity within 48 hours after i.m. injection.

In terms of total dose excretion, the mean percentages of buprenorphine excreted into the urine and feces during a 7 day period were 37 and 16 percent, respectively. Incomplete absorption of the dose combined with an enterohepatic circulation would account for the slow excretion of buprenorphine. A further 31% of the dose was recovered from the carcasses at autopsy (day 7).

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In summary, i.m. administration of buprenorphine results in incomplete mobilization with peak plasma levels occurring at 15 minutes but another peak occurring at 48 hours. At 2 hours post-administration, 48% of the plasma radioactivity was unchanged buprenorphine and 52% appeared to be polar metabolites. The urinary and fecal excretion rates in the rabbit were slow. The predominant urinary metabolite was a glucuronide conjugate whereas the primary fecal metabolite was bupenorphine. The secondary plasma peak, the slow excretion pattern and the presence of conjugated buprenorphine in bile with unconjugated in the feces can be explained by an enterohepatic circulation where glucuronidated buprenorphine is concentrated in bile, deglucuronidated in the gut, with subsequent partial absorption into plasma and partial excretion into the feces.

The distribution study suggested that there was some residual buprenorphine in brain and spinal cord at the end of 1 week. Body fat had a high level of buprenorphine (121-395 ug equivalents/gm) at the end of 7 days after a single i.m. dose.

Species: Dog

Dosing schedule: 100 ug/kg, p.o. or 20 ug/kg, i.m.

Peak blood levels were achieved within 20 minutes after i.m. administration and were maintained for about an hour before gradually declining to a low level by 24 hours. After oral administration, peak blood levels were observed at 2 hours after dosing and gradually declined to a low level by 24 hours. Peak blood levels were similar following 100 ug/kg, p.o. vs. 20 ug/kg, i.m., buprenorphine.

Recoveries from urine and feces were low, respectively 5 and 57% of the administered radioactivity. At 7 days, only trace amounts of the administered dose remained in any tissue studied. The largest proportion of residual radioactivity was associated with the liver.

The majority of the radioactivity excreted in the dog was buprenorphine with traces of N-dealkylated buprenorphine. The baboon and rhesus monkey had similar excretion patterns.

Species: Baboon; Dose: 40 ug/kg, p.o. capsule; 2 ug/kg, i.m.

Objective: absorption, distribution, excretion profile
allowing i.m. injection or p.o. administration

Plasma levels peaked within one hour and then rapidly declined for the next four hours. Thereafter, the rate of decline was slower, reaching a low level 24 hours after dosing.

After oral administration, peak plasma levels occurred in 2 to 6 hours after treatment and thereafter declined slowly.

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About 48-59% of the administered radioactivity was excreted via feces regardless of administration route. Cumulative recoveries were only 66-69% over 7 days despite the fact the tissues had little radioactivity at the end of the time period.

Species: Rhesus Monkey
 Dose: 15 ug/kg by capsule or 2 ug/kg i.m., 15 ug/kg in aqueous solution orally by gavage - ^3H -buprenorphine

Following i.m. dosing, plasma levels of drug peaked within one hour and then rapidly declined. After oral administration, peak plasma radioactivity levels were observed within one hour with a rapid and then a slower rate of decline in plasma.

Brain radioactivity levels were higher after i.m. than oral dosing; peak levels were observed 2 hours after i.m. or oral administration. Higher levels of drug were observed in liver and kidney at 2 and 4 hours after oral administration. In other tissues, 2 hour levels after i.m. dosing were higher but 4 hour levels after i.m. or p.o. administration were similar.

The major route of excretion was the feces with about 80% of the radioactivity recovered after 7 days. This occurred after oral or intramuscular dosing.

A second study was undertaken to compare the metabolism of ^3H -buprenorphine administered by sublingual or intramuscular routes. Two monkeys (one/sex) were dosed with 38 ug/kg ^3H -buprenorphine sublingually and intramuscularly, 23 days apart. Urine and feces were collected at daily intervals for 10 days. Blood samples were collected at various times. The excreta, whole blood and serum were analyzed for total radioactivity. Further, serum and urine were analyzed for free and total unchanged drug by enzymatic and TLC assays.

After 10 days, 73.5% and 98.1% of the total radioactivity from the sublingual and intramuscular dosages, respectively, were collected from urine, feces, and cage washings. The largest proportion of the dose recovery was in the feces.

Peak serum levels were obtained within two hours after sublingual dosing. Of this concentration, 13% was unchanged drug. After 8 days, serum levels of 1.2 ug/ml of buprenorphine equivalents were still present. Following i.m. dosage, a peak serum level of 25 ug/ml of buprenorphine equivalents was reached one hour post-administration, 81% of which was free unchanged drug. By 24 hours, no free drug was detectable in the plasma.

Man: two volunteers

(1) 2 ug/kg ^3H -buprenorphine, i.m. - single dose
 (2) 15 ug/kg, ^3H -buprenorphine, p.o. - single dose (S.A. - 156 mCi/g)

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The major excretory route was the feces, irrespective of route of administration. Over the 7 day period, about 80% was recovered from urine and feces. No significant radioactivity was recovered from urine or feces 14 days after dosing.

Pharmacological literature relating to actions of buprenorphine

There were several buprenorphine publications which were submitted to the NDA. These studies will be cited and briefly summarized.

Kosterlitz, H.W., Leslie, F.M., and Waterfield, A.A. Rates of onset and offset of action of narcotic analgesics in isolated preparations. *Europ. J. Pharmacol.* 32: 10-16, 1975.

Buprenorphine was the most lipophilic narcotic assessed in terms of a partition coefficient (heptane/water) and had a rate of association about 1/7 that of methadone. The rate of offset for buprenorphine was too slow to measure (28% in 90 minutes). The results suggest there is an optimum lipid solubility which ensures rapid penetration into the CNS without a serious slowing down of receptor association and dissociation.

Atkinson, D.C. and Cowan, A. Reversal of yeast-induced motor impairment in rats as a test for narcotic and non-narcotic analgesics. *J. Pharm. Pharmacol.* 26: 727-729, 1974.

The test described is a modification of the Randall and Selitto test. Rats were injected with Brewer's yeast into the left hind paw and then groups of 10 rats were injected with test drugs. Gait was scored as a graded response by a blind observer. The test dose required to produce an antinociceptive response in 50% of the rats was calculated using the minimum logit chi-square test. The test was sensitive to narcotic and antipyretic analgesics.

Martin, W.R., Eades, C.G., Thompson, J.A., Huppler, R.E., and Gilbert, P.E. The effects of morphine and nalorphine-like drugs in the non-dependent and morphine-dependent chronic spinal dog. *J. Pharmacol. Exp. Ther.* 197: 517-532, 1976.

Three different subsets of effects were attributed to three distinguishable receptors (u , k , χ) in the nondependent chronic spinal dog. Morphine is the prototype agonist for the u receptor, ketocyclazocine for the k receptor, and SKF-10,047 for the χ receptor. Buprenorphine was characterized as a partial u agonist which both precipitated and suppressed abstinence in the chronic morphine dependent dog. In terms of intrinsic dependence capacity, buprenorphine had a liminal withdrawal syndrome after naloxone administration. It was predicted that buprenorphine physical dependence in man would be clinically insignificant.

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Costall, B. and Naylor, R.J. Serotonergic involvement with the stereotypy/catalepsy induced by morphine-like agents in the rat. *J. Pharm. Pharmacol.* 27: 67-69, 1975.

Induction of stereotyped behavior is considered to be a result of enhanced dopaminergic function while catalepsy is considered to result from inhibited dopaminergic function. Buprenorphine caused both catalepsy and stereotyped behavior in rats.

The effects of lesioning the dorsal and medial raphe nuclei on catalepsy/stereotypy responses to morphine, buprenorphine or M320 were investigated in the rat. Lesions of both nuclei produced a reduced cataleptic effect of morphine and buprenorphine, and stereotypy became apparent for morphine and enhanced for buprenorphine. The results of this and other studies by these authors suggest that cataleptic/stereotypic balance may depend on both serotoninergic as well as dopaminergic mechanisms.

Cowan, A. Use of the mouse jumping test for estimating antagonist potencies of morphine antagonists. *J. Pharm. Pharmacol.* 28: 177-182, 1976.

Potencies of 19 narcotic antagonists (relative to nalorphine) in the mouse jumping test are presented. A high correlation ($r=0.997$, $p < 0.001$) was observed between quantitative assays based on the total number of jumps per mouse and quantal assays based on mice jumping at least 6 times. A Spearman rank order coefficient of 0.91 was obtained when potency was compared between the mouse test and non-withdrawn morphine-dependent monkeys. Buprenorphine was about equipotent to nalorphine in the mouse jumping test.

Cowan, A., Dettmar, P.W., and Walter, D.S. The effects of buprenorphine, morphine, and pentazocine on turning behavior and stereotypy induced by apomorphine in the rat. *J. Pharm. Pharmacol.* 27: (Suppl.): 15P, 1975.

Buprenorphine (3 mg/kg, s.c.), morphine (10 mg/kg, s.c.) and pentazocine (30 mg/kg, s.c.) all produced ipsilateral turning in unilaterally-lesioned (substantia nigra-6-hydroxydopamine) rats. These analgesics reduced apomorphine-induced circling in lesioned rats in a dose-related manner and slightly potentiated apomorphine stereotypy.

Cowan, A., Dettmar, P.W., and Walter, D.S. Analgesics and rotational behavior in rats with unilateral substantia nigra lesions. Effects in the presence and absence of (+)-amphetamine. *Brit. J. Pharmacol.* 55: 316P, 1975.

Buprenorphine attenuated D-amphetamine-induced turning at 0.10 and 0.30 mg/kg ($p < 0.05$) but not at 0.03 and 1 mg/kg. With morphine (0.03-10 mg/kg) and pentazocine (0.10-30 mg/kg), a significant reduction in turning occurred only at the high dose of each compound.

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Cowan, A., Ghezzi, D., and Samanin, R. Effect of Midbrain Raphe lesions and of 6-hydroxydopamine on the antinociceptive action of buprenorphine in rats. Arch. Int. Pharmacodyn. Ther. 208: 302-305, 1974.

The antinociceptive activity of buprenorphine was little affected by midbrain raphe lesions on 6-hydroxydopamine lesioned animals.

Rance, M.J. and Shillingford, J.S. The role of the gut in the metabolism of strong analgesics. Biochem. Pharmacol. 25: 735-741, 1976.

3 H-labelled samples of dihydromorphine, etorphine, and buprenorphine were used to investigate the role of the gut in metabolism of phenolic analgesics. An everted gut in vitro preparation as well as an in situ absorption preparation were studied. A large proportion (85%) of buprenorphine at a luminal concentration of 1 ug/ml was glucuronidated prior to absorption in the everted gut preparation. Additionally, about 10-11% was dealkylated prior to absorption. A large proportion of etorphine (about 96%) was also conjugated at 1 ug/ml in the everted gut preparation whereas the majority of the absorbed dihydromorphine was the unchanged drug. In the in situ preparation, at 1 ug/ml buprenorphine the conjugated drug was the absorbed species. At 10 ug/ml buprenorphine, the free drug absorbed accounted for 10% of the drug species absorbed. Lipophilicity may determine intestinal conjugation of phenolic analgesic drugs; i.e., buprenorphine and etorphine may be primarily metabolized in the gut whereas the primary site for dihydromorphine metabolism is in the liver.

Costall, B. and Naylor, R.J. A role for the amygdala in the development of the cataleptic and stereotypic actions of the narcotic agonists and antagonists in the rat. Psychopharmacologia (Berlin) 35: 203-213, 1974.

Buprenorphine induced a biphasic behavioral response in rats consisting initially of catalepsy followed by stereotypic gnawing, biting, and licking responses with a transition period in which both behaviors were apparent. Morphine produced a cataleptic response but stereotypy did not develop. Bilateral ablation of the nucleus amygdaloidus centralis abolished the cataleptic phase of buprenorphine and enhanced the stereotypic response. Morphine catalepsy was also abolished in these animals and a stereotypic response developed. The authors hypothesized an amygdaloid cataleptic:striatal stereotypic balance for the action of narcotic agonists and antagonists.

Hambrook, J.M. and Rance, M.J. The interaction of buprenorphine with the opiate receptor: lipophilicity as a determining factor in drug receptor kinetics. In: Opiates and Endogenous Opioid Peptides, edited by H.W. Kosterlitz, Amsterdam, North Holland, p. 259-301, 1976.

Buprenorphine binding in vitro was stereospecific and increased in the presence of Na⁺. Receptor dissociation t_{1/2} was not increased by the addition of 100 mM Na⁺. The authors postulate that a lipophilic partial agonist like buprenorphine has a high ΔG (free energy of activation) and, consequently, is slow to reach equilibrium. Competition between the partial agonist and antagonist may be under kinetic rather than thermodynamic control. In contrast, a hydrophilic agonist (dihydromorphine) would have a low ΔG and would have a fast rate of equilibration. Competition between a hydrophilic agonist and an antagonist would be under thermodynamic control and, thus, antagonism would be more rapidly achieved.

Stephen G.W. and Cooper, L.V. The role of analgesics in respiratory depression: a rabbit model. Anesthesia 32(4): 324-327, 1977.

A respiratory depressant model of induced hypoxia in newborn rabbits was used to study depressant effects of meperidine, meperidine metabolites, fentanyl and buprenorphine (0.1 and 0.5 mg/kg). All drugs were given i.p. 30 minutes prior to the experiment except for meperidine at 5 minutes prior. Animals were placed in a sealed chamber and hypoxia was induced by flushing the chamber with nitrogen (5 liters for 1 minute, then 1 liter per minute). Patterns of breathing were observed and timed. The duration of dyspnea, primary apnea and gasping were measured. Meperidine prolonged the apneic phase and shortened the gasping period as well as the number of gasps. Fentanyl produced an increase in apnea time although not as long as that of meperidine. Buprenorphine (0.1 and 0.5 mg/kg) produced a slight to moderate increase in apnea time. The order of potency for respiratory depression capacity at the doses tested in the newborn rabbit was meperidine fentanyl buprenorphine saline. There was no difference in respiratory depression observed with the low and high dose of buprenorphine.

Cowan, A. Evaluation in non-human primates: Evaluation of the physical dependence capacities of oripavine-thebaine partial agonists in Patas monkeys. Adv. Psychopharmacol. 8: 427-438, 1974.

Buprenorphine precipitated abstinence in cyclazocine-dependent monkeys. There were no physiological signs of withdrawal after abrupt discontinuation or again after naloxone (2 mg/kg, s.c.) challenge. A withdrawal syndrome of mild to moderate intensity was observed after naloxone challenge of monkeys receiving high doses (10 mg/kg) of pentazocine.

Lewis, J.W. and Cowan, A. Rx-6029-M. Presented to the Committee on Problems of Drug Dependence. 34: 514-535, 1972.

A summary of the major pharmacological and toxicological actions of buprenorphine. These data are reviewed elsewhere.

Cowan, A., Doxey, J.C., and Harry, E.J.R. The animal pharmacology of buprenorphine, an oripavine analgesic agent. *Brit. J. Pharmacol.* 60: 547-554, 1977.

Behavioral, cardiovascular, respiratory, gastrointestinal, renal, and antitussive effects of buprenorphine are reviewed in this manuscript. The majority of these data are reviewed elsewhere. Buprenorphine was a potent (30X methadone) antitussive agent against citric acid induced coughing in guinea pigs. At a dose which was 20 times the analgesic ED₅₀ in the rat tail pressure test, morphine was more potent than buprenorphine in suppression of urine output.

Cowan, A., Lewis, J.W., and Macfarlane, I.R. Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. *Brit. J. Pharmacol.* 60: 537-545, 1977.

Antinociceptive profile of buprenorphine in rodents was presented. Buprenorphine had a long duration (6 hours) of action and was more potent than morphine. Antagonist activity was detected against morphine and other narcotics in antinociceptive tests and in precipitation of withdrawal in morphine-dependent mice and monkeys.

Rance, M.J. and Shillingford, J.S. The metabolism of phenolic opiates by rat intestine. *Xenobiotica*. 7: 529-536, 1977.

A series of phenolic opiate agonists and antagonists were studied for conjugation across the rat intestine. The efficacy of conjugation (UDP-glucuronyltransferase) was a function of substrate lipophilicity. With substances such as buprenorphine and etorphine, the gut wall must be regarded as the primary site of metabolism after oral administration.

Matsuki, K., Kato, A., Takei, H., Inomata, E., and Iwabuchi, T. Pharmacological studies on N-cyclopropyl-methyl-7-(1-(s)-hydroxy-1,2,2-trimethyl (propyl)-6,14-endo-ethano-6,7,8,14-tetrahydronororipavine hydrochloride [MR 56] (I) effect on native behavior and analgesic activity in laboratory animals. *Oyo Yakuri* 13: 259-271, 1977.

MR-56 had little effect on behavior except pain responses. Subcutaneously, MR-56 was 18 and 300 times as potent an analgesic as morphine and pentazocine. Orally, MR-56 was 3 and 70 times as potent as morphine and pentazocine in the mouse writhing test.

Francis, D.L., Cuthbert, N.J., Dinneen, L.C., Schneider, C., and Collier, H.O.J. Methylxanthine-accelerated opiate dependence in the rat. In: Opiates and Endogenous Opiate Peptides, edited by H.W. Kosterlitz, Elsevier, Amsterdam, p. 177-184, 1976.

A "quasi-morphine withdrawal syndrome" or "QMWS" can be elicited in rodents by administration of naloxone to animals that had previously received acute doses

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of heroin and 3-isobutyl-1-methylxanthine (IBMX). Buprenorphine (0.01 mg/kg) and IBMX failed to produce as much of a QMWS as with IBMX alone. Buprenorphine also suppressed the QMWS.

Schulz, R. and Herz, A. The guinea pig ileum as an in vitro model to analyse dependence liability of narcotic drugs. In: Opiates and Endogenous Opiate Peptides, edited by H.W. Kosterlitz, Elsevier, Amsterdam, p. 319-326, 1976.

Myenteric plexus-longitudinal muscle strips taken from morphine-tolerant/dependent guinea pigs displayed a tonic contracture when exposed to naloxone. Incubating of tissues with buprenorphine (12 nM) and subsequent naloxone challenge (up to 10 nM) failed to induce a withdrawal sign. In acute experiments, naloxone, up to 5 μ M, failed to reverse the buprenorphine-induced twitch reduction. Recovery in buprenorphine-treated preparations was slow, taking several hours in the presence of the antagonist, naloxone.

Jacob, J.J., Tremblay, E.C., and Michaud, G.M. Antagonism of precipitated abstinence by narcotics, narcotic antagonists and mixed agonist-antagonists. In: Opiates and Endogenous Opioid Peptides, edited by H.W. Kosterlitz, Amsterdam, p. 377-384, 1976.

Buprenorphine was an effective, potent agonist-antagonist which blocked narcotic antagonist precipitated jumping in mice. In rats, buprenorphine also prevented all withdrawal signs produced by naloxone (1 mg/kg, s.c.) in animals treated with morphine 50 mg/kg, s.c.

Wuster, M. and Herz, A. Significance of physico-chemical properties of opiates for in vitro testing. In: Opiates and Endogenous Opioid Peptides, edited by H.W. Kosterlitz, Elsevier, Amsterdam, p. 447-450, 1976.

When a correlation was attempted between concentrations for 50% receptor occupation in a binding assay versus concentrations (ED₅₀) for inhibition of twitch potential, it became obvious that there was an increased activity of the drug on the isolated organ. Lipophilicity or surface activity were suspected to be possible explanations for the observed deviation.

Actual concentrations in the isolated organ were determined after maximal twitch inhibition was established. For hydrophilic drugs like morphine, the concentrations in the bathing medium and the tissue were identical. Lipophilic compounds showed a 5 to 15 fold accumulation in the strip. When the dose-response curves are corrected for the actual drug concentrations in the strip, there was a shift to the right for all compounds (etorphine, fentanyl, loperamide, buprenorphine), except morphine.

Czlonkowski, A., Hollt, V., and Herz, A. Binding of opiates and endogenous opioid peptides to neuroleptic receptor sites in the corpus striatum. *Life Sciences* 22(11): 953-962, 1978.

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Some morphinan and benzomorphan derivatives reduced ^3H -spiroperidol binding with IC₅₀'s in the μM range. Buprenorphine had an IC₅₀ greater than 100 μM . The binding affinities of the opiates for neuroleptic receptors are much higher than the affinities for neuroleptic receptors. The neuroleptic receptor binding of certain morphinan and benzomorphan derivatives may be related to a "bizarre behavior" syndrome observed in rats given very high doses of these compounds. This "bizarre behavior" is not antagonized by naloxone but is antagonized by small doses of dopamine agonists.

Jacob, J.J.C. and Ramabadran, K. Opioid antagonists, endogenous ligands, and nociception. *Europ. J. Pharmacol.* 46(4): 393-394, 1977.

Opioid antagonists (naloxone) enhanced nociceptive reactions in the hot plate test. Buprenorphine pretreatment (10mg/kg, s.c.) prevented the naloxone enhancement of nociceptive reaction time.

Lane, A.C., Rance, M.J., and Walter, D.S. Subcellular localization of leucine-enkephalin-hydrolizing activity in rat brain. *Nature* 269: 75-76, 1977.

Enkephalin-hydrolyzing activity was assayed in brain fractions and subfractions by evolution of ^3H -tyrosine by [^3H -tyr]-leucine-enkephalin. Opiates were studied as possible inhibitors of the enkephalin hydrolyzing enzyme. Etorphine, fentanyl and methadone but not buprenorphine, ketocyclazocine, morphine, nalorphine, naloxone, pentazocine or pethidine inhibited the hydrolytic enzyme.

Jacob, J.J.C. and Ramabadran, K. Enhancement of a nociceptive reaction by opioid antagonists in mice. *Brit. J. Pharmacol.* 64(1): 91-98, 1978.

The narcotic antagonists, naloxone, GPA-2163, levallorphan and MR-2266 reduced the latency of the jumping reaction of mice in the hot plate test. The facilitatory effect of naloxone was not blocked by pretreatment with morphine or etorphine but it was prevented by pretreatment with a high dose of buprenorphine. The enhancing effect of naloxone may be due to an antagonism of endogenous ligands for the opiate receptor. Endogenous ligands may be involved in the reaction to but not the perception of nociceptive stimuli.

Brown, B., Dettman, P.W., Dobson, P.R., Lynn, A.G., Metcalf, G., and Morgan, B.A. Opiate analgesics: the effect of agonist-antagonist character on prolactin secretion. *J. Pharm. Pharmacol.* 30(10): 644-645, 1978.

Morphine increased plasma prolactin levels and naloxone decreased plasma prolactin levels. D-Ala²-Met⁵-NH₂ and Tyr-D-Ala²-Gly-NH₂ increased plasma prolactin levels in a dose-related fashion. Methionine-enkephalin did not produce a significant increase or decrease in plasma prolactin levels.

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Both buprenorphine and cyclazocine decreased plasma prolactin levels. Endogenous peptides may have a role in basal prolactin release.

Pivcic, A.W., Fedele, C.T., and Bierwagen, M.E. A new method for the evaluation of analgesic activity using adjuvant-induced arthritis in the rat. *Europ. J. Pharmacol.* 31(2): 207-215, 1975.

Vocalization displayed by rats injected with adjuvant (mycobacterium butyricum) was defined as an endpoint expression of pain. Analgesics were tested for potency and efficacy against this model of pathological pain. Narcotic agonists and agonist-antagonists but not narcotic antagonists were efficacious in this model. Potencies in this model were in good correspondence to potencies of clinically effective analgesics in man.

Fries, D.S. Narcotic analgetics, endorphins, and the opiate receptor. *Ann. Rept. Med. Chem.* 13: 41-50, 1978.

The author reviews several chemical classes of narcotic analgesics, S-A-R studies of endorphins and endorphin conformations, and evidence for multiple opiate receptors. Buprenorphine is the only oripavine derivative discussed.

Colpaert, F.C. Discriminative stimulus properties of narcotic analgesic drugs. *Pharmacol. Biochem. Behav.* 9(6): 863-887, 1978.

The author reviewed the literature on discriminative stimulus properties of narcotics and concluded that: (1) the chemically heterogenous narcotics generalize with narcotic agonist training drugs; (2) a close correlation exists between narcotic cuing dose and analgesic potency of narcotics; (3) the requirement of steric specificity applies; (4) the cue is naloxone reversible. The data are consistent with the assumption that the narcotic cue in animals is related to and can serve as a preclinical model for opiate-like subjective effects in man. Buprenorphine was equipotent to fentanyl at the level of 50% discrimination but was 1/2 as potent at the level of 100% effect.

Harris, L.S. Interactions of narcotic antagonists. *Ann. N.Y. Acad. Sci.* 281: 288-296, 1976.

Buprenorphine neither exacerbated nor suppressed morphine abstinence in rats.

Dewey, W.L., Patrick, G.A., and Harris, L.S. Annual report: narcotic antagonists in the rat infusion technique. Reported to the Committee on Problems of Drug Dependence, Washington, D.C., May 19-21, 1975.

The author used the 6 day continuous infusion technique of Tieger. Buprenorphine (10 mg/kg/day), pentazocine (20 mg/kg/day) and naltrexone (20 mg/kg/day) failed to substitute for morphine dependence in morphine dependent withdrawn rats.

Martin, W.R., Gilbert, P.E., Eades, C.G., Thompson, J.A., and Huppler, R.E. Progress report of the animal assessment program of the Addiction Research Center. Reported to the Committee on Problems of Drug Dependence, Washington, D.C., May 19-21, 1975.

The data in this report are essentially the same as that in Martin *et al.* J. Pharmacol. Exp. Ther. 197: 517, 1976 article which has been previously noted.

Martin, W.R., Gilbert, P.E., Thompson, J.A., and Jesse, C.A. Progress report of the animal assessment program of the Addiction Research Center: Use of the chronic spinal dog for the assessment of the abuse potentiality and utility of narcotic analgesics and narcotic antagonists.

This is a summary of the data which was published in the Martin *et al.* J. Pharmacol. Exp. Ther. 197: 517, 1976 article. Three distinct receptors are postulated: u receptor which is responsible for producing many of the morphine effects including subjective effects, the k receptor which has the subjective effect of sedation, and the χ receptor which may be related to dysphoric and hallucinatory actions of cyclazocine. Buprenorphine was defined as a partial agonist at the u receptor.

Swain, H.H. and Seavers, M.H. Evaluation of new compounds for morphine-like physical dependence in the rhesus monkey. Reported to the Committee on Problems of Drug Dependence, Washington, D.C., May 19-21, 1975.

At 0.32 mg/kg. s.c., buprenorphine precipitated severe long-lasting (12 hours) abstinence signs. At smaller doses, the abstinence signs were mixed with those of mild, morphine-like depression.

Acute doses of buprenorphine produced signs of mild CNS depression such as those seen with a small dose of a morphine-like drug - body sag, slight ataxia, decreased apprehension, pupil dilatation, and in 2/3 animals, lip smacking. Tolerance developed to these signs.

Animals were dosed with buprenorphine subchronically and precipitated withdrawal was attempted with nalorphine on days 14 and 28 and with naloxone on days 16 and 29. Neither compound precipitated an abstinence syndrome. Abrupt discontinuation of buprenorphine on day 33 also failed to induce a withdrawal syndrome.

Gibbs, J.M. and Johnson, H. Lack of effect of morphine and buprenorphine on hypoxic pulmonary vasoconstriction in the isolated perfused cat lung and the perfused lobe of the dog lung. Brit. J. Anesth. 50(12): 1197-1201, 1978.

In the cat lung and lobar dog lung preparations, a pressor response was elicited to alveolar hypoxia (5% oxygen). Morphine, 4 mg i.v., did not significantly alter the pulmonary vasculature response in the cat. Neither

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morphine, 4 mg i.v., nor buprenorphine, 4 mg i.v., effected a significant change in pulmonary vascular resistance in the lobar dog lung preparation.

Metcalf, G., Rees, J.M.H., and Ward, S.J. In vivo antagonism of analgesia and respiratory depression induced by proposed μ and κ opiate agonists. Proc. Brit. Pharmacol. Soc. Brit. J. Pharmacol. 66(3): 473 (p), 1979.

The μ agonists morphine and methadone and the κ agonists ketocyclazocine and ethylketocyclazocine were investigated for effects on hot plate reaction time and respiratory rate. All four agonists produced dose-dependent increases in hot plate reaction time and depression of respiratory rate. Both naloxone and SKF 10,047 caused a dose-dependent antagonism of these agonist actions.

Martin, W.R. History and development of mixed opioid agonists, partial agonists and antagonists. Brit. J. Clin. Pharmacol. 7 (Suppl. 3): 273S-278S, 1979.

The author presented the history of agonist-antagonist and antagonist development from N-allylnorcodeine to N-allylnormorphine to the benzomorphans pentazocine and cyclazocine to naloxone. He discussed his three opiate receptor (μ , κ , δ) theory in relation to the term agonist-antagonist. The term agonist-antagonist has two meanings: (1) it can indicate that the drug is a partial agonist of a certain receptor type (μ , κ , δ), and (2) the drug may be an agonist at one receptor and an antagonist (partial agonist or competitive antagonist) at another receptor.

Rance, M.J. Animal and molecular pharmacology of mixed agonist-antagonist analgesic drugs. Brit. J. Clin. Pharmacol. 7 (Suppl. 3): 281S-286S, 1979.

The author discussed the pharmacological profile of agonist-antagonist analgesics in terms of drug receptor theory of single and multiple receptors. Evidence for multiple opiate receptors has been reviewed. The pharmacologic and pharmacokinetic profiles of buprenorphine were highlighted. The receptor kinetics of buprenorphine are suggested to attenuate withdrawal symptomatology as homeostatic mechanisms are allowed to slowly re-equilibrate.

Jacob, J.J.C., Michaud, G.M. and Tremblay, E.C. Mixed agonist-antagonist opiates and physical dependence. Brit. J. Clin. Pharmacol. 7 (Suppl. 3): 291S-296S, 1979.

The author discussed various methods for assessment of opiate agonist-antagonists. Buprenorphine has a low intrinsic physical dependence capacity but substituted for morphine in morphine dependent withdrawn mice and partly substituted for morphine in withdrawn subacutely morphine-treated rats. In morphine-dependent withdrawn dogs, buprenorphine substituted for

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morphine although buprenorphine had a shallower slope. Buprenorphine was the most potent and longest lasting drug in preventing precipitated abstinence in mice, rats, and dogs. The low physical dependence capacity of buprenorphine may result in part from the slow receptor dissociation of the buprenorphine-receptor complex.

Rance, M.J. and Dickens, J.M. The influence of drug receptor kinetics on the pharmacological and pharmacokinetic profiles of buprenorphine In: Characteristics and Functions of Opioids: Proceedings of the International Narcotic Research Conference, Noordwijkerhout, Netherlands, July 23-27, 1978, edited by J.M. Van Ree and L. Terenius, Elsevier, Amsterdam, 1978, p. 65-66.

Diprenorphine reduced the level of stereospecific binding of buprenorphine when administered 15 minutes before, concurrently with, or 15 minutes after 3 H-buprenorphine though the effect of the antagonist when administered after 3 H-buprenorphine was significantly reduced. In vivo, a high dose of diprenorphine promoted a dissociation rate from the receptors similar to that seen in vitro ($t_{1/2}$ @ 60 min.).

Manara, L., Cerletti, C., Luini, A., and Tavani, A. Rat brain levels and subcellular distribution of in vivo administered buprenorphine: effect of naloxone. In: Characteristics and Function of Opioids: Proceedings of the International Narcotic Research Conference, Noordwijkerhout, Netherlands, July 23-27, 1978, edited by J.M. Van Ree and L. Terenius, Elsevier, Amsterdam, 1978, p. 225-226.

Naloxone pretreatment was more effective than administration after buprenorphine in terms of reducing the brain subcellular (microsomal P₃ fraction) distribution of buprenorphine. The results may be consistent with the reports of buprenorphine's limited reversibility by narcotic antagonists.

Bryant, R.M., Olley, J.E., Tyers, M.B., and Marriott, A.S. Antinociceptive activities of buprenorphine, morphine, and tilidine injected into the medial raphe nucleus of the conscious rat. In: Characteristics and Function of Opioids: Proceedings of the International Narcotic Research Conference, Noordwijkerhout, Netherlands, July 23-27, 1978, edited by J.M. Van Ree and L. Terenius, Elsevier, Amsterdam, 1978, p. 415-416.

Buprenorphine, morphine and tilidine were effective analgesics in the rat paw pressure and hot plate tests by both subcutaneous injection and intracerebral injection into the medial raphe nucleus.

Toxicity Studies:

Most of the acute toxicity data has been previously submitted and reviewed in IND 11-109 and 11-142. These previously submitted data will be added for the sake of completeness.

Acute Toxicity of Buprenorphine vs. Morphine

(1) Performed at both Reckitt and Colman and Lederle Labs

Species	Sex	Route	LD ₅₀ (mg/kg) + 9.5% confidence limits	
			Buprenorphine	Morphine
Mice	M	i.v.	24 (21-27)	190 (165-217)
	F	i.v.	28 (26-31)	179 (163-197)
	M	i.p.	97 (84-112)	---
	F	i.p.	90 (64-126)	---
	M	s.c.	---	506 (445-575)
	F	s.c.	exceeds 600	733 (635-845)
	M	p.o.	261 (225-291)	exceeds 800
	F	p.o.	260 (223-304)	exceeds 800
Rats	M	i.v.	38 (28-51)	86 (54-136)
	F	i.v.	31 (26-37)	87 (58-130)
	M	i.p.	197 (145-268)	---
	F	i.p.	288 (214-387)	---
	M	s.c.	exceeds 600	164 (128-209)
	F	s.c.	exceeds 600	229 (179-294)
	M	p.o.	exceeds 600	461 (376-565)
	F	p.o.	exceeds 600	281 (218-362)

In mice, buprenorphine was more toxic on a mg for mg basis. However, buprenorphine is also far more potent than morphine in its pharmacological spectrum. Thus, the ratio of pharmacological to toxicological indices compares favorably for buprenorphine relative to morphine.

In the rat, buprenorphine was far less toxic than morphine when administered by the i.v., s.c., or oral routes.

No pharmacotoxic signs were reported in either study.

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The manufacturer, Reckitt and Colman, have performed acute toxicity studies in both mice and rats using a variety of strains as well as several vehicles for buprenorphine (saline, water, citrate buffer). In Vol. 1.1 of the New Drug Application submission the studies were tabulated with respect to species, strain, weight range, group size, route of administration, drug vehicle, dose volume, LD₅₀ (mg/kg) and 95% confidence limits for 24 hours and 7 days. These tables will be reproduced below in their entirety.

TABLE 1: Acute Median Lethal Doses of Buprenorphine in Mice

Strain	Sex	Weight range (gms)	Group Size	Route	Drug Vehicle	Dose Volume (ml/kg)	LD ₅₀ (mg/kg)		95% C.L. (mg/kg)	
							24 hr	7 day	24 hr	7 day
ASL	M	18-22	20	i.v.	saline	20	23.8	23.8	19.6-26.7	19.6-26.7
T0/ASL/R	F	18-22	10	i.v.	saline	20	29.1	28.5	26.4-31.8	25.3-31.5
ASL	M	18-22	10	i.p.	water	20	96.7	96.7	76.5-111.0	76.5-111.0
T0/ASL/R	F	18-20	10	i.p.	water	20	100.9	90.1	78.5-144.2	61.8-162.3
O.L.A.C.	M	18-22	10	s.c.	citrate buffer	60	>150-300	>150-300	-	-
O.L.A.C.	M	--	10	s.c.	saline	60	>600	>600	-	-
O.L.A.C.	F	20-22	10	s.c.	saline	600	>600	>600	-	-
ASL	M	18-20	10	p.o.	water	40	261.4	261.4	223.5-292.9	223.5-292.9
T0/ASL/R	F	18-20	10	p.o.	water	40	260.1	260.1	178.6-309.4	178.6-309.4

Comments: 1) Diet: Spiller's No. 1 (small animal diet)
 2) orally dosed animals were starved overnight before dosing and fed one hour after dosing
 3) LD₅₀ values were calculated on the method of maximum likelihood

TABLE 2: Acute Median Lethal Doses of Buprenorphine in Mice

Strain	Sex	Weight range (gms)	Group Size	Route	Drug Vehicle	Dose Volume (ml/kg)	LD50 (mg/kg) +95% C.L.	Comments
ASL T.0.	M	18-22	20	i.v.	saline	20	23.8 (21-27)	Straub tail convulsions
T0/ASL/R	F	18-22	10	i.v.	saline	20	28.5 (25.9-31.3)	Straub tail convulsions
ASL T.0.	M	18-20	10	p.o.	water	40	261.4 (234.7-291.2)	Straub tail convulsions
T0/ASL/R	F	18-20	10	p.o.	water	40	259.9 (222.6-303.6)	
LACA	M	18-24	10	i.m.	-	-	>100	No deaths
LACA	F	18-24	10	i.m.	-	-	>100	No deaths

Comments: 1) orally dosed animals were starved overnight before dosing and fed one hour after dosing

2) LD50 values were calculated at 7 days by the method of χ^2

3) It was impractical to dose rodents intramuscularly with a dose volume greater than 1 ml/kg and still be reasonably sure that the drug did not leak outside the epimysium.

TABLE 3: Acute Median Lethal Dose of Buprenorphine in Rats

Strain	Sex	Weight Range (gms)	Group size	Route	Drug Vehicle	Dose Volume (ml/kg)	LD ₅₀		95% C.L.	
							24 hrs	7 days	24 hrs	7 days
CFY/R/B4	M	60-80	10	i.v.	saline	10	40	38	--	--
CFY/R/B4	F	60-80	10	i.v.	saline	10	31	31	21.4-36.4	21.4-36.4
CFY/R/B4	M	60-80	10	i.p.	saline	40	234.2	197.3	155-314	114-263
CFY/R/B4	F	60-80	10	i.p.	saline	--	367.5	287.5	292-483	183-405
0.L.A.C.S.D.	F	60-80	10	i.p.	saline	60	237.7	213.3	192-296	177-259
0.L.A.C.S.D.	M	60-80	10	s.c.	saline	60	>600	>600	>600	>600
0.L.A.C.S.D.	F	60-80	10	s.c.	saline	60	>600	>600	>600	>600
CFY/R/B4	M	60-80	10	p.o.	water	40	>600	>600	>600	>600
CFY/R/B4	F	60-80	10	p.o.	water	40	>600	24 hr	14 day	
SIV	M	170-175	10	i.m.	dextrose	--	>100	>100	>100	>100
SIV	F	170-175	10	i.m.	dextrose	--	>100	>100	>100	>100
SIV	M	165-185	10	i.v.	saline	5	26.0	25.5	24.8-27.3	23.8-27.3
SIV	F	165-185	10	i.v.	saline	5	21.3	21.3	19.9-22.8	19.9-22.8

LD₅₀ values in the young rats were calculated using the method of χ^2 .
 The method of Litchfield and Wilcoxon was used in the older rats.

In addition, the comparative acute toxicity of buprenorphine in rodents was presented to the Controlled Substances Advisory Committee in 1978. The results are presented below:

TABLE 4: Comparative Toxicity of four analgesic drugs in the rodent

Drug administered	Mouse LD ₅₀ (mg/kg)			Rat LD ₅₀ (mg/kg)		
	i.v.	s.c.	p.o.	i.v.	s.c.	p.o.
propoxyphene HCl	28	211	282	15	134	230
pentazocine	22	125	330	21	174	---
propiram	48.2	280	1042	--	366	1289
buprenorphine	27	600	260	38	600	600

Additional i.m. and i.v. acute toxicity studies in rodents were done for Reckitt and Colman at Laboratorium fur Pharmakologie und Toxicologie, Hamburg, Germany.

STRAIN = Sprague Dawley SIV, 170-175 gms (n=10/group, 3 groups of ♂ and ♀)
 LD₅₀ value = Litchfield-Wilcoxon at 14 days

TABLE 5: LD₅₀ of buprenorphine in Sprague-Dawley rats

Drug	# of animals	Route	LD ₅₀ (mg/kg)	Toxic Signs
buprenorphine	30 M	i.m.	100	sedation at 68 mg/kg
	30 F	i.m.	100	dyspnea at 100 mg/kg; no reduction in body wgt; no specific pathology or injection site problems
	60 M	i.v.	26 (24.8-27.3)	sedation, ataxia, dyspnea at 14.7 mg/kg; 14.7 mg/kg; reduced food intake, miosis, reduced muscle tone (17.8 mg/kg), dorsal recumbency (31.8 mg/kg)
	60 F	i.v.	21.3 (19.9-22.8)	-death usually occurred within 2-5 min. Animals recovered within 60 min. of dosing.

LD₅₀ studies were also performed on desalkyl buprenorphine and N-butenyl nor-buprenorphine, a trace contaminant of buprenorphine. The butenyl nor compound was about 1/10 as potent an antagonist but 25 times more lethal than buprenorphine.

The desalkyl buprenorphine was tested in mice and rats by a variety of routes of administration in different strains of animals than buprenorphine. The desalkyl was tested in BKW mice and SD B and K rats (see Tables 1, 2, and 3).

TABLE 6: LD₅₀ (mg/kg) in mice of buprenorphine and its desalkyl metabolite

Sex	Route of Administration	desalkyl buprenorphine	buprenorphine
M	i.v.	23	23.8
F	i.v.	23	28.5
M	s.c.	44.8	600
F	s.c.	47.6	600
M	p.o.	154	261
F	p.o.	146	259
M	i.m.	10	100
F	i.m.	10	100

TABLE 7: LD₅₀ (mg/kg) in rats of buprenorphine and its desalkyl metabolite

Sex	Route of Administration	desalkyl buprenorphine	buprenorphine
M	i.v.	13.8	38
F	i.v.	14.9	31
M	s.c.	56.2	600
F	s.c.	41.9	600
M	p.o.	518.7	600
F	p.o.	373	600
M	i.m.	10	100
F	i.m.	10	100

In mice, toxic signs associated with desalkyl buprenorphine were straub tail, exophthalmos, convulsions, and coma, mixed signs, of CNS depression and stimulation. In the rat, toxic signs were similar with the addition of chewing movements. The toxic symptomatology of desalkyl buprenorphine and buprenorphine are similar in the rodent. Desalkyl buprenorphine was more toxic than buprenorphine when administered orally and subcutaneously. In the rat, desalkyl was somewhat more toxic intravenously and far more toxic than buprenorphine when administered subcutaneously.

Interactional acute toxicity studies between buprenorphine and other CNS active drugs were performed in male mice. The studies were performed at Reckitt and Colman Laboratories in England. Aspirin in doses of 35 to 140 mg/kg had no effect on buprenorphine toxicity. Desmethylimipramine (20 mg/kg) or diazepam (2.5 mg/kg) decreased toxicity from 40 to 10 and 40 to 20 percent, respectively. Tranylcypromine at 5 but not 1.25 or 2.5 mg/kg decreased toxicity of buprenorphine. Phenobarbital 10 mg/kg, s.c. and prednisolone (7 x 5 mg/kg, s.c.) both increased death due to buprenorphine administration.

Species: Dog

Study - Acute, single dose toxicity profile and LD₅₀ of buprenorphine, i.v.
Site: Laboritorium fur Pharmakologie und Toxikologie, Hamburg, Germany

Toxic signs were observed at a dose of 2 mg/kg. Dogs reached up to 79 mg/kg without expiring. Two dogs given 100 mg/kg expired. The LD₅₀ was taken to be > 79 mg/kg but < 100 mg/kg.

TABLE 7: Dose-related toxic signs in dogs following i.v. buprenorphine

<u>Dose</u> <u>mg/kg, i.v.</u>	<u>Toxic Signs</u>
2	sedation
10	apathy and ataxia for 30 min. to 4 hours
50.4	ventral recumbency for 1-2 minutes
79.0	marked tremor and epileptiform tonic-clonic seizures but animals survived
100	immediate salivation, marked retching, and vomiting, convulsions, mydriasis, hyperpnea and death at 2.5 and 3 hours in 2/2 dogs

In the EKG, heart rate increased above 1 mg/kg doses. With the exception of male dogs receiving 63.5 or 79 mg/kg and females receiving 50.4 or 78 mg/kg, mild bradycardia was observed in the animals approximately 5 minutes after dosing.

Some local tissue reactions in the form of small hematomas at the injection site were observed. Urinalysis was unremarkable. At autopsy, edema of the lungs was observed in the dogs that died.

Species - Baboon (Papio anubis)

Study - Acute toxic symptoms and LD₅₀ of buprenorphine following a single

i.v. dose

Site - Laboritorium fur Pharmakologie und Toxikologie, Hamburg, Germany

Effects observed were both local and systemic. Local effects were characterized by induration at the injection site and the adjacent tissue showed inflammatory swelling. These changes were observed at 20 mg/kg and were severe at 40 mg/kg.

Systemic reactions included salivation at 40 and 80 mg/kg of buprenorphine immediately after dosing. Both animals given 80 mg/kg of buprenorphine died within 3 hours while the animals given 40 mg/kg survived. Thus, the LD₅₀ was estimated to be between 40 and 80 mg/kg. Tremor and ataxia were observed in the male baboon given 40 mg/kg. Respiration was reduced at 5 minutes after 40 mg/kg but the rate returned to normal within 30 minutes. The EKG of animals given 40 mg/kg showed a bradycardia which appeared and resolved with the same time-course as respiratory depression. The female given 40 mg/kg had tonic-clonic spasms for the first 30 minutes followed by 30 minutes of lateral recumbency followed by 3 hours of ventral recumbency.

In the animals given 80 mg/kg of buprenorphine, i.v., tremors were seen immediately. Tonic-clonic spasms were soon afterwards observed. These episodes recurred every 10-20 minutes until animals were moribund and then died. EKGs immediately preceding death had evidence of bundle branch block. During the dosing period, the heart rate steadily decreased.

There was no effect at any dose level on body temperature, urine, or pupil diameter. Microscopic observation of the two 80 mg/kg baboons at autopsy revealed no specific pathological changes other than local effects.

Subchronic Toxicity Studies with Buprenorphine

Subacute toxicity of buprenorphine

Species/Strain: Rat, Wistar

Site:

b(4)

No. of rats/dose level: 10/sex

Dose levels: 0, 3.2, 16, 80 mg/kg

Route: gavage (5% acacia)

Duration: 4 weeks (dosing 7 days/week)

Two low dose and one mid-dose male died of dosing accidents during the last week of the study. No pharmacotoxic signs were observed during the first two weeks of the study but afterward animals became aggressive and attempted to bite, claw, and struggle with the animal handlers. The effect was neither dose-related nor consistent enough to justify a conclusion of a drug effect.

The treated males showed a uniform (about 10%) weight loss and a non-dose-related depression of food consumption. Treated females showed a non-dose-related decrease in food consumption with HD females showing severe weight loss (about 35%) over the first three weeks but regained all the weight by week 4.

Hematology and urinalysis parameters revealed no drug-related adverse effects. Treated males and high dose females had elevated SGOT values in the high normal range. Mid and HD males and MD females showed dose-related terminal elevations in Na which were in the high normal range. Mid and HD males and HD females showed decreased serum cholesterol.

At necropsy, organ weight changes were not supported by histopathological findings. The decreased organ weight of the liver and kidney in treated males may have been due to glycogen depletion secondary to decreased food consumption. Gross pathology exams were normal and histopathology on control and HD rats revealed no apparent drug related changes.

Species/Strain: Rat/C.F.Y.

Site: Reckitt and Colman, Ltd., Hull, England

No. of Rats/dose level = 20/sex at 0, 0.2, 1.0, and 5.0 mg/kg

Route: Subcutaneous (saline vehicle with pH @ 4)

Duration: 30 days

All rats survived the study. The initial dose produced respiratory depression and sedation which lasted for four hours in the LD group and less than 24 in the HD group. After day 8, LD and MD rats chewed their own hair and their diet cubes excessively. This behavior was suggestive of a dopaminergic-mediated stereotypy and produced some bald patches on the animals. HD rats from day 8 on showed variable signs ranging from excited behavior as described above to normal behavior and sedation. Frequently, the sedation followed a period of excitation.

Treated males showed weight gain depression inversely related to the dose administered. Treated females showed slight non-dose-related weight gain depression. Food intake data paralleled the body weight gain data.

Hematology, serum chemistry and urinalysis parameters failed to reveal any adverse drug-related effects.

Gross and histopathological analysis of tissues revealed no apparent drug-related abnormalities. Liver and kidney weights in the treated males were lower than the corresponding control organ weights. The effect may be secondary to glycogen depletion following depressed food intake.

Species/Strain: Rat, Wistar

Site: England for D.A.E.

b(4)

No. of rats/dose level: 10/sex

Dose levels: 0, 0.1, 1.0, and 5 mg/kg in two divided doses daily.

Route: i.m. (5% dextrose). alternating hind limbs

Duration: 6 months

Mortalities occurred during the study as follows:

Control:

one female during week 9 (faulty cardiac puncture)

one female sacrificed during week 8 (middle ear infection)

one female died during week 11 and another female died during week 19
(both of unknown causes)

Low Dose:

one male during week 26 (faulty cardiac puncture)

Mid Dose:

one male during week 26 (faulty cardiac puncture)

one female during week 18 and another female during week 19 (both of
unknown causes)

High Dose:

one male during week 14, one male and one female during week 24
(all of unknown causes)

In cases where cause of death was unknown, gross necropsy failed to yield further information. Deaths from cardiac puncture accidents were confirmed by gross necropsy.

Treated animals manifested dose-related aggressive behavior. Rats tended to fight among themselves and attempted to bite the handlers when being dosed. This aggressive behavior was evident for 30 minutes after treatment and then the rats became docile. Low and mid dose animals showed a reduction in aggressive behavior by the end of the third month. By the end of the fourth month, aggressive behavior had disappeared in low and mid dose rats.

During week 7 of the study, HD males developed diarrhea which resolved in half the animals by week 9. In the remaining HD animals, diarrhea was no longer observed after the fifth month.

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Hematology, clinical chemistry and urinalysis parameters were not adversely affected by drug treatment.

At necropsy, liver and heart weights of the treated male animals were marginally reduced. Organ weight changes were not supported by histopathological findings. However, rats that had been subjected to cardiac puncture for blood sampling showed changes in the myocardium reflecting this procedure. Gross and histopathological analysis failed to reveal any organ-related toxicity. Control and treated animals showed muscle degeneration with some evidence of fibrosis in the area of the injection sites. As this effect was observed in control animals, it may be attributed to the repeated injection procedure per se.

Species/Strain or breed: dog, beagle
Site: Reckitt and Colman Ltd., Hull, England
No. of dogs/dose level: 3/sex
Dose levels: 0, 0.2, 1.0, 5.0 mg/kg
Route: s.c. (saline) - dose volume = 0.33 ml/kg
Duration: 30 days

One Hd male died on day 28. The cause of death was not established but necropsy and histopathological analysis revealed infections at the site of injection, pneumonitis, thymic hemorrhages, and fatty changes in the liver and kidneys.

Initially, treated animals showed sedation and ataxia for 30 to 120 minutes; thereafter, behavior was normal. One dog/sex at the HD salivated before the first dose and several of the treated dogs vomited before or after dosing during the first 6 days of the study.

Treated males showed a weight gain depression which was non-dose-related. Treated females showed a dose-related weight gain depression. Treated dogs ate less than controls.

Hematology, bone marrow smears, clinical chemistry and urinalysis revealed no apparent drug-related effects.

Gross pathology revealed no drug-related effects other than injection site necrosis in 1/6 MD and 1/6 HD dogs. Histopathology showed slight centrolobular fatty changes in the liver and in the renal tubular epithelium in HD males and to a lesser degree in treated females.

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Species/Strain or breed: dog, beagle, purebred
 Site: Laboratorium fur Pharmakologie und Toxikologie, Hamburg, Germany
 No. of animals/dose level: 3/sex
 Dose levels: 0, 0.5, 4.0, 32 mg/kg
 Route: intravenous (saline vehicle 3.2 ml/kg), rotating veins
 Duration: 4 weeks

<u>Dose</u>	<u>Drug Vehicle and Concentration</u>		
0	3.2 ml/kg saline		
0.5	5% dextrose	0.016%	
4.0	5% dextrose	0.125%	
32.0	original	1.0%	

All dogs survived the study.

<u>Effect</u>	<u>Control</u>	<u>LD</u>	<u>MD</u>	<u>HD</u>
food and water intake	baseline	no effect	slight reduction	significant reduction
body weight	baseline	no effect	no weight gain during study	5% body weight loss in males and females
injection site	no remark	induration (3-12 mm) and edema. Healed within 7-14 days.	induration (15 mm) and edema with small thrombus formation. Healed within 7-14 days.	immediate induration and edema. Thrombi formed up to 10 cm long. Partial healing but none complete by end of study.

EKGs were normal in control and LD dogs. MD and HD dogs showed slight and marked bradycardia, respectively, 5 minutes after buprenorphine administration. At the end of the study, the HD animals' heart rate was significantly decreased before and 5 minutes after the last administration. No significant changes were observed in the P-Q or Q-T intervals. Systolic and diastolic blood pressures in both the general and pulmonary circulation as well as response to noradrenaline stress were unaffected by drug treatment.

Ophthalmological examination in all groups revealed no pathological findings at the end of the treatment period. A simple noise test indicated no impairment of hearing acuity.

Hematologic parameters (Hb, RBCs, WBCs, differentials, hematocrit, thromboplastin time, platelets, reticulocytes, blood clotting time, and ESR) were unaffected by 0.5 to 40 mg/kg, i.v. buprenorphine. However, the ESR at both 1 and 2 hours showed a trend towards an increase.

Clinical biochemistry indicators (glucose, BUN, Na^+ , K^+ , Cl^- , Ca^+ , uric acid, total protein, bilirubin, creatinine, serum alanine aminotransferase (SGPT), serum aspartate aminotransferase (SGOT), alkaline phosphatase, electrophoresis of serum proteins and the BSP test) were unaffected by drug treatment.

Urinalysis (color, pH, S.G., protein, glucose, bilirubin, ketones, Hb, and microscopy) revealed occasional protein which was considered to be of spontaneous origin in 1 LD female.

At necropsy, there were no significant changes in absolute or relative organ weights. Histological examination of 36 tissues was performed. These were:

heart	prostate/uterus	trachea
lungs	stomach	aorta
liver	duodenum	esophagus
spleen	jejunum	pancreas
Kidney	ileum	lymph node
adrenals	colon	peripheral nerve
thymus	rectum	skeletal muscle
pituitary	salivary gland	skin
gonads	eye	tongue
thyroid	urinary bladder	spinal cord
brain	bone marrow	gall bladder
		bone
		mammary glands

Histopathology confirmed the dose-related nature of the injection site lesions. At 0.5 mg/kg buprenorphine, mild perivasculitis and slight venous stenosis were observed. At 4.0 mg/kg, edema and inflammation, occasional thrombus formation, marked lesions of the venous wall and moderate obliteration were observed. At 32 mg/kg, the lesions were similar but marked to severe in appearance. Other possibly treatment-related effects were dilation of zona glomerulosa in the adrenals (2 males and 1 female at the 4.0 and 32 mg/kg groups), cell depletion in the spleen (3/6 HD dogs), slight localized testicular atrophy (1/3 LD males), moderate localized testicular atrophy (1/3 HD males) and moderate diffuse testicular atrophy (1/3 HD males).

Species/Strain: Monkey, _____

b(4)

Site: _____

No. of monkeys/dose level: 3/sex

Dose: 0, 3.2, 16, 80 mg/kg

Route: gavage (vehicle=5% acacia); volume = 2 ml/kg

Duration: 4 weeks

Doses in this study were 64, 320, and 1600 times the proposed human therapeutic dose (.05 mg/kg).

One HD female died on day 14 of the study. This animal showed malaise and anorexia on day 5 which became worse as time passed. This animal showed marked weight loss accompanied by wheezing, severely retarded reflexes, bloody diarrhea, and limb weakness. During the second week of dosing this monkey was virtually inactive, wheezed audibly, and vomited within 30 minutes of treatment.

Gross necropsy revealed hemorrhagic areas in the trachea and lungs with blood grossly visible in the G.I. tract although no lesions were present in the G.I. tract. Histopathology showed marked congestion with alveolar hemorrhages in the lungs. Death was ruled to be due to a pulmonary infection.

Except for occasional slight salivation seen within a few seconds after dosing in MD and HD monkeys, no pharmacotoxic signs were observed. Body weight gain was depressed in a non-dose-related fashion. During the final week of the study, the treated animals showed slight weight losses. Food consumption, although not measured, was observed to have dropped off after 4 or 5 days of dosing.

Hematology, clinical chemistry, and urinalysis revealed no apparent drug-related alterations. Liver and kidney weights were reduced in all treated groups but relative organ/body weight ratios were normal.

Gross necropsy and histopathological analysis did not reveal any drug related abnormalities attributable to a dose of up to 80 mg/kg day, p.o., of buprenorphine.

b(4)

Species/Strain: Monkey,

Site: Lederle Labs, U.S.A. _____

No. of monkeys/dose level: 2/sex

Dose: 0, 0.032, 0.32, 1.6 mg/kg/day

Route: sublingually or into buccal pouch in 2 equally divided doses in the morning and afternoon

Duration: one month

No deaths occurred during the study. In addition to the usual clinical parameters to be evaluated, EKGs, tests of adrenal function, testicular

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biopsies, and testicular measurements were obtained. Assay of blood drug concentration on day 27 revealed that the LD did not produce detectable blood levels but the 0.32 and 1.6 mg/kg doses produced peak blood levels at one hour after dosing; i.e., 1.5 ug/ml and 19 to 28 ug/ml, respectively.

There were no apparent drug-related effects on the oral mucosa or the results of the clinical pathology assays, adrenal function, electrocardiogram, testicular function, or any gross or histopathological changes.

b(4)

Species/Strain:

Site:

No. of animals/dose level: 3/sex

Dose levels: 0, 0.02, 0.60, 18.0 mg/kg (as base)

Route: intravenous (1.8 ml/kg), rotating veins

Duration: 4 weeks

<u>Dose</u>	<u>Drug Vehicle</u>	<u>Concentration</u>
0	saline	isotonic at 1.8 ml/kg
0.02	5% dextrose-water	0.0011
0.60	5% dextrose-water	0.033
18.0	undiluted original	1.0

All animals survived the study although the HD group was discontinued after 9 days due to obliteration of veins used for injections. During the dosing period, no changes in behavior were observed due to buprenorphine treatment. Food intake and body weight were unaffected by 0.02 and 0.6 mg/kg buprenorphine but the 18 mg/kg group had a decreased food intake and a loss (10%) of body weight in 9 days.

Hematological parameters (Hb, RBCs, WBCs, differentials, hematocrit, thromboplastin time, ESR, clotting time, platelet and reticulocytes) were unaffected by 0.02 and 0.06 mg/kg buprenorphine while the leucocyte count, reticulocytes, and ESR were elevated in the high dose group. The changes observed may have been secondary to an inflammatory process at the injection sites.

Clinical biochemistry measurements (Na⁺, K⁺, Cl⁻, Ca⁺⁺, SGOT, SGPT, alkaline phosphatase, BUN, glucose, protein, uric acid, bilirubin, albumin, globulin, A/G ratio, Bromsulphthalein test and creatinine) were unaffected in the LD and MD groups while SGPT and SGOT values were elevated from 18 to 36 and 16 to 28 units/liter, respectively. The enzyme changes were not statistically significant at the p<0.01 level.

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Urinalysis parameters (color, specific gravity, glucose, bilirubin, hemoglobin, ketone bodies, pH, and sediment microscopy) were unaffected by drug treatment.

Electrocardiograms were recorded before and 5 minutes after dosing with the animal in a sitting position (if possible) using limb leads I-III. Limb lead II was also evaluated. Buprenorphine produced a non-statistically significant ($p < 0.01$) decrease in heart rate without changes in PQ and QT intervals. Systolic and diastolic blood pressure as well as response to norepinephrine challenge were unchanged by all dose levels of buprenorphine.

At necropsy, adrenal weights were significantly increased and pituitary weights were significantly decreased in the MD group. Edema of the lungs was observed in 3/6 MD and 3/6 HD animals. The HD group also had microscopic pathology at the injection sites consisting of thrombotic sections up to 10 cm., induration of the vascular wall and paravenous tissues, and swelling of the surrounding tissue. No gross or microscopic changes were observed in the following tissues examined:

heart	prostate/uterus	trachea
lungs	stomach	aorta
liver	duodenum	esophagus
spleen	jejunum	pancreas
kidney	ileum	lymph node
adrenal	colon	peripheral nerve
thymus	rectum	skeletal muscle
pituitary	salivary gland	skin
gonads	eye	tongue
thyroid	urinary bladder	gall bladder
brain	bone marrow	bone
		mammary glands

Species/Strain: Baboon

b(4)

Site:

No. of animals/dose level: 3/sex

Dose levels: 0, 0.05, 0.5, 5 mg/kg buprenorphine

Route: i.m. (5% glucose)

Duration: 26 weeks

All baboons survived the study.

The most outstanding clinical observation of the study was that some of the animals had fright reactions to the injection, more so in the HD group. As the study progressed these baboons showed a greater degree of fright. Minimal

hemorrhage and/or drug leakage from the injection site was observed in a few control and treated monkeys, more so in the HD animals with the incidence increasing as the study progressed.

Swelling of the musculature at the injection site consisting of discrete masses were found in all HD baboons. These masses were distinct by week 6 and were present at all injection sites by week 20. These indurations caused an increase in mechanical resistance to dosing and may be the cause of hemorrhage and leakage in these animals. These changes were not seen in low, mid-dose, or control animals.

Several monkeys developed abcesses at injection sites during the study, the majority being in the HD group. When deemed necessary, dosing was suspended for 1-3 days and in one instance for 2 weeks.

Body weight gain and food intake were not affected by drug treatment although water intake was decreased in HD baboons.

High dose monkeys showed a slight decrease in Hb at termination; however, RBCs and hematocrit were not significantly affected. Other hematological parameters were unaffected by drug treatment.

Clinical chemistry revealed a slight increase in blood glucose in high dose monkeys and a dose-related increase in globulin. High dose monkeys showed a concomitant decrease in A/G ratio. These changes were attributable to local inflammatory reactions due to i.m. injection and subsequent abcess formation.

Urinalysis parameters were not changed by drug treatment.

Relative and absolute organ weights were unaffected by drug treatment. Gross pathology revealed hemorrhages and fibrosis at the injection sites. Histopathology revealed no apparent drug-related organ toxicity with the exception of hemorrhage, loss of muscle fibers with fibrosis and edema, and chronic inflammatory reactions at the injection sites.

Teratology and Reproduction Studies

Type of Study: Segment II teratology study of buprenorphine in rats (Sprague Dawley) 198-250 gms.

b(4)

Site:

No. of pregnant females/dose level: 24

Dose levels: 0, 0.05, 0.20, 0.80 mg/kg

Route: i.v. (diluent: dextrose 5% - water)

Duration of dosing: days 6-15 of gestation

Period of Study: January to June 1979

Sacrifice Day: day 20 of gestation

Maternal observations: Dose-related inflammatory changes at the injection sites progressed from slight hemorrhages in the LD group to large hemorrhages with thrombi up to 3 cm in length.

In the control, LD and MD groups there was no apparent difference in behavior and appearance, food and water intake and body weight gain. In the HD group, food intake was slightly reduced but all other parameters in the HD group were similar to controls.

At necropsy, no pathological changes were observed with the exception of the aforementioned lesions at the injection site. Both MD and Hd groups had evidence of thrombi.

Fetal Observations:

Parameter	Group I control <u>0 mg/kg</u>	Group II LD buprenor- phine <u>0.05 mg/kg</u>	Group III MD buprenor- phine <u>0.2 mg/kg</u>	Group IV HD buprenor- phine <u>0.8 mg/kg</u>
# of rats	28	28	28	28
# pregnant	24	24	24	24
Corpora lutea total	304	310	298	307
#/dam	<u>12.7+2.2</u>	<u>12.9+2.4</u>	<u>12.4+2.2</u>	<u>12.8+2.3</u>
Implantations total	292	297	282	290
#/dam	<u>12.2+2.4</u>	<u>12.4+2.4</u>	<u>11.8+2.1</u>	<u>12.1+2.6</u>
Fetuses total	271	272	260	265
#/dam	<u>11.3+3.4</u>	<u>11.3+2.9</u>	<u>10.9+2.8</u>	<u>11.0+3.7</u>
% male	51	50	48	49
% female	49	50	52	51
# of placenta	271	272	260	265
# of resorptions total	21	25	22	25
#/dam	<u>1.9+1.2</u>	<u>2.1+1.3</u>	<u>2.0+1.1</u>	<u>2.1+2.5</u>
early	15	18	16	18
late	6	7	6	7
% resorption rate	7.2	8.4	7.8	8.6
dead fetuses	0	0	0	0

Fetal parameters:

Parameters	control	Buprenorphine Groups		
		LD 0.05 mg/kg	MD 0.2 mg/kg	HD 0.8 mg/kg
malformations	0	0	0	0
# of fetuses with variants	63	60	53	68
% variation rate	23.2	22.1	20.4	25.7
# of fetuses with variants (macroscopic)	3	0	0	2
% variation rate	1.1	-	-	0.8
Body weight of fetuses	<u>3.52+0.33</u>	<u>3.57+0.30</u>	<u>3.57+0.26</u>	<u>3.55+0.33</u>
% pre-implantation loss	3.9	4.2	5.4	5.5
% post-implantation loss	7.2	8.4	7.8	8.6
Variant type or retardation				
skull	6	2	4	7
sternabrae	62	58	52	66
ribs and vertebral body	4	2	5	6
extremities	6	4	2	7
viscera	3	0	0	2
# of variations	81	66	63	88
# of fetuses with variations	65	60	53	70

No further explanation was given as to the exact description of the variants; e.g., variants may be different with respect to the numbers of rib pairs, degree of ossification, abnormal or "wavy" rib formations, etc.

Type of study: Segment II teratology study of buprenorphine in rats (SD/CD Charles River)

Site:

No. of dams/dose level: 12

Dose levels: 0, 0.05, 0.5, 5.0 mg/kg

Route: i.m. (5% glucose-saline)

Duration of dosing: days 6-15 of gestation

Sacrifice: day 21 of gestation

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Maternal observations: No pharmacotoxic signs were observed and all females survived the dosing period. HD dams showed reduced weight gain during the first three days of treatment.

Fetal parameters: The usual litter parameters were not adversely affected by drug treatment and no drug-related gross, skeletal or visceral anomalies were observed.

Type of study: Segment II teratology study of buprenorphine in rats

Site: Reckitt and Colman Pharmaceutical Division

No. of dams/dose level: 10

Dose levels: 0, 0.2, 1.0, 5.0 mg/kg

Route: s.c.

Duration of dosing: days 7-14 of gestation

Sacrifice: day 22 of gestation

Maternal observations: No pharmacotoxic signs were observed and all dams survived the dosing period.

Fetal observations: The usual maternal and litter parameters were not affected by drug treatment and no drug-related gross, skeletal, or visceral anomalies were observed.

Type of study: Segment I reproduction study in rats (Sprague-Dawley CD)

Site: b(4)

Dose levels: 0, 0.05, 0.5, 5.0 mg/kg buprenorphine

Route: i.m. (dextrose 5%-water used as control)

Duration of dosing: males - 60 days prior to mating
females - 16 days premating through day 21 of lactation

Sacrifice schedule: 1/3 females on day 13 of gestation

1/3 females on day 20 of gestation
and remainder at end of study

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Parameter	Control	Group		
		LD	MD	HD
Dosage (mg/kg)	0	0.05	0.5	5.0
# females mated	44	44	43	47
# females pregnant	39	39	40	44
fertility rate	88.6	88.6	93.0	93.6
mortality during pregnancy	0	0	0	0
# females sacrificed on day 13	15	13	13	15
# females sacrificed on day 20	12	11	13	15
day 13: embryo implants/litter	14.07	12.69	13.02	13.81
# resorptions/litter	.67	1.31	1.31	.37
1) early	.07	.31	.38	.06
2) late	.60	1.00	0.92	.31
# corpora lutea/litter	15.53	13.54	15.54	15.19
mean fetal weight	Not Recorded			
day 20: embryo implants/litter	14.50	12.64	12.61	14.00
# resorptions/litter	0.08	0.18	0.08	0.13
1) early	--	--	--	--
2) late	--	--	--	--
# corpora lutea/litter	15.83	13.54	13.85	15.40
# females giving birth	11	15	14	13
delivery rate	100	100	100	100
avg. length of gestation	22.3	22.6	22.1	22.1
# stillborn/litter	0.45	0.40	0.21	0.62
sex ratio (M viable/F viable)	0.77	0.86	0.98	1.02
# viable progeny				
day 0	130	156	157	137
day 4	101	118	113	9
day 21	97	107	107	8

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mean weight

day 0	5.9	6.1	5.8	5.6
day 4	9.2	10.8	8.9	8.8
day 12	23.3	24.5	22.1	27.8
day 21	48.9	48.9	42.5	51.5

Survival index

day 4	77.7	75.6	72.0	6.6
day 21	74.6	68.6	68.1	5.8

Malformations

# progeny examined	165	129	145	202
minor defects	3	3	4	5
rate	.018	.023	.028	.025
major defects	2	1	2	1
rate	.012	.008	.014	.0049

Mortality in the HD group was apparently due to mothers' failing to nurse offspring. Dystocia was noted during labor in the HD group. The no effect dose was 0.5 mg/kg.

Type of Study: Segment III reproduction study in rats (Sprague-Dawley CD)

b(4)

Site:

Dose levels: 0, 0.05, 0.5, 5.0 mg/kg

of dams/dose level: 17-18

Route: i.m.

Duration of dosing: day 14 of gestation through day 21 of lactation

<u>Parameters</u>	<u>Control</u>	Buprenorphine Groups		
		<u>low dose</u>	<u>mid dose</u>	<u>high dose</u>
Dosage (mg/kg)	0	0.05	0.5	5.0
# mated	17	17	18	17
# pregnant	17	17	18	17
mean length of gestation	21.5	21.8	21.8	21.3
Total # of pups	176	168	197	179
mean # pups/litter	10.35	9.88	10.94	10.53
Total # viable	170	159	195	165
mean # viable/litter	10.00	9.35	10.83	9.70
male/female ratio				
on day 4	0.97	1.14	1.19	1.10
# alive on day 4	132	118	138	61
survival index				
on day 4	77.6	74.2	70.8	37.0
mean #/litter	8.80	6.94	7.67	3.59
# weaned on day 21	101	102	109	53
mean #/litter	6.73	6.00	6.06	3.12
birth weight (g)				
day 0	6.30	6.40	6.30	6.0
day 4	9.30	9.30	8.70	8.6
day 12	23.30	20.90	20.20	20.5
day 21	42.10	38.0	37.4	37.1

High dose mothers failed to nurse, which resulted in loss of several litters. High dose mothers were known to have experienced a difficult parturition producing severe exhaustion. Pup growth appeared to be slightly depressed in the treatment groups.

Buprenorphine - effect on respiration in pregnant and neonatal rats

Site: Reckitt and Colman Laboratories, Hull, England

Method: O₂ consumption measured in a manometric system

Neonatal: pregnant rats were dosed i.m. with one of the following treatments:

morphine - 20 mg/kg

meperidine - 50 mg/kg

buprenorphine - 0.32 mg/kg

Five pregnant animals were used per group. At 1/2 hour following the drug treatments, animals were sacrificed and the pups were removed, weighed, and placed in 250 ml. conical flasks which contained a filter paper damped with 1 ml of water. Four pups were placed in each of two flasks and then 10-15

minutes were allowed for stabilizing with the manometers. Readings were taken at 4 minute intervals with 1 minute between readings with the air tag open to equalize pressures.

Maternal: Pregnant rats were injected intramuscularly with dextrose or test drug (morphine, meperidine, or buprenorphine). After 20 minutes they were placed in a desiccator, and the lid was carefully sealed with soft paraffin. Ten minutes were allowed for stabilization, then manometric readings were taken over a 45 minute period. Five rats were used per drug or dextrose group.

Morphine and meperidine depressed the maternal O₂ consumption rate. The high variability observed with meperidine was responsible for the lack of statistical significance of this response. Buprenorphine caused a slight (16%) non-statistically significant decline in maternal O₂ consumption.

In the pups, no statistically significant differences (p < 0.05) were observed in the rates of O₂ consumption. A trend towards reduced O₂ consumption was noted in the offspring of morphine treated mothers, whereas O₂ consumption rates tended to increase in the meperidine and buprenorphine treated groups.

Type of Study: Teratology (Segment II) study of buprenorphine in rabbits **b(4)**

Site:

Species/Strain: rabbits (New Zealand White)

No. of animals/dose level: 12

Dose levels: 0, 0.05, 0.20, 0.80 mg/kg

Route: i.v. (dextrose 5%-water), dose volume=0.08 ml/kg

Duration of dosing: day 6 to 18 of gestation

Sacrifice: day 29 of gestation

Injections were made into the ear veins of the animals. A dose-related injection site intolerance reaction characterized by hemorrhagic areas and thrombi was observed. These lesions healed at the lower dose levels but were not completely healed by the completion of the study in the high dose group.

Maternal parameters: No pharmacotoxic reaction to buprenorphine was observed at any dose level. In all groups, behavior and general appearance, food and water intake, and body weight gain were within normal limits.

Litter And Fetal Parameters	Control	Group		
		low 0.05 mg/kg	mid 0.20 mg/kg	high 0.80 mg/kg
# rabbits pregnant	12/15	12/15	12/15	12/15
# rabbits evaluated	12	12	12	12
Corpora lutea				
total	105	107	111	112
#/dam	8.8 \pm 1.1	8.9 \pm 1.5	9.3 \pm 1.0	9.3 \pm 1.6
Implantations				
total	98	102	106	107
#/dam	8.2 \pm 0.9	8.5 \pm 1.5	8.8 \pm 1.1	8.9 \pm 1.8
Fetuses				
total	92	94	94	96
#/dam	7.7 \pm 1.7	7.8 \pm 2.2	7.8 \pm 1.9	8.0 \pm 1.9
Male/female %	48/52	53/46	50/50	51/49
# of placenta	92	94	94	96
# of resorptions	6	8	12	11
early	4	4	8	2
late	2	4	4	9
% resorption rate	6.1	7.8	11.3	10.3
dead fetuses				
0-6 hours	1	2	3	4
7-24 hours	3	2	3	1
# fetuses with variants				
(Dawson method)	25	23	21	19
% variation rate	27.2	24.5	22.3	19.8
# of fetuses with				
macroscopic variants	0	0	1	0
% variation rate	-	-	1.1	-
Fetal body weights				
(litter) in gms	35 \pm 3.9	35 \pm 3.8	34.8 \pm 3.2	34.8 \pm 3.9
Weight of placenta				
(gms)	5.48 \pm 0.35	5.41 \pm 0.40	5.49 \pm 0.36	5.49 \pm 0.40
% pre-implantation				
loss	6.7	4.7	4.5	4.5
% post-implantation				
loss	10.2	11.8	17.0	15.0

Post-implantation loss in the MD and HD groups may have been related to a treatment effect.

<u>Variant</u>	<u>Control</u>	<u>Low</u>	<u>Mid</u>	<u>High</u>
skull	3	1	0	4
sternabrae	21	19	21	18
ribs and vertebral body	5	4	6	3
extremities	1	2	4	1
viscera	0	0	1	0
# of variations	30	26	32	26
# of fetuses with variations	25	23	22	19

Type of Study: Segment II teratology study of buprenorphine in rabbits

b(4)

Site:

Species/Strain: Rabbit

No. of pregnant females/dose level: 12

Dose levels: 0, 0.05, 0.5, 5.0 mg/kg

Route: i.m. (5% glucose saline)

Duration of dosing: days 6-18 of gestation

Sacrifice: day 28 of gestation

Maternal observations: No pharmacotoxic signs were associated with buprenorphine administration and all control and treated animals survived the dosing and gestation periods. High dose rabbits showed reduced weight gain during the treatment period which continued after day 18 of gestation.

The usual fetal and litter parameters were not adversely affected by drug treatment and no apparent drug-related gross, skeletal, or visceral anomalies were observed.

Type of Study: Segment II teratology study of buprenorphine in rabbits

Site: Reckitt and Colman Pharmaceutical Division, Hull, England

Species/Strain: Rabbits (New Zealand Albino)

No. of pregnant females/dose level: 10

Dose levels: 0, 0.2, 1.0, 5.0 mg/kg - 150 mg/kg thalidomide used as positive control

Route: s.c. (saline vehicle for buprenorphine; acacia vehicle for thalidomide)

Duration of dosing: days 7-19 of gestation

Sacrifice: day 31 of gestation

No pharmacotoxic signs were observed with buprenorphine administration and all animals survived the dosing and gestation period. In this study, resorptions were observed in the treatment groups although the number of resorptions was inversely related to the dose administered.

No apparent drug-related gross, skeletal, or visceral abnormalities were observed with buprenorphine whereas thalidomide produced its expected embryotoxic, embryocidal and teratogenic effects.

Special Toxicity Studies

Type of Study: in vitro hemolysis study of buprenorphine

Site: Laboratorium fur Pharmakologie und Toxikologie, Hamburg, Germany

Blood: dog, freshly drawn

Method: Buprenorphine solution (0.3 mg/ml) was added to a mixture of physiological saline and 0.05 citrated blood. Final volume was 2 ml. Each sample was mixed by inverting the sample once.

Tests were carried out on a series of buprenorphine concentrations and samples were evaluated visually for hemolysis at 0, 1, 2, 4, 6, 24, and 48 hours after mixing.

Solution	Concentration in ml (final volume=2 ml)	Hemolysis after sample preparation (hrs)					
		0	1	2	4	6	24
Buprenorphine (0.3 mg/ml)	0.72	0	0	0	0	0	0
	1.00	0	0	0	0	0	++
	1.39	0	0	0	0	+	+++
	1.93	0	0	0	0	++	+++
saline (0.9%)	1.95	0	0	0	0	0	0

At the 50% buprenorphine concentration 0.3 mg/2 ml, moderate hemolysis was observed after 48 hours. At the higher concentrations (0.417 and 0.519 mg buprenorphine/2 ml) partial to moderate hemolysis occurred at 24 hours with complete hemolysis occurring at 48 hours.

in vitro hemolysis of human blood by buprenorphine

Site: Lederle Laboratories, Pearl River, New York

The highest concentration of buprenorphine in plasma was 2.5 ug/ml following the administration of a single intramuscular dose of 2 ug/kg. The concentrations tested were x, 10x, and 100x the highest human plasma level of buprenorphine. Hemolysis was quantified by spectrophotometric determinations of plasma at 530-545 nm and 565-578 nm or by chemical determination of the hemoglobins. Samples were evaluated at 1, 3, 6, and 24 hours after incubation at 37 C.

Hemoglobin Levels(mg/100 ml plasma)

Drug concentration mg/ml	Incubation time (hours)					
	1	3	6	24		
0.0	17	5*	19*	13	15	47 50
2.5	10	8	17	10	14	47 62
25	22	19	16	15	9	61 49
50	14	19	10	19	9	62 69

*At 3, 6, 24 hours - the two columns of numbers represent hemoglobin read at 530-545 and 565-578 nm ranges, respectively. An unincubated plasma sample showed a hemoglobin value of 7 mg/100 ml. No hemolysis was caused by buprenorphine at any of the tested concentrations.

Local tissue tolerance to buprenorphine injections in dogs

b(4)

Site:

Species: dogs, cross-bred

Procedure: 3 dogs of both sexes were injected with 2 ml (0.6 mg) buprenorphine base by one of three routes of administration: i.m. (right hind leg muscles), i.v. (right short saphenous vein), and i.a. (right femoral artery). As a control, 2 ml of physiological saline was injected into a homologous site on the left side of the body in each animal. Two dogs of each route of administration were sacrificed at 24, 48, and 96 hours after administration, and the injection sites were examined histologically.

By the intramuscular route, slight hemorrhage was observed at the injection site in 2/6 dogs. By the i.v. route, slight perivascular edema and a spongy inflamed infiltrate around the injection site were observed in 2/6 treated and 1/6 controls. Intraarterial administration resulted in hemorrhage in 3/6 treated and 3/6 controls and perivascular edema in 2/6 treated and 1/6 controls.

The changes produced by buprenorphine in the clinical concentration (0.3 mg/ml) were minimal in dogs when administered by the intramuscular, intravenous, and intra-arterial routes. These results demonstrated that an approximate dose of 0.05 mg/kg did not produce local irritative phenomena at the injection sites. In several species in the toxicity and reproduction studies, slight to marked irritation potential of buprenorphine was observed. In some instances, this may have been explained by injection technique per se or the effect of repeated injections. In other studies, this may have been due to a higher dose being administered. However, there may also be species differences in the local tissue response to buprenorphine. Rats, rabbits, and baboons exhibited some local tissue pathology to buprenorphine.

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Phototoxic potential of buprenorphine in the albino guinea pig**b(4)**

Site:

Species/Strain: albino guinea pig,

Dosing groups:

- 1) chlorpromazine or buprenorphine
 Route of administration: intraperitoneal 20 mg/kg (n=5/group)
 topical 10% (n=10/group)

Chlorpromazine-treated animals were irradiated with UV light and the time to minimal dermal reaction was recorded. Ears were subsequently examined for erythema at 24, 48, 72, and 96 hours after minimal reaction. Edema and erythema and eschar were rated on a three point scale.

For topical application, a 4 x 6 cm shaved area in the dorsal thoracic region received an application of drug (10% w/w) in petrolatum for 1.5 hours. After removal, the guinea pigs were irradiated with UV light and the average time to produce a minimal dermal reaction was taken as time 0. Animals were then rated for edema and erythema at 24, 48, and 72 hours.

Intraperitoneal administration of chlorpromazine produced mild to moderate erythema of both ears which progressed to marginal necrosis in 3/5 animals at 72 hours. Topical application of chlorpromazine produced mild to moderate edema in 5/5 animals combined with marked erythema and scabbing and cracking of the skin in 4/5 animals and marked erythema in the fifth animal.

Intraperitoneal buprenorphine may have produced a reaction in 2/10 animals while most animals had either a mild reduction or a mild exacerbation of erythema during the 72 hour observation period. No marginal ear necrosis occurred.

Topical application of buprenorphine produced a mild erythema in 1/10 animals. No edema was observed.

Although this experiment did not have a control group it can be concluded that buprenorphine (at the doses tested) did not have the phototoxic potential of chlorpromazine.

Delayed dermal sensitization in the guinea pig**b(4)**

Site:

Species/Strain: guinea pig,

Dose and Route:

- 1) Induction phase - 10% buprenorphine dilution in paraffin oil
- 2) Induction phase, topical application - 50% dilution in petrolatum
- 3) Challenge phase - 50 and 20% dilutions in petrolatum

Control received paraffin oil and petrolatum at induction. At challenge, controls received test substance in the same manner as the test animals.

Induction: Each animal received 3 pairs of simultaneous intradermal injections on a 4 x 6 cm area of the shoulder. The injections were:

1) 0.1 ml Complete Freund's adjuvant; 2) 0.1 ml of test substance alone; and 0.05 ml of test substance emulsified with 0.05 ml Adjuvant.

One week after injection, the same area was clipped and shaved closely with an electric razor. A dermal patch was saturated (no dose given) with test substance, applied to the area, and secured for 48 hours and then removed.

At challenge (2 weeks post), an area on the flank was shaved and then a 2 x 2 dermal patch soaked in 50% and 20% buprenorphine dilutions was applied for 24 hours. Reactions were evaluated on a 4 point scale and allergenic potency was ascribed by sensitization rate.

Buprenorphine did not produce any delayed dermal sensitization.

Mutagenicity testing of buprenorphine

Site:

b(4)

Buprenorphine was tested for mutagenic potential in a bacterial (Salmonella typhimurium) assay system. 2-aminoanthracene was used as a positive control and distilled water was used as a negative control. Test compounds were dissolved in dimethylsulfoxide with the highest concentration of stock solution being 16.65 mg/ml of buprenorphine or 2-aminoanthracene.

<u>Bacteria</u>	<u>Strain</u>	<u>his operon mutation</u>	<u>type of mutation</u>
<u>S. typhi-murium</u>	TA 1535	<u>his</u> G 46	mis-sense causing base pair substitution
	TA 100	<u>his</u> G 46	mis-sense causing base pair substitution
	TA 1537	<u>his</u> C 3076	frameshift with addition of G base pair C
	TA 1538	<u>his</u> D 3052	frameshift with addition of C G base pairs G C
	TA 98	<u>his</u> D 3052	deletion of the two base pairs reverts

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Compounds were tested in both the presence and absence of an S-9 fraction (post mitochondrial) from rat liver. Agar plates were counted for colonies. The plates were also examined for precipitates and microscopically for microcolony growth.

The plate test functioned in the expected manner for both positive and negative controls. The activity of the S-9 preparation was demonstrated by its ability to metabolize 2-aminoanthracene.

Buprenorphine was not mutagenic in any of the 5 S. typhimurium strains. It was cytotoxic at a dose of 1 mg/plate and also precipitated at 1 mg/plate.

EVALUATION:

Buprenorphine was a potent antinociceptive agent in rodent antinociceptive screening procedures by both oral and parenteral routes of administration. The drug was longer acting than morphine and was anywhere from 25 to 200 times as potent as morphine, depending on the test procedure. The antagonist profile of buprenorphine was demonstrated in the mouse tail-flick test and against phenazocine-induced antinociception in the rat. Additional evidence for an antagonist effect of buprenorphine was demonstrated by reversal of etorphine narcosis as well as precipitation of an abstinence syndrome in morphine dependent dogs and monkeys.

Buprenorphine-induced antinociception was antagonized by narcotic antagonists in the mouse tail-flick, the order of antagonist potency being diprenorphine > nalorphine=levallorphan. In the mouse hot plate, naloxone was ineffective as an antagonist up to 30 mg/kg against buprenorphine-induced antinociception. In the rat tail pressure test, buprenorphine antinociception was antagonized by narcotic antagonists, the order of potency being diprenorphine > naloxone > levallorphan > nalorphine. In the rat tail flick, naloxone (10 mg/kg) antagonized the antinociceptive effects of buprenorphine.

In a multiple dosing experiment, tolerance developed to the antinociceptive effects of buprenorphine. In a subsequent experiment, cross tolerance between buprenorphine and morphine was shown to be bidirectional.

In direct dependence studies, buprenorphine had a liminal withdrawal syndrome upon naloxone challenge in the mouse, no physical dependence upon abrupt withdrawal in the rat, a mild abstinence syndrome in the chronic spinal dog, no physical dependence signs after abrupt withdrawal or nalorphine or naloxone challenge in the — monkey, and no withdrawal signs were observed upon abrupt discontinuation or antagonist (naloxone) challenge in the — monkey. In the dog, the buprenorphine abstinence score was the equivalent of that observed with chronic dosing of 10 mg/kg/day of morphine. The maximal abstinence obtained in the dog occurred with a morphine dose of 125 mg/kg/day.

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Buprenorphine was also tested for its precipitation and substitution ability in morphine-dependent and morphine-dependent withdrawn animals, respectively. In the rat, buprenorphine neither precipitated nor substituted for morphine in morphine-dependent animals. In the dog, buprenorphine (0.001 to 0.016 mg/kg, i.v.) substituted in morphine-dependent withdrawn animals with a slope gentler than that of propoxyphene, and i.v. doses (0.024 to 0.096 mg/kg) precipitated abstinence with a lesser slope than that observed with naloxone. In the ~~monkey~~, 0.32 mg/kg buprenorphine precipitated severe abstinence for 12 hours. Lower doses (0.02 to 0.16 mg/kg) both precipitated and partially substituted for morphine abstinence. In the morphine-dependent Patas monkey, buprenorphine (0.1 and 10 mg/kg) precipitated a dose-related moderate to severe abstinence syndrome. In a single dose suppression test in morphine-dependent withdrawn Patas monkeys, buprenorphine neither suppressed nor exacerbated the morphine withdrawal syndrome. In cyclazocine-dependent Patas monkeys, buprenorphine (0.5 mg/kg, s.c.) precipitated a moderate abstinence syndrome characterized by scratching, yawning, and shaking. The results are consistent with buprenorphine being characterized as a partial agonist. Further characterization of single dose effects led Martin *et al.* (J. Pharmacol. Exp. Ther. 197: 517, 1976) to characterize buprenorphine as a partial agonist of the morphine (u) type.

b(4)

The effects of buprenorphine on respiratory parameters were investigated in several species. In mice, buprenorphine produced an inverted "U" shaped dose-effect curve in terms of respiratory rate, whereas morphine and to a lesser extent, pentazocine, produced a dose-related respiratory depression. In the rat, buprenorphine (0.001 to 0.1 mg/kg, s.c. and i.a.) depressed the respiratory rate and pCO_2 rose, but the response was not dose-related. In the rabbit, buprenorphine (0.1 - 40 mg/kg, s.c.) failed to alter pO_2 , pCO_2 , and pH whereas pentazocine and morphine produced dose-related decreases in pO_2 and pH and increased pCO_2 in doses which paralleled their analgesic potency. A 10 mg/kg, i.v. dose of buprenorphine depressed pO_2 to 60% of control values. In the dog, buprenorphine produced respiratory depression, although of a different character than that produced by morphine. Buprenorphine (0.1-1.0 mg/kg, i.v.) respiratory depression was characterized by a slight decrease in the respiratory rate and a large decrease in tidal volume with pCO_2 rising in a non-dose-related fashion. Morphine (3 mg/kg, i.v.) depressed the respiratory rate and tidal volume increased with pO_2 decrease but pCO_2 was not significantly elevated. Naloxone (0.1 mg/kg) promptly reversed morphine-induced respiratory depression whereas a 1 mg/kg dose of buprenorphine could not be reversed by 10 mg/kg of naloxone.

A study in rats was undertaken to establish whether a respiratory component was involved in buprenorphine-induced lethality. Rats were infused at one of three infusion rates (6, 9, or 12 mg/kg/min) and received no pretreatment (control), artificial respiration, or naloxone (1 mg/kg, i.v.). Both artificial respiration and naloxone pretreatment effectively antagonized

buprenorphine-lethality by a two to four fold factor. Respiration ceased before cardiac arrest. There was a possible confounding effect of the drug infusion volume on the experiment. With the solubility of buprenorphine (10 mg/ml), some rats received a volume of drug solution equivalent to their blood volume, producing a dilutional hypervolemia which may have complicated the toxicological evaluation. In rats with established respiratory depression, high doses (23 mg/kg, i.v.) of naloxone were needed for reversal. However, hypotension and bradycardia were exacerbated by this dose of naloxone.

The effects of buprenorphine on the cardiovascular system were studied in the rat, guinea pig, cat and dog. Buprenorphine produced bradycardia in every species studied in the absence of major effects on blood pressure. In the rat, isoproterenol reversed the bradycardia without arrhythmic production. In the dog, administration of epinephrine or norepinephrine exacerbated the bradycardia and led to the development of arrhythmias.

The behavioral responses to buprenorphine administration were observed in the rat, cat, dog, and monkey. In the rat, buprenorphine produced both catalepsy and stereotypy (gnawing, sniffing, licking) with catalepsy occurring first followed by a mixed catalepsy-stereotypy period which progressed to stereotypy. In contrast, morphine produced only catalepsy in the rat. The effects of buprenorphine (0.3-1.0 mg/kg) were antagonized by high doses of naloxone (10-100 mg/kg). Buprenorphine lacked classical morphine-like activity in the cat. Instead of morphine-like "mania", mydriasis, slight behavior depression at low doses (2.0 mg/kg) and darting movements (5 and 10 mg/kg) were observed. In the dog, buprenorphine produced slight behavioral depression in the absence of morphine-like "sham-rage." No consistent effects on body temperature, heart rate, and pulse rate were noted in a ten day rising dose (0.05 to 10 mg/kg) study, although buprenorphine induced vomiting during the first week of a subacute toxicity study. Patas monkeys appeared slightly dazed after a high dose of buprenorphine (10 mg/kg, s.c.) whereas _____ monkeys demonstrated mild morphine-like signs after administration of 0.32 mg/kg buprenorphine. The overall behavioral response to buprenorphine encompassed some mild morphine-like signs but marked differences also occurred.

b(4)

In a discriminative stimulus generalization paradigm in which rats were trained to discriminate fentanyl from saline, buprenorphine was 1/2 as potent in being recognized as fentanyl-like. Both fentanyl and buprenorphine interoceptive cues were antagonized by naloxone (0.02-0.31 mg/kg, s.c.).

b(4)

In — monkeys which were lever-trained to high response rates with codeine, buprenorphine was actively self-administered. In separate experiments, in Rhesus monkeys trained to self-administer morphine, buprenorphine (3 to 300 ug/kg) pretreatment had no effect on morphine response rates. The effect of continuous buprenorphine infusions (20 and 40 ug/kg/hr) was dependent on the dose of morphine; i.e., low doses were administered less whereas high doses were administered more often at both infusion rates of buprenorphine.

In a gastrointestinal propulsion test in rats, the buprenorphine dose-effect curve was curvilinear; i.e., an inverted "U" shape. This may be the result of "autoantagonistic" effects.

In isolated tissue preparations, buprenorphine was a non-competitive smooth muscle depressant but had no effect at the neuromuscular junction.

In the rat, buprenorphine had a greater antidiuretic effect than morphine at equianalgesic doses but had less antidiuretic effect at twenty times the equianalgesic doses.

In terms of drug interactions, buprenorphine was used with either alphaxolone (6 mg/kg, i.v.) or halothane/oxygen for surgical anesthesia. No acute problems occurred and at 7 days post-anesthesia there were no differences in weight gain across saline vs. buprenorphine treated groups. In the dog, buprenorphine was substituted for meperidine as a surgical premedicant. No adverse effects were observed on cardiovascular or respiratory parameters or general behavior, although salivation took longer to dry up after atropine in combination with buprenorphine.

Absorption, distribution, metabolims, and excretion studies of buprenorphine have been carried out in the rat, rabbit, dog, and monkey. In the rat, buprenorphine absorption was studied by i.m., sublingual, and oral routes of administration. After oral and i.m. dosing, peak blood levels occurred at 10 minutes after dosing and declined for 8 hours. A second peak occurred at 8 hours and then declined to a low level by 24 hours post-administration. The oral/parenteral ratio was about 1/5 and the sublingual/parenteral ratio was about 1/3. Sublingual dosing produced a slightly delayed peak blood effect; i.e., at 2 to 4 hours. The kinetic profile of buprenorphine in the rat suggests an enterohepatic circulation. Further experiments established that biliary excretion accounted for 65% of the administered dose in a 24 hour period. The drug is metabolized to a glucuronide conjugate in the intestine. Glucuronidation takes place at the dealkylated piperidyl N or the phenolic hydroxy group. The N-dealkylated product may be present as an O or N-glucuronide.

The pharmacokinetic profile of buprenorphine was studied in both pregnant and non-pregnant rats. After i.m. injection, distribution and excretion were similar in both groups. At day 11 of gestation, maternal and fetal kinetics were in parallel, but by gestation day 21 clearance from the fetus was slower than clearance from the plasma. It was subsequently determined that in the mature rat fetus, there is a high degree of localization and conjugation in the fetal gastro-intestinal tract, suggesting biliary excretion of conjugated drug in the mature fetus.

In interaction studies of drug metabolizing enzyme systems, oral buprenorphine increased zoxazolamine paralysis time by 60% in the rat. It could not be determined whether the effect on zoxazolamine paralysis time was due to a change in hepatic enzyme activity or residual buprenorphine acting as a competitive substrate. The activities of p-nitroanisole-O-demethylase and biphenyl 2 and 4-hydroxylase and the levels of cytochrome P450 and b₅ were significantly reduced. The relevance and significance of this observation in the rat to metabolism of drugs and other compounds by the mixed function oxidase system in man during buprenorphine therapy remains to be elucidated.

In equilibrium dialysis studies, buprenorphine was 96% bound to plasma proteins, more so to γ and B-globulins than to α -globulins or albumin. Binding to albumin was increased by defatting, indicating a competitive interaction between buprenorphine and lipids.

Buprenorphine absorption in the female rabbit demonstrated peak plasma levels within 15 minutes. A second plasma peak occurred at 48 hours, suggesting enterohepatic circulation. In terms of total dose excreted over a 7 day period, 37% of the dose was excreted in the urine primarily as glucuronide conjugates and 16% was excreted in the feces as buprenorphine. The results suggest that enterohepatic circulation of buprenorphine occurs with subsequent de-glucuronidation in the gut with partial absorption of free buprenorphine and partial excretion of buprenorphine in the feces. On day 7, 31% of the dose was recovered from the carcass.

In the dog, peak plasma levels of buprenorphine occurred within 20 minutes of i.m. dosing and two hours after oral administration. A slow decline for the next 24 hours was observed after either i.m. or oral dosing. The oral/parenteral ratio was about 1/5. Recovery from urine was 5% of the total dose, whereas 57% of the dose was excreted in the feces as unchanged buprenorphine.

In the baboon, peak plasma levels of buprenorphine were achieved within one hour of i.m. injection and 2 to 6 hours of oral administration. After i.m. injection, the decline of buprenorphine in plasma appeared to be biphasic, reaching a low level 24 hours after administration. The major route of excretion was the feces, irrespective of the route of administration. Cumulative recoveries were 66 to 69% over 7 days despite the fact the tissues had little radioactivity at the end of the time period.

In the ~~monkey~~, buprenorphine was well absorbed from either i.m., oral, or sublingual administration. Brain radioactivity levels were higher after i.m. than oral dosing; peak levels occurred two hours after dosing. In general, at 2 hours, higher tissue levels were observed after i.m. dosing except in the liver and kidney. The majority (80%) of the drug + (metabolites?) was excreted into the feces after both i.m. or oral administration. b(4)

Two hours after sublingual administration, only 13% of the buprenorphine equivalents in plasma was unchanged drug whereas one hour (peak) after i.m. administration, 81% was unchanged drug. By 24 hours, no free drug was detectable in plasma.

A metabolism study in 2 human volunteers demonstrated that 80% of a single dose of buprenorphine was excreted within one week. The major route of excretion was the feces, irrespective of route of administration (p.o. or i.m.).

The acute toxicity (LD₅₀s) studies of buprenorphine were performed at both Reckitt and Colman and Lederle Labs. In mice, the order of lethality was i.v. > i.p. > p.o. > s.c. and in rats the order of lethality was i.v. > i.p. > p.o. = s.c. By the intravenous route, buprenorphine was approximately 3 and 10 times as toxic as morphine on a mg for mg basis in rats and mice, respectively. By the oral route, buprenorphine is 4 times as toxic as morphine in mice but less toxic than morphine in rats. However, buprenorphine is far more potent than morphine in terms of their antinociceptive activity in rodents. Thus, the therapeutic ratio for buprenorphine is far improved over that of morphine. When the therapeutic ratio of buprenorphine was compared to pentazocine, propiram, and propoxyphene, the ratio was favorable (@ 50 to 100) for buprenorphine vs. propiram and pentazocine and highly favorable (@ 100 to 300) relative to propoxyphene.

Lethality studies comparing buprenorphine and its desalkyl metabolite were obtained in rodents. The desalkyl metabolite was more toxic by i.v., s.c., and p.o. routes in mice and rats. The N-butenyl norbuprenorphine contaminant was about 1/10 as potent an antagonist as buprenorphine but 25 times as lethal as buprenorphine. Toxic signs associated with desalkyl buprenorphine in mice were straub tail, exophthalmos, convulsions, and coma. In the rat, toxic signs were similar with the addition of chewing movements. Buprenorphine produced sedation, ataxia, and dyspnea in the rat which progressed to miosis, reduced muscle tone, and dorsal recumbency at higher doses.

Interactional acute toxicity studies of buprenorphine and other CNS active drugs were performed in mice. Aspirin had no effect on acute buprenorphine toxicity, whereas desmethylimipramine, diazepam, and tranylcypramine reduced toxicity associated with buprenorphine. Phenobarbital or prednisoline increased buprenorphine lethality. As single doses of many of these drugs were studied, these studies should be extended to more doses of these agents.

Dose-related toxic signs were associated with acute buprenorphine. At near lethal doses, tremors and epileptiform seizures were observed. At lethal doses, salivation, marked retching and vomiting, convulsions, mydriasis and hyperpnea preceded death. In most dogs, bradycardia was observed at 5 minutes after dosing. Small hematomas were observed at the injection site. At autopsy pulmonary edema was observed in the dogs that died.

In baboons, acute non-lethal doses of buprenorphine produced local injection site reactions characterized as induration with swelling of the adjacent tissue. The local reactions appeared to be dose-related. Tremor, ataxia, bradycardia, and respiratory depression, tonic-clonic spasms, and lateral followed by ventral recumbency in high non-lethal (40 mg/kg, i.v.) doses. At 80 mg/kg, tonic-clonic spasms with increasingly progressive bradycardia with bundle branch block in the EKGs were observed shortly before death. Outside of injection site reactions, no macroscopic pathology occurred in the high dose group.

The subchronic toxicity of buprenorphine was investigated in rodents by oral (3.2 to 80 mg/kg - 4 weeks), subcutaneous (0.2 - 5.0 mg/kg - 30 days) and intramuscular (0.1 - 5 mg/kg - 6 months) routes of administration. The parenteral HD in the rodent studies was 50 to 150 times the ED₅₀ value of the tail pressure and hypertonic saline antinociceptive tests. Some abnormal behavior was manifested in these studies which was suggestive of a dopaminergically mediated stereotypy. Acute high doses of buprenorphine also produced this result. In the long term i.m. study, this effect abated with time and by the end of the fourth month the LD and MD animals did not manifest this effect. Buprenorphine depressed weight gain although the effect was inversely related to dose in males in the s.c. study. In general, food intake paralleled the body weight data. No adverse drug-related effects were observed in the clinical biochemistry, hematology, and urinalysis data. Gross and histopathologic examinations of tissues failed to reveal any drug-related organ pathology. In the 6 month i.m. dosing study, both control and treated animals showed muscle degeneration with some evidence of fibrosis in the area of the injection sites. As this effect was observed in control animals, it may be attributable to repeated injections per se.

Subchronic toxicity studies of buprenorphine were investigated in beagle dogs by both subcutaneous (0.2 to 5.0 mg/kg, 30 days) and intravenous (0.4 to 32 mg/kg, 4 weeks) routes of administration. In the subcutaneous study, one HD male dog died on day 28. The cause of death was not established although histopathology revealed infections at the injection sites, pneumonitis, thymic hemorrhages, and fatty changes in the liver and kidneys. Non-dose-related weight gain depressions were observed. Hematology, bone marrow smears, clinical biochemistry, urinalysis, and ophthalmologic exams (i.v. study only) did not reveal any drug-related effects. Injection site necrosis was recorded in 1/6 MD and 1/6 HD dogs in the s.c. study and dose-related injection site pathology which progressed to vessel wall lesions with moderate obliteration in the i.v. study. Slight centrilobular fatty changes in the liver and renal tubular epithelium in HD males and to a lesser extent in treated females were observed in the s.c. study whereas possible drug-related pathology in the i.v. study included dilatation of the adrenal zone glomerulosa (3/6 MD and 3/6 HD), cell depletion in the spleen (3/6 HD), slight (1/3 LD) to moderate (1/3 HD) localized or diffuse (1/3 HD) testicular atrophy.

In the monkey, buprenorphine was administered by gavage at 3.2 to 80 mg/kg for 4 weeks. During the last week of the study slight weight losses were recorded. Food intake dropped off after the 4th or 5th day of dosing. No clinical biochemical, hematologic, or urinalysis abnormalities were attributed to drug treatment, and no gross or histopathologic abnormalities were observed with an oral dose up to 80 mg/kg.

A sublingual administration of buprenorphine to cynomolgus monkeys in doses of 0.032 to 1.6 mg/kg/day produced no apparent drug-related effects on the oral mucosa, clinical biochemistry, hematology, and urinalysis, EKGs, adrenal function, testicular biopsy, or any gross or histopathological measurements.

In the baboon, subchronic toxicity studies of buprenorphine were performed by the i.v. (0.02 to 18 mg/kg, 4 weeks) or i.m. (0.05 to 5 mg/kg, 26 weeks) routes of administration. In the i.v. study, the HD group was discontinued after 9 days due to obliteration of the veins. No changes in behavior or food or water intake were recorded for the LD and MD buprenorphine groups. In the i.m. study, body weight gain and food intake were not affected by drug treatment while water intake was reduced in the HD group. In the i.v. study, hematologic parameters were normal in the LD and MD group while the HD group had an elevated leucocyte and reticulocyte count and ESR. These changes may have been attributable to the inflammatory process at the injection sites. In the i.m. study, HD monkeys showed a slight decrease in Hb at termination; however, RBCs and hematocrit were not significantly affected.

In the i.v. study, SGOT and SGPT values were in the high normal range in the HD group. In the i.m. study, animals had a dose-related increase in globulin with a decreased A/G ratio. These changes were attributable to inflammatory reactions and abscess formation at the i.m. injection sites.

Urinalysis parameters were unaffected by drug treatment in both the i.v. and i.m. studies.

In the i.m. study, discrete masses at the injection sites were observed by week 6 and were present at all injection sites by week 20. These indurations caused an increase in mechanical resistance and may have caused hemorrhage and leakage at the injection site. Histopathology confirmed hemorrhage, loss of muscle fibers with fibrosis, and edema and chronic inflammatory reactions at the injection sites. In the i.v. study, histopathology of the injection sites revealed induration of the vascular wall and paravenous tissues. Edema of the lungs was observed in 3/6 MD and 3/6 HD animals.

Segment I, II, and III teratology and reproduction studies were performed in rats and segment II teratology studies were performed in rabbits. In the Segment I reproduction study in rats, graded doses of buprenorphine (0.5 to 5 mg/kg) were administered i.m. prior to mating and through lactation. Dystocia was noted at parturition in the HD group. This result was confirmed in the

Segment III study. The no effect dose was 0.5 mg/kg. In the Segment III study, HD mothers failed to nurse, resulting in a high mortality rate in the pups. Segment II teratology studies in the rat were performed by administering buprenorphine by the i.v., i.m., and s.c. routes. With the exception of dose-related inflammatory changes in the i.v. buprenorphine treated mothers, no drug-related maternal organ pathology was observed. Buprenorphine did not adversely affect litter parameters and was not embryotoxic or teratogenic in the rat.

The effects of buprenorphine, morphine, and meperidine on pregnant rats and pups were compared. Morphine and meperidine depressed the maternal O₂ consumption rate. Buprenorphine caused a slight (16%) non-significant decrease (n=5) in maternal O₂ consumption.

In the pups, no statistically significant differences were noted in O₂ consumption rates. In morphine treated pups, O₂ consumption tended to decrease whereas O₂ consumption rates tended to increase in the meperidine and buprenorphine treated groups.

Segment II teratology studies of buprenorphine were performed by i.v., i.m., and s.c. routes of administration. In the i.v. study, an injection site intolerance was noted in the treated doses. The only possibly drug-related effect in the i.v. study was an increased post-implantation loss in MD and HD groups. In the i.m. and s.c. studies, buprenorphine did not produce any apparent drug-related embryotoxic, embryocidal, or teratogenic effects.

In in vitro hemolysis studies, the no-effect hemolysis concentration in dog blood was 72 mg %. In human blood, a 50 mg % (100x greater than the highest human plasma level) did not produce any hemolysis.

A local tissue tolerance study of buprenorphine utilized the clinical dosage form. Dogs were injected i.v., i.m., or i.a. and sacrificed at 24, 48, and 96 hours, and the injection sites were examined histologically. Changes produced by the clinical concentration (0.3 mg/ml) were minimal and consisted of mild edema and slight hemorrhages which were observed with a lesser incidence in the control groups. The rat, rabbit, and baboon exhibited slight to marked tissue intolerance to buprenorphine. These data are confounded by the effects of repeated injection although they do demonstrate that higher concentrations of buprenorphine can produce local injection site pathology in certain species. The relevance of this effect to man is questionable.

Buprenorphine was tested for phototoxic potential and delayed dermal sensitization in the guinea pig. Results were essentially negative; i.e., no phototoxicity or delayed dermal sensitization were observed in buprenorphine treated groups.

Buprenorphine was tested for mutagenic potential in five strains of Salmonella-typhimurium. No positive mutagenic events were recorded in buprenorphine-inoculated cultures.

Comments with respect to labeling:

[] b(4)

Statement of foreign data: Some of the data provided in the pharmacology and toxicology studies of buprenorphine were generated in foreign countries:

- 1) Analgesic data in rodents Reckitt and Colman, England
- 2) Buprenorphine as a narcotic antagonist in rodents Reckitt and Colman, England
- 3) Tolerance and cross tolerance to morphine in rodents Reckitt and Colman, England
- 4) Physical dependence in Rhesus and Patas monkeys Reckitt and Colman, England
- 5) Effects on respiration in mice, rats, rabbits, and dogs Reckitt and Colman, England
- 6) Cardiovascular effects in rats, guinea pigs, cats, and dogs Reckitt and Colman, England
- 7) Effects on ongoing behavior in rats, cats, dogs, monkeys Reckitt and Colman, England
- 8) Discriminative stimulus properties of buprenorphine [] b(4)
- 9) Effects of buprenorphine on G.I. propulsion Reckitt and Colman, England

- 10) Effects of buprenorphine on isolated tissue preparations Reckitt and Colman, England
- 11) Effect on prolactin secretion Reckitt and Colman, England
- 12) Neuropharmacology-effect of lesions and 6-hydroxydopamine on buprenorphine Reckitt and Colman, England **b(4)**
- 13) Metabolic studies on absorption, distribution, metabolism, and excretion, in vitro gut metabolism and in vitro protein binding Reckitt and Colman, England
- 14) Acute toxicity studies in rodents toxicity of desalkyl buprenorphine, interactional acute toxicity Reckitt and Colman, England
- 15) Acute toxicity studies in dogs and baboons
- 16) Six-month i.m. toxicity in rats and baboons
- 17) Local tissue tolerance study in dogs
- 18) One month toxicity in Wistar rats and — monkeys
- 19) Four week i.v. toxicity in beagle dog and baboons
- 20) i.v. buprenorphine-effects on pregnancy in rat and rabbit
- 21) Teratology studies in the rat and rabbit
- 22) Fertility and peri- and post-natal toxicity study in rats
- 23) Placental transfer and pharmacokinetics in pregnant and non-pregnant rats Reckitt and Colman, England
- 24) Teratology studies in rats and rabbits Reckitt and Colman, England

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- 25) Phototoxic potential in guinea pigs
- 26) Mutagenicity testing

b(4)

- 27) In vitro hemolysis properties of buprenorphine in dog blood

Reckitt and Colman, England

Recommendations:

- 1) that the pharmacology and toxicology data be accepted towards fulfilling the NDA requirements for approval;
- 2) that the labeling changes in the evaluation section be communicated to the sponsor of the NDA;
- 3) Further studies are suggested in the following areas:

b(4)

Frank J. Voccio Jr., Ph.D.
Frank J. Voccio, Jr., Ph.D.
May 1, 1980

cc
NDA
INDs 11-109, 11-142, 12-851
HFD-180
HFD-120
HFD-120 /FVoccio/5/1/80
Init. ECTocus/6/12/80
FT:klt/6/25/80
DOC#2571

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-401

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

May 4, 1981

MAY 12 1981

NDA#: 18-401

Applicant: Eaton-Reccol, Inc.

Name of Drug: buprenorphine hydrochloride injectable

Documents Reviewed: Volumes 3.1-3.5 dated 1/16/81, 2.3-3.10 dated 8/6/80
by the Bureau of Drugs

Background and Summary

Volumes 3.1-3.5 contain the sponsor's response to a nonapprovable letter dated 7/15/80 from Marion Finkel, M.D., HFD-100, along with the results of four additional animal safety studies and pharmacology studies. On August 6, 1980 the sponsor submitted the results of a multi-investigator study of buprenorphine and morphine in patients with moderate to severe pain.

It is my opinion that the sponsor has collected and submitted data capable of providing adequate statistical evidence in support of the claims being made for the drug. In terms of pain relief, pain intensity, level of sedation these data provide sufficiently high statistical power to conclude the comparability of buprenorphine and morphine. The sponsor has not provided statistical evidence to support a claim of superiority of buprenorphine to morphine in terms of pain relief, pain intensity or any other efficacy variables. The results of the new multi-investigator study confirm the efficacy findings of the eight studies submitted with the original NDA. This is so even after the data from Dr. Martin Mok's study are excluded from consideration as will be argued below. Dr. Martin Mok will imminently undergo disqualification proceedings according to a letter from Alan Lisook, M.D., to HFD-123 dated April 6, 1981.

The sponsor concluded that buprenorphine is associated with significantly altered respiration rates and blood pressure measurements. The data from the Ouellette studies appear to show that blood pressure and respiration are more responsive to changes in doses of morphine than to changes in doses of buprenorphine for the ranges studied there (0.15, 0.20, 0.30 and 0.40 mg buprenorphine and 5 and 10 mg morphine).

The sponsor's response to the seven questions raised by the Division of Biometrics was not complete in all aspects. In addition, the data from the new multi-investigator trial were submitted before the sponsor received the

7/15/80 regulatory letter, with the result that the statistical analyses of the data from the new multi-investigator study suffer the same flaws as did those of the original eight studies.

In spite of these deficiencies as described in the sections below this reviewer has determined that the data submitted by the applicant provide adequate statistical evidence to support the claims made for the drug.

I have discussed the conclusions drawn in this review with Howard Gross, M.D., HFD-120, the reviewing medical officer. He is in agreement with the conclusions.

Sponsor's Response to Division of Biometrics Comments in the 7/15/80 Letter

- (1) The sponsor indicated adequately how sleeping patients had been evaluated. This question was not addressed by the sponsor for the multi-investigator study (to which we shall henceforth refer as the Gilbert study).
- (2) The sponsor gave the distribution of patients by site and nature of pain for the Robbie and Hovell studies. The sponsor showed that the randomization scheme was successful in distributing patients to the various sites and nature of pain categories in a statistically comparable way so that, on the average, differences among patients in these categories would not alter the conclusions about treatments drawn in the original submission. The sponsor did not relate these distributions to the observed response to therapy. This would have been desirable as a means of providing more information about the drug in terms of labeling details. It is not required in the demonstration of efficacy. The question concerning site and nature of pain could still be examined in the Gilbert study.
- (3) The sponsor provided an acceptable response to the question concerning entry order of patients into the studies by Hovell (comparing buprenorphine with pethidine and pentazocine; comparing buprenorphine with morphine), Robbie and by Ouellette. The possibility of a mix up remains with regard to the Robbie study, a crossover design with four different nurse observers as the sponsor indicates on page 11, Volume 3.1. The explanation provided by the sponsor with regard to Dr. Hovell's study comparing buprenorphine to Omnopon is inadequate.
- (4) The sponsor inadequately described the model according to which the Robbie crossover study data were reanalyzed. However, the analysis of variance tables reflect an appropriate treatment of the analyses as suggested in the 7/15/80 regulatory letter.

- (5) The sponsor attempted to follow our suggestion to adjust for baseline values the analyses of changes in vital signs but used an inappropriate model in doing so. The sponsor used a model in which differences from baseline in vital signs were subjected to a one-way analysis of covariance with baseline as covariate, making in this way a double adjustment (of different magnitudes) for baseline. This analysis ignores the day on which the observations were made. The procedure in the original submission is more appropriate than the one in their resubmission, the one asked for in the 7/15/80 letter being a refinement on the former one. It is my opinion that the reanalyses requested in 7/15/80 letter need not be performed.

The sponsor's analysis of the Ouellette and Dobkin studies suggests that buprenorphine may be associated with statistically significant changes in respiration rate and in systolic and diastolic blood pressure from those observed in the control morphine treated groups. This is depicted in the figures from the sponsor's summary of the data from the Ouellette studies reproduced in the Appendix to this review. In these studies the doses of buprenorphine were 0.15, 0.20, 0.30, 0.40 mg and those of morphine 5 and 10 mg. The analysis of the data provided by the sponsor ignores the day on which these observations on vital signs were taken. This will affect the results of the analysis since the day-to-day observations on the same patient are highly correlated and not independent as the sponsor's statistical methods require. This fact is illustrated in the results of the Gilbert et al multi-center study where (in Volume 2.3 pages 93, 95, 96; 107, 109, 110; and 114, 116, 117) the sponsor provided separate analyses by day and combined over all days for respiratory rate, systolic and diastolic blood pressure, respectively. The figures on respiration rates are reproduced in the Appendix to this review. In this study the dose of buprenorphine was 0.3 mg/ml and that for morphine 10 mg/ml with 1.0, 1.5 or 2 ml injections administered every 3 or more hours and no more than 6 ml allowed in any 24 hour period. Based on this analysis presented by the sponsor it is my opinion that there is no statistically significant difference between 0.3 mg/ml buprenorphine and 10 mg/ml morphine in terms of respiration rate. A similar opinion is rendered concerning diastolic and systolic blood pressure. From the Ouellette studies one can see that one can change respiration and blood pressure more by doubling the dosage of morphine from 5 to 10 mg than by doubling the dose of buprenorphine from either 0.15 to 0.30 or from 0.20 to 0.40 mg. Doubling the dose of morphine (5 mg to 10 mg) reduces respiration rates by as much as 4 units, systolic blood pressure by as much as 16 mmHg and diastolic blood pressure by as much as 10 mmHg while a doubling of the buprenorphine dose from 0.15 to 0.30 mg/ml reduces respiration rate by as much as 4 units, increases systolic blood pressure by as much as 8 mmHg and increases diastolic blood pressure by as much as 10 mmHg.

- (6) The sponsor provided an adequate explanation of the extended weight cut-off points in the second Hovell study.

- (7) The sponsor attempted to provide a power analysis of the statistical tests for SPID, TOTPAR scores, vital signs and adverse reactions for the double-blind controlled clinical studies but was unsuccessful. The sponsor based his power calculations (a) on the wrong statistical test (a pairwise comparison where in some cases 3 or 4 treatments were part of the experimental design) and (b) on the incorrect error terms from the analysis of covariance in (5) above.

Adequate estimates of the power of the sponsor's statistical tests have been provided by the statistical reviewer in the 2/12/80 and the 4/22/80 statistical reviews.

In addition to these comments there were several questions in the medical portion of the letter which had some statistical content. These are listed below:

1. The Agency requested an analysis of pre-study analgesics in the Ouellette, Dobkin, Robbie and Hovell studies. The sponsor presented analyses to show that treatment groups were not statistically different from each other in terms of the number of patients receiving various types of pre-study medications including analgesics and anesthetics, or the times at which such medications were received. This comparability allows one to have continued confidence in the sponsor's statistical inferences drawn in the original submission where these factors were not considered. The sponsor's present analysis does not, however, help in selecting out in a more refined way, subpopulations of patients who might benefit more from the test drug than another subpopulation. The sponsor's response to our request is thus minimally adequate from a statistical viewpoint.

The Agency requested that the sponsor reanalyze the adverse reaction data taking pre-study medication into account. The sponsor responded again that since the numbers of patients in the treatment groups were comparable with regard to their various pre-study medications the inferences drawn before are valid. The sponsor claims "therefore there is no evidence of bias due to this factor." Bias in the results is only part of the concern. The additional concern is one of being able to show whether there is a particular subpopulation for which the drug is clearly contraindicated. In a sense the sponsor's reply is minimally adequate with regard to the statistical requirements for the demonstration of efficacy.

The Gilbert Multi-investigator Study

The sponsor submitted on 8/6/80 the results of a study conducted under a common protocol by six investigators (Gilbert, Mok, Wang, Zeedick, Filtzer

and Ouellette) of the effect of buprenorphine and morphine in patients with moderate or severe initial pain.

Alan Lisook, M.D., HFD-180, has informed HFD-123 in a memorandum dated 4/6/81 that Dr. Martin Mok's records were recently audited. The results of that audit, according to Dr. Lisook, have lead to disqualification procedures against Dr. Mok by the Agency. Dr. Gross asked us, therefore, to examine the results of the Gilbert multi-investigator study with Dr. Mok's data excluded.

Reproduced in the Appendix to this review is the sponsor's Table 3 which shows the number of patients enrolled by each investigator on each treatment. In total number Dr. Mok's patient's are similar to those enrolled by Dr. Ouellette and Dr. Gilbert. A graph in the Appendix of the TOTPAR scores for each of Days 1, 2 and 3 illustrates that Dr. Mok's data do not differ substantially from those of the other investigators. Dr. Mok's buprenorphine patients represent 27% (48/175) and his morphine patients also 27% (49/181) of the total number of patients on each treatment. Given the total sample sizes in each treatment the omission of Dr. Mok's data would, in my opinion, neither alter the conclusions drawn by the sponsor concerning the drugs nor change significantly the power of the statistical tests performed by the sponsor.

Conclusions

It is my opinion that the two Ouellette studies, the studies by Dobkin, Downing and Hovell (buprenorphine vs pethidine and pantazocine) all provide statistical evidence to support the sponsor's claims for the drug. The Gilbert multi-investigator study, excluding Dr. Mok's data on his disqualification, would, in my opinion, support the claims of efficacy made for the drug as well. The sponsor has been asked to provide a data tape of the Gilbert multi-investigator study in the event that HFD-120 feels a detailed reanalysis of the data excluding Dr. Mok's patients is essential.

It is my opinion that the Hovell study comparing buprenorphine to morphine provides only weakly supportive statistical evidence and should not be considered pivotal because of the large number of missing data values in the efficacy, pre-study and vital sign variables observation. Dr. Robbie's study and Dr. Hovell's study comparing buprenorphine to Onnmpoⁿ should also be considered in this category since the sponsor's explanation of out-of-sequence patient assignments was inadequate.

Comments that Should be Conveyed to the Sponsor

This submission contains data which provide statistical evidence of the efficacy of buprenorphine HCl as an analgesic agent in patients with

moderate or severe pain. The studies of Ouellette, Dobkin, and Hovell (buprenorphine versus pethidine and pentazocine) provide statistical evidence to support these claims. The multi-investigator study by Gilbert et al provides supportive statistical evidence of the claims made.

The effect of buprenorphine on respiration and blood pressure is dose dependent, there being no statistically significant difference between 0.30 mg/ml buprenorphine and 10 mg/ml morphine in terms of respiration rate, diastolic and systolic blood pressure as you claim based on the data from the Gilbert multi-center study. The Ouellette studies illustrate that doubling the morphine dose reduces respiration and blood pressure while doubling the buprenorphine dose lowers respiration but increases blood pressure to a lesser degree. This should be reflected in the labeling of the drug.

Jerome Senturia
Jerome Senturia, Ph.D.
Group II Leader

cc:

✓ Orig. NDA 18-401
HFD-120
HFD-120/Dr. Gross
HFD-180/Dr. Lisook
HFD-232/Dr. Dubey
HFD-232/Dr. Senturia
Chron.
JSenturia/pak/rb/5/1/81/#4045B

Concur: Dr. Dubey

6/25/81

April 22, 1980

NDA# 18-401

Applicant: Eaton-Recol, Inc.

Drug Name: Buprenorphine Hydrochloride Injectable

Documents Reviewed: Volumes 1.10 and 1.11 stamped 11-1-79 by the Bureau of Drugs

I. Background and Summary

A previous statistical review on five of the eight controlled double-blind clinical trials in this submission has been issued on 2/12/80. Howard Gross, M.D., HFD-120, requested that we review the remaining three studies which compared buprenorphine with potent analgesics other than morphine. In Dr. Robbie's within patient (crossover) study, 2 doses of buprenorphine (2 and 4 g/kg) were compared with pentazocine (0.6mg/kg) in patients who suffered from pain due to cancer. The other two studies were parallel, post-surgical pain model studies which compared various doses (2, 4 and 8 g/kg) of buprenorphine with pentazocine (0.6mg/kg) and pethidine (1 mg/kg) and buprenorphine (0.3mg) with Omnopon (20mg) respectively. Patients were evaluated for pain intensity, pain relief (not compared with Omnopon), time to remedication, vital signs and side effects.

The applicant concluded that buprenorphine was safe and more effective than pethidine. Buprenorphine was also safe and equally as effective as pentazocine and Omnopon.

It is my opinion that there is some evidence in this submission to support the applicant's claims. However, the evidence as presented here cannot be considered sufficient from a statistical viewpoint since there are some questions about the study designs that need to be clarified. Moreover, inappropriate statistical procedures were employed in the analysis of the data.

In all three studies, no statement was made as to how patients were evaluated for pain when they were sleeping during the evaluation periods. Provisions for recording site and nature of pain were made in the protocols of two studies but none of these items was available either in the case reports or in the

summary. Patients' sequential entry number did not agree with their chronological orders raising the question as to the ways patients were selected for the studies.

Statistical analysis in Dr. Robbie's crossover study was inappropriate. A standard analysis of the crossover design should have been provided but was not. In all three studies, no adjustment was made for baseline values in the analyses of the changes in vital signs. Buprenorphine appeared to give higher sedation levels than pethidine. Two patients in the buprenorphine groups in Dr. Hovell's first study died. The cause of death of one patient was attributed to liver bleeding. Other side effects appeared to be comparable among treatment groups.

I have discussed the conclusions of this review with Dr. Gross and he is in agreement with them.

II. Clinical Studies

1. Investigator: D. S. Robbie

a. Study Description

Patients suffering moderate to severe pain of cancer received intramuscular injections of three treatments (buprenorphine 2 and 4 μ g/kg and pentazocine 0.6mg/kg) in random order within 6 to 10 days. Of the 22 patients who entered, 20 patients completed the study. Each patient was evaluated for pain intensity (in movement and at rest), pain relief, pulse rate, blood pressure, respiratory rate and side effects at each of the following observation periods -- Pre-therapy, 0.25 hour, 0.5 hour, 1 hour and then hourly up to 7 hours post therapy.

b. Applicant's Findings

The Friedman two-way (patient and treatment) analysis of variance was used to analyze the initial pain intensity and no significant difference among treatments was found. The same technique was used in other efficacy variables such as the sum of pain intensity difference (SPID), total pain relief (TOTPAR), maximum PID and time to remedication. No significant difference was found in any of these variables. For time to maximum PID, six and eight patients were excluded from analysis for pain on motion and pain at rest respectively because their pain level was constant throughout the assessment period. Pentazocine 0.6mg/kg appeared to act faster than the 4 μ g/kg dose of buprenorphine ($p < .10$).

For each of the vital signs, data for each treatment group was analyzed separately using a two-way analysis of variance. The main effects in the analysis were time and patient. All treatments produced similar small decreases in pulse rate and respiration rate and buprenorphine (4 μ g/kg) produced a small fall in blood pressure at certain times of the observation period. All three treatments produced a similar side effect profile with sedation being the commonest effect.

c. Reviewer's Comments

- (i) The design of the trial was a crossover type. The use of a two-way (patients and treatments) analysis of variance in this design is not appropriate. The applicant ought to provide a standard analysis for this design taking into account the treatment effect, period effect, treatment by period interaction and residual effects uncontaminated by patient-to-patient (subjects within sequence) variability.
- (ii) No adjustment was made for the baseline values in the analysis of changes in vital signs.
- (iii) During the observation period, 25% (5/20) of the patients were given radiotherapy. The effect of this treatment on the patients' pain relief and side effects was not known.
- (iv) There was no statement as to whether patients were roused for pain evaluation when they were sleeping.
- (v) Some of the patients' entry numbers were not in alignment with their chronological order of entry. For example, if we arrange the patient numbers according to chronological order, then patient #5 should follow patient #9 and patients #16-20 should precede patient #10. The applicant should explain this anomaly.
- (vi) The description of the analgesic study forms (p. 141, Vol. 1.10) in the protocol provides assessments for pain site, pain character and whether a patient had 50% relief. However, such items could not be found either in the case reports or in the study summary itself. The applicant needs to explain this lack of adherence to the protocol.
- (vii) All patients received each of the three treatments. The protocol indicated that the spacing in time of treatments was not fixed but would be arranged so that the round would be completed within 6 to 10 days. However, upon examination of

the case reports, it was found that only one patient satisfied this requirement. Among the other 19 patients, 15 of them completed the round in 3 days and the other 4 patients completed the round in 4 to 17 days.

2. Investigator: B. C. Hovell

a. Study Description

This was a single dose parallel study in which patients suffering moderate to severe post-operative pain were treated with buprenorphine ($2\mu\text{g}/\text{kg}$ or $4\mu\text{g}/\text{kg}$) or pethidine ($1\text{mg}/\text{kg}$) or pentazocine ($0.6\text{mg}/\text{kg}$). Of the 152 patients who entered the study, 134 patients completed treatment according to the protocol. Subsequently, an additional group of 34 patients received buprenorphine $8\mu\text{g}/\text{kg}$. Efficacy and safety parameters measured were similar to the Robbie study described above except that the post-treatment observation period was only 4 hours.

b. Applicant's Findings

Data were analysed first by excluding the buprenorphine ($8\mu\text{g}/\text{kg}$) group and second by including this group. The mean body weights among treatment groups were significantly different ($p=.05$). However, this was judged to have a negligible effect on the response to treatments and was therefore not considered in the analyses of efficacy variables by the applicant. Baseline pain intensity was comparable among treatment groups. However, this was used as a covariate in the analysis of SPID's and TOTPAR's.

All five treatments gave pain relief. However, the maximum pain relief and also the proportion of patients experiencing complete relief was significantly greater for buprenorphine ($4\mu\text{g}/\text{kg}$) and ($8\mu\text{g}/\text{kg}$) than for pethidine. This difference was also detected for SPID (on movement and at rest) and TOTPAR. Buprenorphine ($8\mu\text{g}/\text{kg}$) had a significantly longer duration of action than all the other treatments, as measured by time to remedication.

Patients receiving buprenorphine (2 and $4\mu\text{g}/\text{kg}$) experienced a significantly greater level of sedation than patients receiving pethidine. For blood pressure, all five treatments had similar profiles. A fall in respiration rate was observed in buprenorphine (2 and $8\mu\text{g}/\text{kg}$). The behavior of pulse rate was different between pethidine (no significant changes) and the buprenorphine groups. Other side effects were comparable among treatment groups.

c. Reviewer's Comments

(i) There was no statement in the protocol as to whether patients were roused for evaluation of pain when they were sleeping. Upon examination of the case reports, it appeared that some patients were roused for evaluation when they were asleep (based on the comments in some of the case reports that the patient was rousable). However, in some other cases, the nurse observer commented that the patient (sleeping during the observation period) was not a good historian (patients #108, 109) which implied that evaluations were based on the patients' recollection. The applicant needs to clarify this, since in many cases, patients appeared to have good pain relief when they were sleeping.

(ii) The buprenorphine groups appeared to give greater pain relief than the pethidine group, but at the same time the sedation level of the buprenorphine groups was also significantly higher than that of the pethidine group.

(iii) No adjustment of the baseline values was made in the analyses of the changes in vital signs, although the applicant admitted that differences in treatment groups may be nominally affected by minor variations in the baseline values (p. 143, Vol. 1.11).

(iv) Pre-anesthetic medications appeared to be comparable among treatment groups. Some patients (30/186) had no records of anesthetics used and some patients (66/186) had no records of other drugs used during anesthesia. The applicant has not examined the comparability among treatment groups with regard to the missing records and explained how this would effect their analysis.

(v) The highest dose buprenorphine groups ($8\mu\text{g}/\text{kg}$) was added later after the completion of the study of the first four groups. Thus, the patients in this group were not randomized. Results of the efficacy of this treatment group would be inconclusive.

(vi) One patient (#153) who received buprenorphine ($8\mu\text{g}/\text{kg}$) became heavily sedated. He was conscious the next day but died 3 days later. Another patient (#104) who received buprenorphine ($4\mu\text{g}/\text{kg}$) died one day post-treatment. Cause of death was cited as "bleeding from liver site."

(vii) Except for higher level of sedation of the buprenorphine groups, other side effects were generally not significantly different among treatment groups. However, side effects might be masked or complicated by anesthetic or other drugs used during anesthesia.

(viii) Comment (vi) of Study Number 1 also applies here.

(ix) Comment (v) of Study Number 1 also applies here. It should be noted that disagreement in patient entry numbers and their chronological sequence occurred only in the buprenorphine groups.

3. Investigator: B. C. Hovell

a. Study Description

This was a double-dose study comparing buprenorphine (0.3mg) with Omnopon (20mg) given intramuscularly to patients suffering from moderate to severe pain. Of the 55 patients who entered the study, 45 patients were evaluated for efficacy. Patients were observed pre-drug and hourly post-drug up to six hours after the first dose. The second dose was given either when the pain intensity was increased by one unit or at the end of the 6 hours after the first dose. Observations were made at 1, 3 and 5 hours post-drug. Efficacy and safety parameters measured were similar to those of study number 2 except that pain relief was not evaluated. Nine patients had biochemical evaluations performed prior to and following treatments.

b. Applicant's Findings

There was no significant difference in any of the efficacy parameters between treatment groups. Sedation was the most common side effect, buprenorphine (0.3mg) seeming to cause a greater degree of sedation than Omnopon (20mg). Otherwise the drugs were very similar in side effect profile.

c. Reviewer's Comments

(i) The range of the weights of patients was specified as 50-80kg in the protocol. However, the applicant decided to extend the range to 45-85kg upon examination of the data and excluded 4 patients whose weights were over 85kg. The reason for extending the range of weight and the cut-off point chosen after looking at the data was not clear. The applicant needs to explain this.

(ii) No distinction was made between pain at rest and pain on motion.

(iii) Comment (v) of Study Number 1 also applies here. Beginning with patient number 37, the chronological dates of subsequent patients jumped back and forth out of sequence. Also, patient number 55 was missing. The applicant needs to explain this.

(iv) Although there was no significant difference in SPID between treatment groups, the power of detecting a clinically meaningful difference was not provided by the applicant. The following table is prepared by this reviewer to illustrate the magnitudes of the minimum differences in SPID that could be detected with the corresponding minimum acceptable powers. It must be emphasized that if the required minimum difference to be detected is smaller than the figures in the table, the power will be lowered to an unacceptable level.

	Mean SPID	Min. Difference	Power
	Min. Max.	to be detected	
First dose	6.8 7.4	3.0	0.74
Second dose	8.7 9.3	2.0	0.74

(All power figures are approximate and are based on 2-sided t-tests with significance level .05.)

(v) Analysis on the changes in vital signs was not adjusted for baseline values.

(vi) Comments (ii) and (iv) of Study Number 1 also apply here.

(vii) There appeared to be no significant difference in side effects between treatment groups.

(viii) The pulse rate behavior between treatment groups appeared to be different (see p. 341, Vol. 1.11).

III. Conclusions that should be conveyed to the applicant

This submission contains some evidence that buprenorphine is more efficacious and at the same time more sedative than pethidine. There is also some evidence that buprenorphine provides comparable levels of analgesia when compared with pentazocine and Omnopon. There appeared to be no significant difference in side effects among the test drugs. However, the

evidence of efficacy and safety (vital signs) could not be considered sufficient from a statistical viewpoint because of inadequacy in the study design and inappropriate statistical procedures. The applicant is requested to clarify the following comments with regard to the protocols and reanalyze the data with regard to comments on statistical procedures.

(i) In all three studies, no statement was made as to how patients were evaluated for pain when they were sleeping during the observation period.

(ii) In the studies of Robbie and Hovell (5 treatment groups), the protocols had provisions for the site and nature of pain. However, none of these items was reported either in the case reports or in the summary.

(iii) In all three studies, when the patient numbers are arranged in order, some of their dates when they entered the studies were not in chronological order. In addition, patient number 55 in Hovell's second study (buprenorphine vs. Omnopon) was deleted without explanation in case reports and the analysis.

(iv) The statistical procedures employed in Robbie's study are inappropriate. The applicant should provide a standard analysis of the crossover design taking into account the treatment effect, period effect, treatment by period interaction and residual effect. A reference for the appropriate analysis is W. Federer Experimental Design MacMillan 1955.

(v) In all three studies, the analysis in changes in vital signs should be adjusted for baseline values.

(vi) In Hovell's second study, the reason for extending the range of cut-off points for weight and the inclusion of those patients whose weights were outside the range specified in the protocol are not clear.

(vii) Power analysis should be provided in the cases where no statistical significance was found.

cc:

✓ Orig. NDA 18-401

HFD-120

HFD-120/Dr. Gross

HFD-180/Dr. Lisook

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FEB 14 1980

February 12, 1980

NDA #: 18-401

Applicant: Eaton-Recol, Inc.

Drug Name: Buprenorphine Hydrochloride Injectable

Documents Reviewed: Volumes 1.8, 1.9 and 1.10 stamped 11/1/79 by the Bureau of Drugs

I. Background and Summary

The purpose of this submission was to demonstrate that buprenorphine in the dosage range of 0.3 mg to 0.6 mg is an effective and safe potent analgesic agent. Among the eight controlled double-blind clinical trials comparing buprenorphine with morphine and other potent analgesics, seven studies involved patients with moderate to severe post-surgical pain and one study involved patients with pain associated with cancer. Howard Gross, M.D., HFD-120, requested that we review the five post surgical pain model studies that compared buprenorphine with the standard reference agent morphine. All five were randomized, parallel, double-blind studies. A total of 479 patients who experienced moderate to severe post surgical pain were involved. Both buprenorphine and morphine were given in single dose administrations by the intramuscular route only. The study doses ranged from 0.15 mg to 6 mg in buprenorphine and 5 mg to 15 mg in morphine. Patients were evaluated for pain intensity, pain relief, time to remedication, vital signs and side effects.

Based on these five studies, the applicant concluded that buprenorphine was either equal or superior to morphine in relieving moderate to severe post surgical pain at the various test dose levels. The applicant further claimed that both test drugs were equally safe.

It is my opinion that this submission contains some evidence supporting the applicant's claims of the efficacy and safety of buprenorphine as a general analgesic agent. However, the evidence as presented cannot be considered substantial since there are some flaws in the design of most of the applicant's studies and some potentially serious omissions in the analyses of the data. Adequate arrangements (such as rousing a sleeping patient for evaluation of pain level) were not made in the experimental designs for separating out fully a sedation

response from a pain relief response. In addition, in all but one study no distinction was made between pain on motion and pain at rest.

While the flaws alluded to are not fatal from a clinical point of view they do limit the statistical inferences one can draw from these data to ones in terms of sedation and pain relief considered jointly and sedation and total pain intensity differences considered jointly. One cannot, however, make the analogous inferences for the efficacy variables singly because of the correlation structure of the data and the experimental design. The clinical importance of those limitations is referred to the medical officer for comment.

In the statistical analyses of the data no adjustments were made for the influence of pre-study analgesics and anesthetics; no adjustments in the analyses of vital signs were made for baseline values; and some data gathered after remedication were included in the analyses, contrary to the protocol. It should be noted that not all of the above deficiencies apply to all studies. Where no significant differences ($p>0.05$) were found, the sensitivity of the statistical procedures is marginally acceptable ($power=0.74$ to 0.80).

According to the medical officer, the applicant is preparing an additional study of buprenorphine. The design flaws should be addressed in the new study. While there is no way to correct the stated design flaws, the omissions from the statistical analyses can be corrected by suitable reanalyses of the data. The medical officer has indicated his belief that such reanalyses would have impact on his evaluation of the claims made for the drug.

I have discussed the conclusions of this review with Dr. Gross and he is in agreement with them.

II. Clinical Studies

1. Investigator: Robert D. Quellette, M.D.

a. Study description

The purpose of this study was to compare the analgesic activity of 0.15 mg and 0.3 mg of buprenorphine with 5 mg and 10 mg of morphine sulfate. There were 67 patients in this study. Post-medication evaluations were assessed by a trained observer pre-drug and at 10, 20, 30 minutes and 1, 2, 3, 4, 5 and 6 hours after drug administration. Variables recorded were pain intensity (none (0), mild (1), moderate (2), severe (3) and very severe (4)), pain relief (none (0),

slight (1), moderate (2), good (3), and complete (4)), sedation (alert (1), mildly drowsy (2), moderately drowsy (3) and asleep (4)), time to remedication and vital signs (supine blood pressure, pulse and respiratory rate). Any tissue reactions and side effects were noted. Derived variables included the sum of pain intensity differences (SPID), total pain relief (TOTPAR) and the sum of sedation level differences (SSLD).

b. Applicant's findings

The comparability of the four treatment groups with respect to weight and age was assessed separately using a two-way analysis of variance model with sex as a blocking factor. While the mean weights and baseline pain intensity were comparable, the mean age in the 5 mg morphine group was significantly greater than the mean ages of the three other groups (here and elsewhere in this review, the level determining statistical significance is 0.05 unless otherwise noted). The plots of pain intensity and pain relief scores showed that reduced pain was evidenced within 10 minutes in all drug groups. Peak levels occurred at one hour post injection and subsequently gradually returned towards the baseline values. The return to baseline was much more rapid and complete for the 10 mg morphine group than for the other groups.

Pairwise comparisons between adjusted means using t-tests showed only that the 0.3 mg buprenorphine group was significantly higher than the 10 mg morphine group in both SPID and TOTPAR. Time to remedication was not significantly different among drug groups by the chi-square test. The number of patients requiring remedication at each hour was analyzed by the life table techniques and was found to be non-significant. SSLD was evaluated using baseline sedation level and age as covariates but no significant difference among treatment groups was found. All drug groups showed some decrease in respiratory rates and blood pressure but there were generally no significant differences among the treatment groups in changes from baseline. Pulse rates remained relatively constant over time in all drug groups. Treatment emergent symptoms were reported in 4 patients. Among them, only one received buprenorphine. This patient reported mild nausea and did not require treatment for it.

The applicant concluded that single doses of 0.15 mg and 0.3 mg of intramuscular buprenorphine had a clinical analgesic profile comparable to 5 mg and 10 mg of morphine. The 10 mg morphine provided less pain relief.

c. Reviewer's comments

(i) Statistical methods in the comparability of demographic variables and baseline sedations are acceptable. For baseline pain intensity, the standard chi-square test would have been more appropriate than the analysis of variance method because of the categorical nature of the data and concentration of most of the data in two categories. However, both methods yielded non-significant results in this study.

(ii) Within the 6-hour study period, clinical evaluations for pain and vital signs were discontinued after remedication. The applicant explained that this was to avoid the effects of the additional analgesics administered on remedication from entering into the analyses. However, over half of the patients received pre-study analgesics within 6 hours prior to the start of administrations of the study drugs. Ten patients received pre-study analgesics as late as 2 to 3 hours prior to the study drugs (pages 38-44, Volume 1.8). The applicant ignored the possible influence of pre-study analgesics in all the analyses. According to the reviewing medical officer, the consequences of this are important. The applicant should either have stratified or made adjustments in the analyses for the type of and elapsed time since the administration of pre-study analgesics.

(iii) In this study there was no distinction made between pain at rest and pain on motion. This distinction was made in study number 5 discussed later in this review and the results of some of the analyses were different between pain at rest and pain on motion. The reviewing medical officer agreed that the applicant should demonstrate the role this distinction plays in all these studies.

(iv) Methods of assessments for pain intensity and pain relief were not clearly specified when patients were asleep. The buprenorphine groups appeared to have higher mean sedation levels than the 5 mg morphine group although this difference was not statistically significant. A comparison of the individual patient's pain relief scores with sedation

levels revealed that most of the patients who obtained complete pain relief were patients who were asleep. The following table shows the number of patients cross-classified by pain relief scores and sedation levels at 3 hours after administration of study drugs.

		Pain Relief Score									
		Buprenorphine					Morphine				
		0	1	2	3	4	0	1	2	3	4
Sedation Level	1	0	2	1	6	1	2	3	0	12	0
	2	1	0	0	4	0	0	0	2	4	0
	3	0	0	0	3	0	0	0	0	0	1
	4	0	0	0	1	12	0	0	0	0	8

This table demonstrates that of the 22 patients who had complete relief (score=4), 20 were asleep (sedation=4). The table illustrates clearly the importance of the investigator's rousing a sleeping patient to assess the pain relief. In the case illustrated by the table one cannot entirely separate out sedation effects from pain relief effects. The medical officer agreed that in the opinion of some experts in this field this distinction must be made and the clinical way is to rouse the patients. The sponsor has not done this. One would have to conclude from the sponsor's analyses that in terms of both SSLD and TOTPAR jointly as well as SSLD and SPID jointly buprenorphine is significantly superior to morphine. One cannot, however, make the analogous statements for the efficacy variables SSLD, TOTPAR or SPID separately because of the correlation structure and the way the data were collected. The clinical importance of this observation is left to the medical officer for interpretation.

(v) The reviewing medical officer indicated that changes in vital signs due to morphine usually depend on the baseline values. The applicant did not adjust for the baseline values in these analyses either.

(vi) The nature of side effects was comparable among treatment groups with slightly higher occurrences in the morphine groups. However, it should be noted that side effects might be masked or complicated by the pre-study medications including type and amount of anesthetic.

2. Investigator: Robert D. Quellette, M.D.

a. Study description

This study was designed to compare the analgesic activity of 0.2 mg and 0.4 mg of buprenorphine with 5 mg and

10 mg of morphine sulfate. There were 133 patients in this study. The study design and the variables measured were similar to those of study number 1 above except that observations were recorded at 0.5, 1, 2, 3, 4, 5 and 6 hours post-medication. In addition, it was specified that when a patient was asleep and in no obvious pain, ratings of zero for pain intensity and 4 for pain relief were assigned. If the patient was asleep but appeared to be in pain, he/she would be roused for the usual ratings.

b. Applicant's findings

Statistical techniques similar to those in study number 1 were used in this case. All of the demographic variables were comparable among treatment groups.

The 0.4 mg buprenorphine appeared to produce greater pain reduction than did the 5 mg or 10 mg morphine. The differences were statistically significant for SPID and peak PID. For TOTPAR, the 0.4 mg and the 0.2 mg buprenorphine were significantly higher only compared with 5 mg morphine. The group receiving 0.4 mg buprenorphine was significantly longer in time to remedication than the 5 mg morphine group.

For SSID, the 5 mg morphine had less sedative effect than either the 10 mg morphine or the 0.4 mg buprenorphine. Except for the pulse rate which exhibited no significant changes, other vital signs decreased initially and then began to return towards baseline after about 2 hours in all treatment groups. The higher doses of both medications exhibited larger decreases and a slower return to baseline. Treatment emergent symptoms were reported in 8 cases, 3 in the buprenorphine groups and 5 in the morphine groups. The most frequent sign was nausea.

The applicant concluded that buprenorphine and morphine provided adequate analgesia and appeared equally safe at the doses used in this study. In addition, 0.4 mg buprenorphine produced significantly better pain relief than did the doses of morphine.

c. Reviewer's comments

Comments of (ii) through (vi) (except for the first statement in (iv)) for study number 1 above are applicable here. In addition, in this study data were recorded after remedication and these observations, contrary to the protocol, were included in the analyses (patients numbered 107, 110, 179, 192, 126 and 255). There were also missing data

prior to remedication (patients numbered 199, 132 and 151). Although the small number of data points involved is not likely to affect our conclusions, these inconsistencies should be explained by the applicant.

3. Investigator: Allen B. Dobkin, M.D.

a. Study description

The protocol of this study was practically identical to that of study number 2. There were 166 patients in this study.

b. Applicant's findings

The statistical methods employed were identical to those of study number 2. All demographic variables were comparable among treatment groups. Both buprenorphine groups had significantly higher SPID and TOTPAR than the 5 mg morphine group. For peak PID, only the 0.4 mg buprenorphine group was significantly higher than the 5 mg morphine group. Tests on time to remedication showed that both buprenorphine doses provided significantly longer duration of action than the 5 mg morphine group and that the 0.4 mg buprenorphine group did significantly better than the 10 mg morphine group.

For safety variables, the 0.4 mg buprenorphine had significantly higher SSLD than the 5 mg morphine. Means of the respiratory rates for the buprenorphine groups tended to remain slightly below baseline whereas for the morphine groups, the opposite was true. Pulse rates and blood pressure had similar profiles in all treatment groups, decreasing initially and then gradually returning towards the baseline values. Treatment emergent symptoms were reported in 7 patients receiving buprenorphine and in 12 receiving morphine. One patient receiving 0.2 mg of buprenorphine experienced moderate hypotension, but the symptom lasted only 5 minutes.

The applicant concluded that both buprenorphine groups gave better pain reduction than the 5 mg morphine group and all treatments appeared equally safe.

c. Reviewer's comments

Since the protocol and the statistical methods in this study were practically identical to those of study number 2, all of the comments in study number 2 apply equally here.

It is interesting to note that the results of study number 2 and this study were not comparable though they had nearly identical protocols. The mean values of SPID and TOTPAR in study number 2 were almost twice those in this study and the average times to remedication in study number 2 were also much longer. The mean values of SSLD in study number 2 were 5 to 18 times larger than those in study number 3. The following table provides a summary comparison.

Treatment	SPID		TOTPAR		Duration (hr.)		SSLD	
	Study 2	3	Study 2	3	Study 2	3	Study 2	3
0.2 mg Bupr.	11.0	6.0	13.7	8.3	6	4	4.7	0.72
0.4 mg Bupr.	12.5	6.6	13.6	9.1	>6	4.5	5.1	0.89
5 mg Morp.	8.2	3.2	10.6	4.6	6	3	3.0	0.21
10 mg Morp.	9.5	5.0	12.8	6.6	>6	3.5	5.1	0.28

The applicant needs to explain this further. There were more patients with severe initial pain intensity in this study than in study number 2. This might account for some of the differences. Different nurse observers in different studies might be another reason for this difference. It should be noted that the table also shows good general agreement between studies 2 and 3 on the relative effect of buprenorphine to morphine despite the disparity in response level.

Observations (mostly in vital signs) that were either missing for no reason or recorded after remedication and later incorporated into the calculations (contrary to the protocol) included the following patients' numbers: 174, 203, 242, 248, 256, 304 (0.2 mg buprenorphine); 219, 243, 272, 283, 287 (0.4 mg buprenorphine); 196, 244, 249, 255, 281, 309 (5 mg morphine) and 245, 246, 251, 268, 278, 286, 297 (10 mg morphine).

4. Investigator: J. W. Downing, M.B. B.Ch.

a. Study description

The original purpose of this study was to compare two doses of buprenorphine (0.3 mg and 0.6 mg) and two doses of morphine (7.5 mg and 15 mg). From the considerations of the results of another open study and the first two patients receiving 0.3 mg buprenorphine, the study design was modified to compare for a 4 hour period only buprenorphine (0.6 mg) and morphine (15 mg). The test drugs were given intramuscularly to female patients suffering moderate to severe pain following elective Caesarean section. Fifty-eight female patients were admitted to the study. Subsequently it was decided to study a

number of patients receiving 0.6 mg buprenorphine for an 8-hour period on an open basis. Nine patients involved in the double-blind study had their code broken at the end of 4 hours and were studied for an additional 4 hours. Six additional patients were studied for eight hours on an open label basis. Patients were evaluated pre-drug and at 0.25, 1, 2, 3 and 4 hours post-drug. Patients involved in the open study were also observed at 5, 6, 7 and 8 hours post-drug. Variables observed included pain intensity, pain relief, pulse rate, blood pressure, vital capacity, peak flow and side effects.

b. Applicant's findings

The treatment groups were comparable with respect to demographic variables, according to the applicant. All patients in the double-blind study had severe initial pain. The additional six patients in the open study had moderate/severe initial pain. Analyses of efficacy variables where these six patients were included were adjusted for initial pain intensity. Only 4 patients (2 in each treatment group) needed remedication during the 4 hour study period.

SPID was significantly higher for the buprenorphine group with or without the six additional patients in the open study. TOTPAR also favored the buprenorphine group ($p=0.07$) in both instances. Maximum PID was compared using a Mann-Whitney U-test. The buprenorphine group was favored ($p=0.02$) in the double-blind study. Inclusion of the six additional patients reduced the significance level to 0.12. Time to maximum PID indicated that maximum pain relief occurred at a significantly later time in the buprenorphine group than in the morphine group ($p<0.0001$) whether the six patients were included or not.

The number of patients suffering from sedation (mostly mild) was comparable between treatment groups. Over the 4-hour evaluation period, pulse rate, systolic and diastolic blood pressure decreased significantly below baseline while vital capacity and peak flow rose significantly in both treatment groups. Nausea and vomiting were observed in only one patient.

The applicant concluded that 0.6 mg buprenorphine gave a higher level of analgesia, with a longer duration of activity than 15 mg morphine with no increase in unwanted effects.

c. Reviewer's comments

(i) The comparability of age and weight between treatment groups was based on all patients including the six patients in the open study. The p-value for age would have been

0.06 (2 sided t-test) instead of 0.09 when those six patients were excluded from the calculation. This indicated that more younger patients were assigned to the buprenorphine groups. The p-value for the comparison of weight would also be lower but is still not significant.

(ii) As a consequence of comment (i), it would be more appropriate to adjust for age when analyzing the efficacy and safety variables. The applicant has not done this.

(iii) The applicant's claim that 0.6 mg buprenorphine had longer duration of action than 15 mg morphine is not acceptable since it was based on the significant later time to maximum PID of buprenorphine than morphine and also on the assessment of the 8 hour open study of buprenorphine alone. Only direct comparison of time to remedication over an extended period of time could substantiate this claim.

(iv) Because of the uniform nature of operations and pre-study medications, the issue of pain at rest and pain on motion raised in connection with the previous study appears not as important in this case.

(v) The proportion of patients who suffered from sedation was small (6 patients in the buprenorphine group and 4 in the morphine group) and these 10 patients had only mild to moderate sedation. Thus, the effects of sedation in this study would not be expected to affect the analyses seriously as in the previous studies.

(vi) Comparisons of changes in vital signs should have been adjusted for baseline values but were not.

(vii) Both drugs appeared to be equally safe at their respective doses since only one patient who received morphine experienced nausea and vomiting.

5. Investigator: B. C. Hovell, M.B., Ch.B., F.F.A.R.C.S.

a. Study description

Fifty one patients experiencing moderate to severe pain following general surgical procedures were assigned randomly to either the 0.3 mg buprenorphine group or the 10 mg morphine group. One patient was excluded from the efficacy analyses because he was noted to be confused prior to and during the early study period. Observations of pain intensity (motion), pain intensity (rest), pain relief, pulse rate, blood pressure, respiratory rate and side effects were made pre-drug,

and at 0.25, 0.5, 1, 2, 3, 4, 5 and 6 hours post-drug. Time to remedication was also recorded.

b. Applicant's findings

Statistical methods employed in this study were similar to those in study number 4. There were some missing data due to the misunderstanding of a nurse observer. Demographic factors and baseline pain intensity (motion and rest) were shown to be comparable between treatment groups.

SPID (motion and rest) and TOTPAR after adjustment for baseline pain were significantly in favor of the buprenorphine group. Maximum PID was greater for buprenorphine as was the proportion of patients experiencing no pain at some time during the post-drug evaluation period for pain at rest.

Missing data on vital signs were excluded in the analyses of safety variables. A significant decrease in pulse rate was observed in the buprenorphine group over the first hour. For systolic and diastolic blood pressure, both treatments produced a decrease from the baseline over the first two hours. Thereafter, the levels began to return towards the baseline. For respiratory rate, buprenorphine appeared to have a greater decrease than morphine. Side effects were similar in both drug groups but the sedation was greater after buprenorphine than after morphine.

c. Reviewer's comments

(i) Missing data is a major problem in this study, leading one to question the level of clinical control exercised by the investigator and the reliability of the remaining data. For example, 40% of the patients had no records of anesthetic and/or other drugs used during anesthesia. Five patients had missing pain scores at some observation periods. Estimated values were used in these cases. Nearly half of the patients had missing observations in their vital signs at some period of observation. Thus, analyses of changes in vital signs would not be reliable.

(ii) Buprenorphine (0.3 mg) appeared to have a higher sedative effect than did morphine (10 mg). As I have illustrated above in study number 1 pain relief and sedation could not fully be separated when comparing the treatment groups. Those comments would also be appropriate for this study.

(iii) Since side effects due to the test drugs might be confounded with those induced by anesthetic or other drugs used during anesthesia, and 40% of the patients had no such records, it is not possible to draw any conclusions regarding the comparability of side effects.

Power Calculations

In the case where there were no significant differences in the analyses of efficacy and safety variables, one must also be able to estimate the probability of detecting clinically meaningful differences between treatments at given levels of significance. This probability is referred to as the power of the statistical procedure. The applicant did not provide any power analysis for such cases. The following table is prepared by this reviewer to illustrate the magnitudes of the minimum differences in SPID and TOTPAR that could be detected with the corresponding minimum acceptable powers in the various studies when these variables were not statistically significant between treatments. It must be emphasized that if the required minimum differences to be detected are lower than the figures in the table, the power will be lowered to an unacceptable level.

Study No.	Mean SPID		Mean TOTPAR		Min. Difference to be Detected	Power
	Min.	Max.	Min.	Max.		
1	8.0	11.9	10.6	15.3	4.5	0.80
2	8.2	12.5	10.6	13.7	3.5	0.80
3	3.2	6.6	4.6	9.1	3.5	0.75
4	4.3	5.9	7.5	8.9	2.0	0.74
5	7.9	10.5	13.8	17.7	3.5	0.79

(All power figures are based on 2-sided t-tests with significance level of 0.05.)

III. Conclusions that should be conveyed to the applicant

This submission contains some evidence that buprenorphine was at least as efficacious and safe as morphine in treating patients with moderate to severe post-surgical pain. This evidence and the evidence of buprenorphine's superiority to morphine is, however, not substantial because of aspects of the experimental design in which not all sleeping patients were roused for the assessment of their pain levels and relief. This limits the inferences one can make based on these data since the distinction between SSLD, TOTPAR and SPID is masked. In addition, important factors were ignored in the applicant's analyses of the data. These factors are influence of pre-study

analgesic and/or anesthetic within 6 hours of drug administration, adjustment of vital signs for baseline values and the treatment of data after remedication.

The two studies by Quellette and the study by Dobkin have both the design and the analysis problems; that by Downing has only the analysis problem; and the study by Hovell suffers from inordinately large amounts of missing data.

The limitations on the statistical inferences engendered by the failure to rouse sleeping patients for the purpose of assessing pain and an additional failure to maintain a distinction between measurements taken of pain at rest and pain on motion cannot be remedied by reanalyses. In the context of the more limited statistical inferences, however, the studies reviewed here appear to be adequate for the purposes of the present submission. In contemplating additional studies of buprenorphine the applicant should bear in mind those important aspects of the experimental design.

We do feel that reanalyses of some of the data are warranted. The applicant is requested to:

- (i) reanalyze the TOTPAR and SPID data from studies by Quellette and Dobkin adjusting for the level and type of pre-study analgesics administered within 6 hours of the beginning of treatment;
- (ii) reanalyze the data from the Downing study adjusting for the age of the patients;
- (iii) reanalyze the vital signs data adjusting for baseline values in all studies.

In doing this the applicant should exclude from the analyses, in adherence to the protocol, data obtained after remedication.

The applicant should comment on the fact that nearly identical protocols were used in the Quellette (0.2 mg buprenorphine) and the Dobkin studies and yet patients exhibited dramatically different values of SPID, TOTPAR and SSLD between these two studies.

cc:
Orig. NDA 18-401
HFD-120
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6/21/80

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-401

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA 18-401

Drug/Drug Product: Buprenex ® (buprenorphine HCl) injectable

Sponsor: Reckitt & Colman

Date of Submission: 9/30/83 (Received on 10/4/83)

Date of Review: 12/5/00

Reviewer: Young Moon Choi, Ph.D.

Type of Submission: A study report of Phase 4 commitment

1

1. Background

Drug information: Buprenex (buprenorphine HCl) is a parenteral opioid analgesic and is classified as a narcotic under the Controlled Substance Act. Each ml of Buprenex contains 0.324 mg of buprenorphine HCl (equivalent to 0.3 mg of buprenorphine), 50 mg anhydrous dextrose, water for injection and HCl to adjust pH.

This drug is indicated for the relief of moderate to severe pain. The recommended dosage regimens are as follows:

For adult, 1 ml of Buprenex (0.3 mg buprenorphine) given by deep intramuscular (IM) or slow (over at least 2 minutes) intravenous (IV) injection up to 6-hour intervals. Repeat once (up to 0.3 mg) if required 30 to 60 minutes after initial dosage.

For children (2-12 years of age), doses between 2-6 µg/kg of body weight given every 4-6 hours.

History: The original NDA for this drug (NDA 18-401) was submitted on 10/31/1979 and was approved on 12/29/81 with the sponsor's agreement upon post approval commitments of a comparative bioavailability (BA) study after IV injection and IM injection in normal subjects. As agreed, the sponsor conducted a BA study and submitted the study report on 9/30/83.

2. Reviewer's Comments:

The present review is focused on the following questions with the above regulatory background:

- (1) Is the study conducted appropriately as the agency recommended?
- (2) Does the labeling need to be changed due to the BA study results?

This reviewer found that the study was conducted as the agency recommended.

The study design was a randomized, crossover, and open label in healthy male volunteers (n=18). Blood was collected to measure plasma concentrations of buprenorphine for 10 hours following a single dose of 0.3 mg by IV and IM.

Radioimmunoassay (RIA) method was utilized to measure plasma levels of buprenorphine.

The pharmacokinetic parameters are summarized in the following table.

Table I. Pharmacokinetic parameters after a single dose of buprenorphine HCl (0.3 mg of free base) administered by IV and IM routes.

Parameters	Intravenous (IV) administration	Intramuscular (IM) administration
Cmax (ng/ml)	1.45-24.0 (mean 8.11 ± 1.61)	0.6-5.0 (mean 2.32 ± 0.3)
Tmax (hour)	0.017-0.167 (mean 0.048 ± 0.009)	0.083-0.5 (mean 0.22 ± 0.03)
AUC 0-inf (ng·hr/ml)	0.875-5.435 (mean 2.377 ± 0.331)	0.73-4.092 (mean 2.524 ± 0.314)
T1/2 (hour)	0.28-4.79 (mean 1.61 ± 0.37)	-

The Cmax after IV administration was much higher than after IM. T max was delayed after IM injection. This result is supporting the present labeling language; "when used intravenously, the time of onset and peak effect are shortened." Therefore, labeling change based on this data is not recommended.

The total AUC data indicates a similar systemic availability for both routes. It is important to note that the total AUC (AUC0-inf) after IM administration appeared to be larger than that after IV administration. The mean ratio, AUC (im)/AUC (iv), appeared 1.366 ± 0.230 with large intersubject variance. This larger value after IM than IV may be due to (1) the cross reactivity of the metabolite and (2) AUC estimation by ignoring the very initial high concentration after IV injection for 10 seconds. Therefore, labeling change based on this data is not recommended.

The elimination half-life in the present study 0.28-4.79 (mean 1.61 ± 0.37) is shorter than the value in the current labeling (1.2- 7.2 hours with mean of 2.2). This difference may be due to the fact that the patients had been in surgery in which varying amounts of blood was lost and replaced by transfusion in the earlier data.

Overall, it is now known that RIA method cross reacts with buprenorphine metabolites and the terminal half-life of the drug is very long. Therefore, the results of this study may not be accurate per current knowledge. However, the sponsor in good faith promptly conducted the study within two years of approval in 1981 using then available analytical method. Therefore, the commitment is fulfilled.

3. Recommendation

The Division of Pharmaceutical Evaluation II at the Office of Clinical Pharmacology and Biopharmaceutics has completed the review on Phase IV commitment study report and found that the sponsor conducted the study as agreed in the letter dated 12/29/81. The results of this study do not warrants any labeling changes.

Young Moon Choi, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence

Suresh Doddapaneni, Ph.D.
Team leader
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CC:

HFD-170	Div.,CSO
HFD-870	Hunt, Doddapaneni, Malinowski, Choi
CDR	Attn: Barbara Murphy (1x)

Appendix I: Summary of the Study

Appendix I. Summary of the study

Title: A study to compare the bioavailability of buprenorphine administered by the intravenous and intramuscular route

Objectives: To determine and compare the bioavailability of buprenorphine HCl administered as a dose level of 0.323 mg by the intravenous and intramuscular route.

Study design: Open label, crossover study. One-week apart between treatment.

Inclusion criteria: Healthy male volunteers (18-50 years old, 60-85 kg)

Exclusion criteria

- ✓ A past history of cardiovascular or respiratory illness
- ✓ In the presence of active disease, major illness or surgery in the three months prior to the study.
- ✓ Past history of drug abuse or hypersensitivity to buprenorphine

Study medication: Buprenorphine HCl in 1 ml ampul containing 0.323 mg for IV injection

Procedures: The volunteers were fasted overnight. A standard mid-day meal was taken four hours after dosing. An indwelling cannula was inserted into a suitable peripheral vein and kept in situ for the first six hours of the study.

Each subject received intravenous injection into a suitable peripheral vein at a rate of 1 ml in ten seconds in the contralateral arm to the indwelling cannula or intramuscular injection into the deltoid muscle of the contralateral arm at a similar rate of administration.

Blood sampling: A 5 ml venous blood sample was taken via the indwelling cannula immediately prior to each dose, and at 1, 2, 5, 10, 30, 45, 60, 120, 180, 240, 360, 480, and 600 min.

Data analysis: Radioimmunoassay was used. Limit of quantitation was 0.05 ng/ml. It should be noted that the assay sensitivity was 0.25 ng for the original NDA data.

Pharmacokinetic parameters:

C_{max} and t_{max} were obtained by inspection of the data for each volunteer.

The elimination rate constant and plasma elimination half-life were calculated for each subject from the intravenous data after curve-fitting using NONLIN.

Areas under the plasma level/time curve were calculated on a Wang desktop computer by the trapezoidal rule using computer program. AUC_{0-inf} was similarly calculated with the addition of the terminal area calculated using C_t/k_{el}, where C_t is the concentration in the last plasma sample and k_{el} is the elimination rate constant.

The best correlation to the data was obtained using the biexponential (for 13 subjects) or monoexponential (for five subjects) equation:

Although the statistical comparison of AUC was invalidated by a significant or nearly significant difference between the treatment order groups (carryover), the elimination profiles were very similar following both routes of administration (Figure 1).

Results

Individual plasma levels and mean values are listed in Table II and III and shown in Figure 1. Pharmacokinetic parameters were shown in Table I (page 2 of the present review), IV, and V.

Table 2 - Plasma concentration of buprenorphine in volunteers after an intravenous dose of 0.3 mg of buprenorphine, base, as hydrochloride.

Subject	Plasma concentration of Buprenorphine (ng ml ⁻¹)										Calibration Curve No. s.					
	Time (hours)															
Zero	0.017	0.033	0.083	0.167	0.25	0.5	0.75	1.0	2.0	3.0	4.0	6.0	8.0	10.0		
1	<0.05	24.0*	9.40	3.90	1.82	0.74	0.32	0.23	0.16	-	<0.05*	-	<0.05	<0.05*	1,*19,*20	
2	<0.05	2.11	1.56	1.30	1.20	1.48	0.84	0.40	0.07	<0.05	<0.05	<0.05	<0.05	<0.05	1,*19,*20	
3	<0.05	-	16.0*	2.70	1.50	1.06	0.58	0.38	0.33	-	<0.05	<0.05	<0.05	<0.05	2,*39	
4	<0.05	5.30*	1.48*	4.45*	2.13	1.30	0.90	0.74	0.60	0.23	0.18	0.20	0.14	0.11	0.05	3,*40
5	<0.05	2.80	10.5	2.80	1.80	1.37	0.96	0.42	0.28	0.18	0.22	0.12	0.05	<0.05	4,*19	
6	<0.05	3.70	9.70	6.10	1.83	1.10	0.48	0.53	0.31	0.19*	0.18	0.18	0.12	0.22	<0.05	6,*19
7	<0.05	6.20*	7.00	2.90	1.05	0.98	0.29	0.31	0.26	0.19	0.27	0.09	0.10	<0.05	<0.05	7,*19
8	(0.11*)	3.90	11.0	3.10	1.50	1.07	0.50	0.66	0.40	0.29	0.10	0.11	<0.05	<0.05	<0.05	5
9	<0.05	22.0*	8.40*	3.55	1.77	1.36	0.84	0.76	0.55	0.38	0.29	-	0.30	0.096	<0.05	9,*19,*20
10	<0.05*	0.50	3.75	3.80	3.80	3.60	1.60	1.70	1.16	1.29	0.56	0.22	<0.05	<0.05	<0.05	10,*19
11	<0.05	3.20	4.70	2.40	1.65	1.24	0.76	0.35	0.18	>0.05*	<0.05	-	<0.05	<0.05	<0.05*	8,*20
12	<0.05	0.96	8.40	5.80	2.60	1.67	0.66	0.38	0.42	0.17	0.22	0.17	0.05	0.06	<0.05	9,*19
13	-	0.50	1.17	3.30	1.79	1.11	0.60	0.45	0.42	-	0.21	0.29	0.12	<0.05	<0.05	10,*19
14	<0.05	1.00	1.60	2.36	0.92	0.90	0.49	0.44	0.21	0.26	0.09	0.11	<0.05	<0.05	<0.05	11,*19
15	<0.05	6.95*	11.1	3.15	1.53	1.44	0.96	0.94	0.45	0.38*	0.30	0.33	0.08	<0.05	<0.05	11,*19
16	<0.05	0.084	40.05*	1.40	1.45	1.00	0.46	0.25	0.39	0.26	0.24*	0.06	<0.05	<0.05	<0.05	16,*19
17	<0.05	0.80	1.08	1.58	1.10	0.74	0.49	0.50	0.44	0.34	0.24	0.22	0.18	<0.05	<0.05*	17,*20
18	<0.05	1.50	1.63	1.41	1.11	0.60	0.67	0.56	0.74	0.32	0.13	0.07	<0.05	-	-	18
Mean	Zero	5.02	9.03	3.11	1.69	1.26	0.69	0.55	0.41	0.30	0.18	0.14	0.06	0.03	Zero	-
	-SEM	±1.72	±1.11	±0.32	±0.16	±0.15	±0.07	±0.00	±0.06	±0.08	±0.03	±0.02	±0.01	-	-	-

() = Contamination suspected, not included in means

- = No result

<0.05 = Taken as zero

Table 3 - Plasma concentration of pipermorphins in volunteers after an intramuscular dose of 0.3 mg of buprenorphine base as hydrochloride

Subject	Plasma concentration of Buprenorphine (ng ml ⁻¹)												Calibration Curve No. 1, 3.			
	Time (hours)															
Zero	0.017	0.033	0.083	0.167	0.25	0.5	0.75	1.0	2.0	3.0	4.0	6.0	8.0	10.0		
1	<0.05	-	<0.05	2.75	2.06	1.80	1.32	1.06	0.58	0.27	0.44	0.24	-	<0.05	<0.05	21
2	<0.05	0.68	2.90	3.30	2.23	2.44	1.23	1.20	0.72	0.49	0.41	0.18	0.12	0.18	<0.05	22
3	<0.05	0.06	1.60	4.30	3.70	2.40	0.90	0.92	0.54	0.38	-	0.33	0.14	<0.05	<0.05	23
4	<0.05	-	0.25	0.78	1.26	0.71	0.45	0.43	0.08	0.08	<0.05	<0.05	<0.05	-	-	24
5	<0.05*	0.24	0.89	3.10	5.00	3.50	1.57	1.04	0.88	0.36	0.25	0.31	0.17	0.11	<0.05	25,*39
6	<0.05*	0.07	0.29	4.60	4.25	4.00	1.10	0.56	0.35	0.31	0.38	0.33	0.19	0.07	<0.05	26,*39
7	<0.05	0.06	1.50	2.11	1.80	2.16	1.30	0.46	0.38	<0.05*	<0.05*	0.06	<0.05	<0.05	<0.05	27,*39
8	<0.05	<0.05	0.24	0.64	2.00	0.50	0.41	0.33	0.26	0.31	0.24	0.20	0.05	<0.05	<0.05	28
9	<0.05	0.19	1.17	1.54	1.54	1.60	0.62	0.41	0.33	0.20	0.35	0.25	0.10	0.10	<0.05	29
10	<0.05	<0.05	0.28	1.07	2.20	1.18	0.70	0.19*	0.08*	0.41	0.22	0.13	<0.05	<0.05	30,*39	
11	<0.05	<0.05	0.27	1.75	2.00	1.45	0.72	0.60	0.38	0.08	<0.05	<0.05	<0.05	<0.05	31	
12	<0.05	<0.05	<0.05*	<0.05	0.33	0.56	0.70	0.42	0.31	0.24*	0.13	0.31	0.12*	0.08	<0.05	12,*19
13	<0.05	<0.05	0.10	0.20	1.20	2.20	1.45	0.68	0.50	0.23	0.44	0.44	0.22	<0.05	<0.05*	33,*39
14	(0.18*)	<0.05	1.10	2.50	2.30	1.60	0.84	0.65	0.38	0.47	0.28	0.10	0.12	<0.05	34,*39	
15	(0.09)	0.07	0.30	1.52	1.30	2.00	1.16	0.94	0.72	0.37	0.25	0.25	0.06	<0.05*	<0.05*	35,*39
16	<0.05	<0.05*	1.20	0.98	0.60	0.74	0.31	0.28	0.21	0.23	0.21	0.12	<0.05	<0.05	36,*39	
17	<0.05	<0.05	<0.05	0.16	0.38	0.60	0.21	0.18	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	37
18	<0.05	<0.05	0.05	0.72	1.04	1.14	1.39	1.26	0.99	0.48	0.42	0.39	0.10	<0.05	<0.05	38
Mean	Zero	0.09	0.63	1.65	1.88	1.87	1.07	0.73	0.55	0.25	0.26	0.27	0.13	0.04	Zero	-
	-	0.04	0.25	1.34	0.31	0.23	0.08	0.08	0.18	0.04	0.04	0.02	0.02	0.01		

“ ” = Contamination suspected, not included in means

- = NO result

100,000 = Werkzeug 35 zaro

Figure 1 - Mean plasma levels of buprenorphine in volunteers after a single dose of 0.3 mg by intravenous and intramuscular routes

BUPRENORPHINE PLASMA LEVELS

MEAN DATA (N=18)
IV + IM 0

CONCN. (NG ML⁻¹)

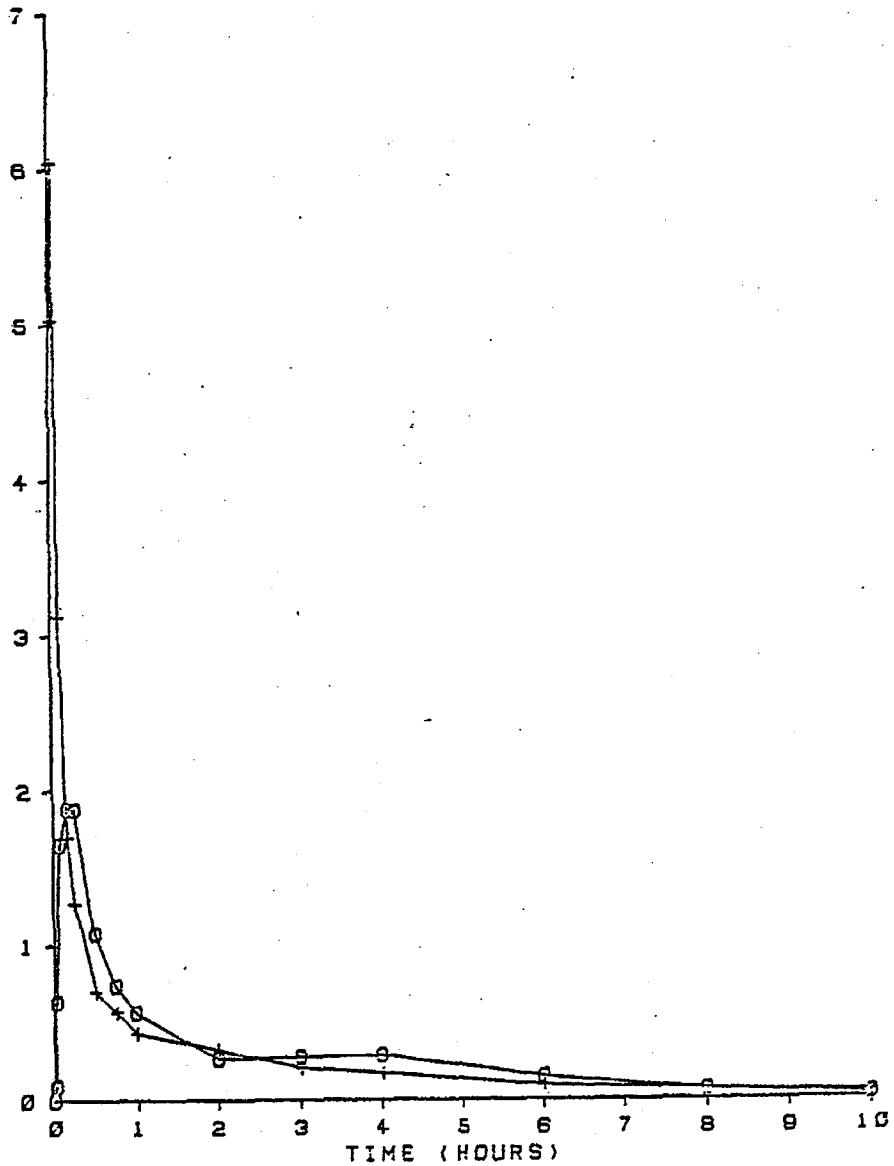


Table 4 - Pharmacokinetic Parameters After Intravenous Buprenorphine

Subject	C _{max} ngml ⁻¹	t _{max} h	k _{el} h ⁻¹	t h	AUC (o-Tn) ngml ⁻¹ h	AUC (o-oo) ngml ⁻¹ h
1	24.0	0.017	-	-	1.376	-
2	2.11	0.017	1.91	0.36	0.839	0.875
3	16.0	0.033	-	-	1.428	-
4	5.3	0.017	0.60	1.16	2.874	2.957
5	10.5	0.033	2.11	0.33	1.939	1.996
6	9.7	0.033	0.15	4.79	2.672	4.192
7	7.0	0.033	1.58	0.44	1.786	1.849
8	11.0	0.033	1.27	0.55	1.943	2.031
9	22.0	0.017	-	-	3.802	-
10	3.8	0.083	0.35	1.96	4.813	5.435
11	4.7	0.033	2.48	0.28	1.013	1.086
12	8.4	0.033	0.36	1.95	2.504	2.673
13	3.3	0.083	0.24	2.90	2.207	2.709
14	2.36	0.083	1.26	0.55	1.223	1.310
15	11.1	0.033	-	-	3.071	-
16	1.45	0.167	0.27	2.60	1.347	1.572
17	1.58	0.083	0.22	3.22	1.982	2.818
18	1.63	0.033	0.47	1.46	1.621	1.768
Mean	8.11	0.048	0.95	1.61	2.136	2.377
± SEM	±1.61	±0.009	±0.21	±0.37	±0.241	±0.331
Parameters from mean plasma data	6.03	0.033	1.10	0.63	2.247	2.275

- = Elimination phase not present in data

Table 5 - Pharmacokinetic Parameters After Intramuscular Euprenorphine

Subject	Cmax	tmax	AUC (0-Tn)	AUC (0-oo-)	Ratio AUC _(0-Tn) / AUC _(0-oo-)	im / iv
1	2.75	0.083	2.443	-	*1.775	
2	3.30	0.083	3.568	3.661	4.184	
3	4.30	0.083	3.279	-	*2.296	
4	1.26	0.167	0.596	0.730	0.247	
5	5.00	0.167	3.969	4.021	2.015	
6	4.60	0.083	3.609	4.092	0.976	
7	2.11	0.083	1.202	1.443	0.780	
8	2.00	0.25	1.966	2.125	1.046	
9	1.60	0.25	2.229	-	*0.586	
10	2.20	0.25	2.013	2.381	0.438	
11	2.00	0.167	1.142	1.174	1.081	
12	0.70	0.5	1.750	1.974	0.738	
13	2.20	0.25	2.878	3.799	1.402	
14	2.50	0.167	3.272	3.367	2.570	
15	2.00	0.25	2.584	-	*0.841	
16	1.28	0.083	1.580	2.030	1.291	
17	0.60	0.5	0.302	1.138	0.404	
18	1.39	0.5	3.192	3.403	1.925	
Mean	2.32	0.22	2.310	2.524	1.366	
± SEM	±0.30	±0.03	±0.254	±0.314	±0.230	
Parameters						
from mean	1.88	0.167	2.610	2.646	1.163	
plasma data						

- = Elimination rate data not available

* = AUC_(0-Tn) used

/s/

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