

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207975Orig1s000

PHARMACOLOGY REVIEW(S)



FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Avenue, Silver Spring, MD 20993

Secondary Pharmacology Toxicology Review

Application number: 207975
Supporting document/s: 001, 002 & 036
Applicant's letter date: 9/30/2014, 12/23/2014 & 12/4/2015
CDER stamp date: 9/30/2014, 12/23/2014 & 12/4/2015
Product: VANTRELA ER (hydrocodone bitartrate)
extended-release tablets
Indication: Management of pain severe enough to require
daily, around-the-clock, long-term opioid treatment
for which alternative options are inadequate
Applicant: Teva Branded Pharmaceutical Products R&D Inc.
Review Division: Division of Anesthesia, Analgesia, and Addiction
Products
Reviewers: Elizabeth A. Bolan, PhD & Huiqing Hao, PhD
Supervisor/Team Leader: R. Daniel Mellon, PhD
Division Director: Sharon Hertz, MD
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Executive Summary:

Dr. Elizabeth Bolan completed the primary nonclinical pharmacology and toxicology review of NDA 207975. She concludes that the NDA may be approved as a 505(b)(1) application if the Agency is willing to waive pharmacology, ADME, and chronic toxicology studies. The Applicant's request for a waiver of these studies is based on Teva's assertion that the studies are "unnecessary based upon general knowledge of hydrocodone and complimentary data generated by Teva." This waiver request is discussed in this review. Given the extensive history of use of well-known opioid analgesics, like hydrocodone, the requested waiver of dedicated pharmacology and ADME studies is justifiable, since it is general knowledge that hydrocodone is an opioid agonist, and human ADME data exist to inform labeling. Although chronic toxicology data do contribute to the understanding of the potential adverse effects of a drug by providing histopathological data that one cannot obtain from human experience, chronic toxicology studies with opioids cannot fully characterize the toxicity of the high doses that can be achieved in opioid tolerant patients and there is an extensive clinical experience with well-known opioids such as hydrocodone. Therefore, the NDA may be approved as a 505(b)(1) application if the clinical team concludes that chronic nonclinical toxicology studies are not necessary, based on general knowledge obtained from the extensive human experience with well-understood clinically-used opioid agonists and the Phase 3 studies conducted by Teva to support the Vantrela ER application.

Regulatory Background for NDA 207975:

Teva Branded Pharmaceutical Products R&D originally submitted a 505(b)(2) application for VANTRELA ER (hydrocodone bitartrate) tablets on December 23, 2014 intending to rely, in part, on the Agency's previous finding of safety and effectiveness for Vicoprofen (NDA 20716). The proposed drug product is formulated in 15, 30, 45, 60, and 90 mg strengths and is intended for twice a day (BID) dosing.

The development program for this NDA was completed under IND 105587, which was submitted to the Agency on September 29, 2009. There was no preIND meeting for this program. The first meeting between the Agency and the Sponsor of the IND occurred at the End-of-Phase 2 (EOP2) on July 14, 2010. At that time the Agency outlined the studies that were deemed necessary to support approval of the proposed 505(b)(2) NDA.

The Division provided the following advice:

As a single entity hydrocodone formulation, the proposed drug product will yield exposures of hydrocodone much greater than seen with previous clinical experience. For a 505(b)(2) NDA, although the extensive clinical experience with hydrocodone combination products and opioids in general can be used to reduce the standard ICH requirements for repeat-dose toxicology, additional toxicology studies will be required for the NDA, including the following:

- a. a 3-month toxicology study using the clinical formulation and placebo,
- b. standard reproductive and developmental toxicology battery for hydrocodone,
- c. standard genetic toxicology battery for hydrocodone, and,
- d. carcinogenicity assessments in two species for hydrocodone.

Prior to initiation of carcinogenicity studies, you are encouraged to submit your study protocols to the IND and obtain concurrence from the Executive Carcinogenicity Assessment Committee (eCAC). Please refer to the following guidance document: Carcinogenicity Study Protocol Submissions (May 2002), which is available on the CDER website at the following location:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078924.pdf>.

Should you elect to file a 505(b)(1) NDA, you must own or have right of references for all nonclinical toxicology studies, including basic pharmacology, safety pharmacology, ADME, general toxicology, reproductive toxicology, genetic toxicology, and carcinogenicity, as per ICHM3(R2).

In this meeting, the Agency noted that the 505(b)(2) referenced product would have to be an NDA, such as Vicoprofen. The development program outlined at this time was consistent with advice we gave other sponsors with similar 505(b)(2) development programs which were initiated as early as 1999 and 2001. At that time, development programs were informed that they only needed to rely upon an Agency finding for a hydrocodone-containing drug product to support a 505(b)(2) application. The referenced product proposed by the companies was generally an ANDA indicated for "moderate to severe pain", an indication that does not include any limitation on the duration of use in the indication. Although the only available NDA

that could be referenced was Vicoprofen, which is only approved for an acute indication, the Agency elected to not impose additional requirements on these 505(b)(2) programs that were relying on Vicoprofen based on the extensive clinical experience with hydrocodone and the conclusion that chronic toxicology studies were unnecessary as they would not impact the overall clinical safety assessment of the drug product and were not necessary to inform product labeling.

NDA 207975 was submitted on December 23, 2014 as a 505(b)(2) application referencing, in part, the Agency's previous finding of safety and effectiveness for Vicoprofen (NDA 20716). However, on July 1, 2015, AbbVie submitted to the FDA a letter of authorization granting TEVA right of reference to NDA 20716 to support NDA 207975 and on July 21, 2015, Teva amended the FDA Form 356h to describe the application as a 505(b)(1) application.

On December 4, 2015 Teva submitted a request for a waiver of certain nonclinical pharmacology and toxicology studies under 21 CFR §314.90¹ stating that pharmacology (primary, secondary, and safety), ADME, and chronic toxicology studies of hydrocodone are not necessary for FDA to make an evaluation on the safety and effectiveness of Vantrela ER. This memorandum is intended to summarize the adequacy of the nonclinical pharmacology and toxicology section of NDA 207975.

Nonclinical information submitted by TEVA in NDA 207975:

As per 21 CFR §314.50(d)(2) the nonclinical pharmacology and toxicology section of an NDA should contain the following:

- i. Studies of the pharmacological actions of the drug in relation to its proposed therapeutic indication and studies that otherwise define the pharmacologic properties of the drug or are pertinent to possible adverse effects.
- ii. Studies of the toxicological effects of the drug as they relate to the drug's intended clinical uses, including, as appropriate, studies assessing the drug's acute, subacute,

¹ §314.90 Waivers.

(a) An applicant may ask the Food and Drug Administration to waive under this section any requirement that applies to the applicant under §314.50 through 314.81. An applicant may ask FDA to waive under §314.126(c) any criteria of an adequate and well-controlled study described in §314.126(b). A waiver request under this section is required to be submitted with supporting documentation in an application, or in an amendment or supplement to an application. The waiver request is required to contain one of the following:

- (1) An explanation why the applicant's compliance with the requirement is unnecessary or cannot be achieved;
 - (2) A description of an alternative submission that satisfies the purpose of the requirement; or
 - (3) Other information justifying a waiver.
- (b) FDA may grant a waiver if it finds one of the following:
- (1) The applicant's compliance with the requirement is unnecessary for the agency to evaluate the application or compliance cannot be achieved;
 - (2) The applicant's alternative submission satisfies the requirement; or
 - (3) The applicant's submission otherwise justifies a waiver.

and chronic toxicity; carcinogenicity; and studies of toxicities related to the drug's particular mode of administration or conditions of use.

- iii. Studies, as appropriate, of the effects of the drug on reproduction and on the developing fetus.
- iv. Any studies of the absorption, distribution, metabolism, and excretion of the drug in animals.

The nonclinical data recommendations for marketing authorization of a drug product are also outlined in the ICH M3(R2)² guidance document. The table below summarizes the information/studies submitted or referenced by TEVA, or studies for which a waiver was requested. Discussion of each of these categories with respect to the application follows the table.

Nonclinical Data Category as per M3(R2)	Data Submitted by TEVA
Pharmacology (safety pharmacology and pharmacodynamic studies)	<ul style="list-style-type: none">• TEVA submitted right of reference to the Vicoprofen NDA.• TEVA submitted a request for waiver of any additional pharmacology studies.
ADME	<ul style="list-style-type: none">• An in vitro metabolism study was submitted.• TEVA submitted right of reference to the Vicoprofen NDA.• TEVA submitted a request for waiver of any additional nonclinical ADME studies.
Toxicology	<ul style="list-style-type: none">• TEVA submitted 90-day oral toxicity studies in the dog, rat and mouse• TEVA submitted right of reference to the Vicoprofen NDA.• TEVA submitted a request for waiver for chronic toxicology studies.
Genetic Toxicology	<ul style="list-style-type: none">• TEVA conducted the full standard battery of genetic toxicology studies.
Reproductive and Developmental Toxicology	<ul style="list-style-type: none">• TEVA conducted the full standard battery of reproductive and developmental toxicology studies.
Carcinogenicity	<ul style="list-style-type: none">• TEVA submitted right-of-reference to carcinogenicity studies from Zogenix.

Pharmacology

The ICH M3(R2) guidance document subdivides pharmacology studies into three categories: safety pharmacology, primary pharmacodynamics, and secondary

² M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

pharmacodynamics studies. These will be discussed below followed by a discussion of the historic knowledge of the pharmacology of hydrocodone and similar opioid receptor agonists.

Safety Pharmacology. As per ICH M3(R2) (p. 6), “Safety pharmacology and pharmacodynamic (PD) studies are defined in ICH S7A (Ref. 5). The core battery of safety pharmacology studies includes the assessment of effects on cardiovascular, central nervous, and respiratory systems, and should generally be conducted before human exposure ...” Although 21 CFR §314.50(d)(2) does not specifically require safety pharmacology studies be completed for an NDA, these studies could be considered pertinent to define possible adverse effects in the absence of previous human experience. Safety pharmacology studies are further described in the ICH S7A guidance document³ (p. 9), which states that “The effects of a test substance on the functions listed in the safety pharmacology core battery should be investigated prior to first administration in humans.” Follow-up and supplemental safety pharmacology studies “should be assessed prior to product approval, **unless not warranted**, in which case this should be justified. Available information from toxicology studies adequately designed and conducted to address safety pharmacology endpoints, **or information from clinical studies**, can support this assessment and replace safety pharmacology studies.” (Emphasis added).

Reviewer Comment: Safety pharmacology studies are needed to support the first-in-human exposure to drugs or to follow-up on unexpected adverse effects noted in clinical studies. The results of these studies do not appear in labeling and the studies are unnecessary for drugs for which there is an extensive history of clinical use. Teva’s request for a waiver of safety pharmacology studies is justified.

Primary Pharmacodynamics. Primary pharmacodynamic studies, as defined by the S7A guidance (p. 10), are “[s]tudies on the mode of action and/or effects of a substance in relation to its desired therapeutic target”.

Reviewer Comment: The proposed therapeutic indication of hydrocodone is analgesia. As noted in the Vicoprofen labeling:

Hydrocodone is a semisynthetic opioid analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opioids is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system.

Therefore, the NDA contains adequate information to characterize the pharmacological actions of the drug in relation to its proposed therapeutic indication and otherwise define the pharmacologic properties of the drug. Likewise, the intended effect of hydrocodone is considered general knowledge. As noted in *Goodman & Gilman’s The Pharmacological Basis of*

³ S7A Safety Pharmacology Studies for Human Pharmaceuticals
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Therapeutics chapter on Opioid Analgesics⁴, “Morphine and most other clinically used opioid agonists exert their effects through μ opioid receptors.” Therefore, no further primary pharmacodynamics studies are necessary to support approval of the application. Teva’s request for a waiver of further primary pharmacodynamics studies is justified.

Secondary Pharmacodynamics. Secondary pharmacodynamic studies, as defined by the S7A guidance (p. 10), are “[s]tudies on the mode of action and/or effects of a substance **not** related to its desired therapeutic target” (Emphasis added).

Reviewer Comment: Secondary pharmacology studies (receptor binding studies and functional assessments) are conducted for new molecular entities to characterize the potential unintended effects of a drug. The results of these studies can help in the interpretation of general toxicology study results and inform the clinical studies with respect to possible adverse effects.

There is an extensive clinical history of use of hydrocodone and similar mu-opioid receptor agonists such as morphine. As noted in *Goodman & Gilman's The Pharmacological Basis of Therapeutics* chapter on Opioid Analgesics, “The first undisputed reference to opium is found in the writings of Theophrastus in the third century B.C.” Morphine was first isolated from opium by Sertürner in 1806 and codeine was isolated by Robiquet in 1832 (Gutstein and Akil, 2001). Hydrocodone is a semi-synthetic opioid that was first synthesized from codeine in Germany in 1920 by Carl Mannich and Helene Löwenheim and was first approved by FDA on March 23, 1943 (NDA 5213; Hycodan, homatropine methylbromide and hydrocodone bitartrate for cough).

Most textbooks do not specifically discuss hydrocodone (or codeine, oxycodone, morphine, oxymorphone, and hydromorphone) separately because these older well-known clinically-used opioids are discussed as a class. As noted in Gutstein and Akil’s chapter on opioid analgesics (Gutstein and Akil, 2001), “Morphine and most other clinically used opioid agonists … affect a wide range of physiological systems. They produce analgesia, affect mood and rewarding behavior (see also Chapter 24), and alter respiratory, cardiovascular, gastrointestinal, and neuroendocrine function.” As a class, the secondary pharmacodynamics properties of well-understood opioids, like hydrocodone and morphine, are discussed in common textbooks and can be considered to be general knowledge. These unintended effects include alterations in mood (euphoria, tranquility) and rewarding properties, other CNS-mediated effects (temperature, neuroendocrine effects, miosis, convulsions, depression of respiration, depression of the cough reflex, nausea, emesis), cardiovascular effects (peripheral vasodilation), gastrointestinal effects (e.g., decreased peristalsis, constriction of the sphincter of Oddi), other smooth muscle effects (e.g., increased muscle tone

⁴ Gutstein HB, Akil H (2001) Opioid Analgesics. In: Goodman & Gilman's The Pharmacological Basis of Therapeutics (Hardman, J. G. et al., eds), pp 569-619 New York: McGraw-Hill.

of the external sphincters of the urinary bladder, inhibition of micturition), skin effects (e.g., flushing due to dilation of cutaneous blood vessels), immune effects (generally suppressive) and tolerance and physical dependence (Way et al., 1995, Gutstein and Akil, 2001).

Teva claims that based on general knowledge and the fact that the side-effect profile of hydrocodone has been characterized in the clinical studies conducted with Vantrela ER, further secondary pharmacodynamics studies are unnecessary as they would not further contribute to the understanding of the effects of hydrocodone in humans. Given the extensive history of clinical use, I agree that nonclinical secondary pharmacodynamics studies to characterize the adverse effects of hydrocodone would not provide any data that would alter the current clinical use of the drug or inform physicians of potential toxicities that they are not already well aware of. Therefore, a waiver of these studies for hydrocodone based on general knowledge of well-known opioids in this class with extensive human experience is justifiable (refer to the Division Director Review for discussion of the clinical experience).

Toxicology

As per 21 CFR §314.50(d)(2), the nonclinical pharmacology and toxicology section of an NDA should contain “Studies of the toxicological effects of the drug as they relate to the drug’s intended clinical uses, including, **as appropriate**, studies assessing the drug’s acute, subacute, and chronic toxicity ...” (Emphasis added)

As per the ICH M3(R2) Guidance, to support clinical trials of > 6 months duration and a marketing application for a chronic indication, a 6-month repeat-dose toxicology study in a rodent and a 9-month repeat-dose toxicology study in a nonrodent model should be completed.

Chronic toxicology studies are conducted to characterize potentially clinically relevant toxicity in order to inform the design of the long-term clinical studies. For example, if significant adverse effects in the toxicology studies are observed at clinically relevant exposures, the nonclinical study results could indicate the need to impose dosing limitations in proposed clinical studies or inform the need for additional clinical monitoring. For a new molecular entity, these repeat-dose toxicology studies are essential to characterize the potential toxicity of the drug and to support the safety of the proposed doses to be employed in the clinical studies. However, when considerable clinical experience exists, it is not unusual for clinical studies to proceed without repeat-dose toxicology data. For example, there are no GLP chronic general toxicology data for morphine, oxymorphone, or oxycodone, all of which are approved drug products with chronic indications. Likewise, Phase 3 clinical studies for hydrocodone have been allowed to proceed without these data based on extensive clinical experience and our general knowledge of opioids.

Teva's request for a waiver of the requirement for conducting chronic toxicology studies focuses on the following general points:

1. "The safety profile of selective μ -receptor opioid agonists (which include hydrocodone, hydromorphone, oxymorphone, oxycodone, morphine, and fentanyl) has been well-characterized in nonclinical animal safety studies, clinical studies; as well as through decades of use as analgesics. Repeat-dose animal studies with hydrocodone and other opioids have indicated that the dose-limiting effects in both rodents and non-rodents are related to exaggerated pharmacology, which include CNS effects (sedation, hypoactivity, uncoordinated movements), respiratory effects (decreased respiratory rates), cardiovascular effects (hypotension), and/or gastrointestinal effects (decreased motility). The dose-limiting effects of opioids in animal studies are therefore well-characterized and similar to those effects observed in human patients."
2. "[T]he side effects observed in nonclinical studies do not allow for an assessment of higher doses because these effects are dose-limiting. Additionally, systemic exposures in animal studies are also limited by these [dose limiting] effects, such that systemic exposures in human patients are considered to be more relevant for safety evaluation than those achievable in repeat-dose animal studies. Because of this, additional repeat-dose animal studies are not considered to be warranted for human safety assessment, which is why such studies can be waived in this situation."
3. In Teva's 13-week toxicology "studies with hydrocodone, no unexpected toxicities were identified, and the results, including full histopathologic evaluation of tissues/organs, were similar to those observed with other selective μ -receptor opioid agonists."
4. Teva obtained right of reference to data from two carcinogenicity studies with hydrocodone which included "full evaluation of clinical signs, survival and growth of the animals, standard hematological parameters, as well as full histopathological examination at the end of the studies."
5. Teva stated that their "long-term safety data collected in our phase 3 studies did not identify any unsuspected safety findings."

Reviewer Assessment of Waiver Request for Chronic Toxicology Studies

Each of Teva's points will be discussed below both individually as well as collectively.

Point Number 1: Repeat-dose toxicology studies of common opioids in animals have demonstrated expected dose-limiting toxicities consistent with exaggerated pharmacology and these effects have been observed in humans.

Reviewer Comment: Teva has completed 13-week toxicology studies for hydrocodone in rats, mice, and dogs. The adverse effect profile is consistent with predicted opioid toxicities taking into consideration the known physiological effects of opioids. For example, adverse effects noted in Teva's animal studies include sedation, hypoactivity, ataxia, decreased food intake, tremors, and body weight loss. At higher doses of opioids, respiratory depression and convulsions are well known risks of opioids. The latter two findings are considered to have exceeded the maximum tolerated dose in toxicology studies. All of these findings are known side effects of opioids in humans. One finding in the Teva animal toxicology studies that has not been routinely described in humans is scabs in the skin and self-mutilation. These findings may be due to histamine release and subsequent itching and scratching of the skin by the animals. Although not reported in humans, these findings are well-known and expected to occur in opioid toxicology studies. Overall, I agree with Teva's conclusion that the toxicities noted in animals do appear to be primarily exaggerated pharmacological effects. However, the 13-week studies with hydrocodone they can refer to are not chronic toxicology studies and therefore this point alone does not justify a waiver.

Point Number 2: The nonclinical dose limitations preclude testing of clinically relevant higher doses and humans are the only feasible species to test higher doses of hydrocodone.

Reviewer Comment: Chronic toxicology studies with opioids intending to characterize the safety of opioid exposure levels predicted to be obtained in opioid-tolerant patients are not feasible due to dose limiting toxicities. The design of such a study is extremely complicated.

The study design of a chronic toxicology study should include three different doses of a drug administered daily over the course of the study. The top dose should produce frank toxicity, when feasible, and the low dose should help to define a No Adverse Effect Level (NOAEL). The study is intended to characterize the toxicologic profile of a compound at and above the intended clinical exposures. For opioid agonists, tolerance develops to the analgesic effects following repeated drug administration (Gutstein and Akil, 2001). In order to obtain the same desired analgesic effect, the dose of the drug has to be increased as needed on an individual basis in order to maintain efficacy. In the clinic, a physician may decide to increase the dose when a patient reports that the drug is no longer having the same analgesic effect as it used to. This is far more challenging to do in nonclinical toxicology studies since the animals are not in pain and cannot tell you that the drug is not producing the same effect as it did previously. In order to obtain this type of data, the animals would have to be tested periodically via a physiological assessment of an opioid effect, such as pain sensation (nociception) in order to determine if they are now tolerant to the antinociceptive effects of the drug. If tolerance is detected in the physiological assessment, the dose of the opioid could be increased gradually over time. Dose escalation would have to be done in a

manner to avoid producing respiratory depression, a well-known pharmacodynamic effect of opioids which is potentially fatal.

Designing a repeat-dose toxicology study that includes assessment of each animal's development of tolerance to an opioid agonist and includes dose escalation presents considerable challenges. Specifically, a 6-month chronic toxicology study in the rat model typically includes 20 animals per sex per group with additional satellite animals used for toxicokinetic analyses. Therefore, a normal dose-escalation study would include at least 160 animals, 120 of which would require frequent nociception or other physiological assessments to assess tolerance of the opioid agonist and dosing solution adjustments to gradually ramp up the dose. Given the distinct potential for non-uniform tolerance development, a decision to increase the dose for any given treatment group could result in the inadvertent death of some animals from respiratory depression. Not all groups will show tolerance at the same time and each group will have to be considered independently. If too many animals are lost during the course of the study as a result of the adverse events associated with the drug, the study could be compromised and not accomplish the desired objective of characterizing the effect of different doses of the drug over the entire duration of study.

The same challenges would exist for a nonrodent study; however, as the number of animals in a typical nonrodent study is 4-6 per sex per group, loss of even a few animals can compromise the study. In reality, humans tolerate gradual dose-escalation of opioids over the course of chronic therapy in their lifetime that exceeds doses that can be achieved over the course of 6- or 9-month nonclinical studies. As such, to date, the Division has not requested toxicology studies be designed in a manner that includes careful but aggressive dose escalation for a well-understood opioid with considerable clinical experience. Dosing regimens of opioid agonists in chronic toxicology studies are not expected to be able to reach exposures that are comparable to exposures ultimately obtained in humans due to the development of tolerance in humans over time (the maximum theoretical daily dose or MTDD for an opioid-tolerant patient). The animals would likely die from respiratory depression or have to be sacrificed moribund due to some other adverse event (e.g., significant weight loss, self-mutilation) before exposure levels could be reached that would be comparable to exposure levels associated with the MTDD for an opioid-tolerant patient. This is evident in the exposure margins that were obtained in the 13-week dose-range finding studies in rats conducted by Teva to support carcinogenicity studies. As noted in Dr. Bolan's review, doses that produced a dose-limiting suppression of body weight gain and were deemed unacceptable for an ultimate 2-year rat study produced exposures that were at best 1/5th the human AUC following a 90 mg dose of hydrocodone.

That being said, for a novel opioid, the chronic toxicology studies would still be required to determine if the toxicity profile was consistent with what would be

expected for an opioid agonist and determine if there were unexpected adverse effects from a new drug for which neither nonclinical nor clinical data exist. When an opioid compound is truly novel, the Agency has discussed the challenge of designing a toxicology program for the compound with sponsors and encouraged them to consider if their compound will develop tolerance and propose methods to characterize the safety of their compound at higher doses.

Unlike a novel opioid, characterizing the chronic toxicity of an opioid analgesic with decades of clinical experience, such as with hydrocodone, is not necessary to support the safety of long-term clinical studies. For example, large-scale Phase 3 clinical studies for hydrocodone, morphine, oxymorphone, and oxycodone drug products have been allowed to proceed without any chronic nonclinical toxicology studies, based an understanding of the safety profile of these compounds due to extensive previous clinical experience.

Collectively, I agree with Teva's statement that opioid toxicology studies are limited in terms of their ability to characterize high doses of the opioid and that the ultimately safety for many of these well-known compounds is derived from human experience.

Point Number 3: The 13-week toxicology studies conducted by Teva demonstrated only expected toxicities for a mu opioid agonist

Reviewer Comment: As noted above, the 13-week studies did demonstrate effects that are consistent with our understanding of what a morphine-like compound displays in a toxicology study. However, the studies are not chronic toxicology studies. This alone does not justify a waiver request.

Point Number 4: The carcinogenicity studies obtained by right of reference inform the chronic toxicity profile.

Reviewer Comment: As we have with other Sponsors, we agree to consider the utility of Teva's carcinogenicity studies in the rodent models in lieu of a rodent chronic toxicology study, if the carcinogenicity study design included an interim sacrifice group and incorporated all endpoints found in a standard toxicology study (i.e., hematology, clinical chemistry) and establish a NOAEL. As Teva does not have access to the actual study reports, the company may not be aware that the studies did not include an interim sacrifice or any clinical chemistry or urinalysis endpoints. Nonetheless, the studies do provide histopathological evaluation for non-neoplastic lesions. As noted in Dr. Bolan's review of the rat carcinogenicity study, from a histopathological standpoint, a clear NOAEL for retinal atrophy and pododermatitis was not defined. Likewise, in the mouse study, ulcerative dermatitis was noted in all groups which could be attributed to either overgrowth of endogenous skin flora or histamine release. A clear NOAEL level in a carcinogenicity study is not unusual, as these studies are designed to specifically push the dose to a maximum tolerated dose without resulting in a significant impact on survival to

preclude reaching the 2 year planned sacrifice time. Therefore, this alone does not justify a waiver request for chronic toxicology studies.

Point Number 5: Teva's Phase 3 studies did not identify any unexpected safety findings.

Reviewer Comment: Please see the clinical reviews for a discussion of the adverse event profile of the drug product.

Overall Reviewer Evaluation of Teva's waiver request for chronic toxicology studies.

Collectively, I agree that it is difficult to design a chronic toxicology study that would be able to fully characterize the toxicologic potential of the exposures to opioids that would occur in opioid tolerant patients who may take up to the maximum theoretical daily dose of hydrocodone (revised to 1500 mg/day). At best, toxicology studies can characterize the effects of lower doses of hydrocodone within the range that most patients will consume.

For well-known opioids with a long history of clinical use, such as morphine and hydrocodone, general toxicology studies are not likely to provide any data that would alter the current clinical use of the drug or inform physicians of potential toxicities that they are not already well aware of. Therefore, a waiver of chronic toxicology studies for hydrocodone is justifiable based on both the limitations of the existing nonclinical study designs and on extensive human experience with the well-known drugs in this class. The reader is referred to the Division Director's review for a discussion of the clinical experience with hydrocodone and related well-known opioids.

ADME

As per 21 CFR §314.50(d)(2) the nonclinical pharmacology and toxicology section of an NDA should contain "**Any** studies of the absorption, distribution, metabolism, and excretion of the drug in animals" (emphasis added). As such, the amount of animal ADME data required for any specific program is determined by the Agency during drug development.

As per ICH M3(R2):

In vitro metabolic and plasma protein binding data for animals and humans and systemic exposure data (ICH S3A, Ref. 7) in the species used for repeated-dose toxicity studies generally should be evaluated before initiating human clinical trials. Further information on pharmacokinetics (PK) (e.g., absorption, distribution, metabolism and excretion) in test species and in vitro biochemical information relevant to potential drug interactions should be available before exposing large numbers of human subjects or treating for long duration (generally before phase 3). These data can be used to compare human and animal metabolites and for determining if any additional testing is warranted.

As noted in the ICH M3(R2) guidance, animal ADME data are used to assure that the nonclinical toxicology studies adequately characterize the safety of human metabolites and assist in the interpretation of the nonclinical toxicology studies. However, because nonclinical toxicology studies for hydrocodone were not necessary to support human studies nonclinical ADME data are also not necessary for this product based on extensive human experience.

As per 21 CFR 201.57, Section 12 of the labeling, Clinical Pharmacology, "must contain information relating to the human clinical pharmacology and actions of the drug in humans." Animal data are only included in the product labeling if the data are "necessary for the safe and effective use" of the drug and the data "have not been shown by adequate and well-controlled studies" in humans. Given the human experience with hydrocodone, animal data are not necessary for the safe and effective use of the drug and there exists human data that can inform labeling. Teva submitted [REDACTED] ^{(b) (4)} study primarily to support their conclusion that [REDACTED] ^{(b) (4)} in order to support their proposed drug product specification for this degradant as it exceeded the ICH Q3B(R2) qualification threshold.⁵ Additional animal ADME data are not necessary to support approval of this drug product and a waiver request is justified. The reader is referred to the clinical pharmacology review and Division Director's review for a discussion of the human data submitted by Teva to support Section 12 of their drug product labeling.

Genetic Toxicology

Teva conducted the full battery of genetic toxicology studies for hydrocodone that are necessary to support a 505(b)(1) application. Dr. Bolan reviewed these studies and has concluded that the weight of evidence suggests no safety concerns. The results will be described in the product labeling.

Carcinogenicity

Teva submitted a right of reference to carcinogenicity data submitted by Zogenix to IND 65111. Dr. Bolan reviewed these studies and, in conjunction with the Executive Carcinogenicity Assessment Committee (ECAC), concluded that the studies are valid and there is no evidence of carcinogenicity. The studies will be described in the product labeling.

Reproductive and Developmental Toxicology

Teva completed the standard battery of reproductive and developmental toxicology studies as outlined in the ICH M3(R2) guidance. Dr. Bolan reviewed these studies and the results will be presented in the drug product labeling.

⁵ See also Vicoprofen NDA (labeling describes absorption, distribution, metabolism, and elimination related hydrocodone.)

Recommendation:

Teva completed the full standard batteries of both genetic toxicology and reproductive and developmental toxicology studies. Teva submitted carcinogenicity studies via a right of reference to studies completed by Zogenix. Teva has requested a waiver of dedicated pharmacology, ADME, and chronic toxicology studies primarily based on the extensive clinical experience with opioids and the clinical studies conducted with their drug product. The reader is referred to the Division Director's review for a discussion of the clinical experience. Teva's request for a waiver for these studies cites decades of clinical use of well-understood opioids as well as their own clinical studies with the Vantrela drug product.

Dr. Bolan recommended that the NDA may be approved if the Division grants the waiver request for pharmacology studies, nonclinical ADME data (if needed), and chronic toxicology studies. As discussed above, nonclinical pharmacology and ADME data are not necessary to support approval of a well-understood opioid with extensive clinical experience. The adverse histopathological effects of hydrocodone in animal models are not reported. However, completion of standard chronic toxicology studies will not result in exposures that would approach exposures expected to be obtained for a single-entity hydrocodone drug product in an opioid-tolerant individual. Given the extensive clinical history of use of hydrocodone in combination drug products and the extensive clinical history of use of single-entity morphine-related opioids, results of standard chronic nonclinical general toxicology studies are not expected to provide any new information beyond the general knowledge of dose-limiting opioid adverse effects that would likely impact how this drug product is prescribed or labeled.

Therefore, the NDA may be approved as a 505(b)(1) application if the clinical team concludes, that based on generally accepted scientific knowledge obtained from the extensive human experience with well-understood clinically-used opioid agonists, chronic nonclinical toxicology are not necessary.

References Cited

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/s/

RICHARD D MELLON
01/13/2017

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 207975
Supporting document/s: SDN 001
Applicant's letter date: 9/30/2014
CDER stamp date: 9/30/2014
Product: VANTRELA ER (hydrocodone bitartrate extended-release tablets)
Indication: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative options are inadequate
Applicant: Teva Branded Pharmaceutical Products R&D Inc.
Review Division: Division of Anesthesia, Analgesia, and Addiction Products
Reviewers: Elizabeth A. Bolan, PhD & Huiqing Hao, PhD
Supervisor/Team Leader: R. Daniel Mellon, PhD
Division Director: Sharon Hertz, MD
Project Manager: Kimberly Compton

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 207975 are owned by Teva or are data for which Teva has obtained a written right of reference. Any information or data necessary for approval of NDA 207975 that Teva does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 207975.

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1 Executive Summary

1.1 Introduction

Teva submitted NDA 207975 in support for VANTRELA ER, an extended-release hydrocodone (HC) product which contains excipients that are intended to confer abuse-deterrent properties. This NDA has been submitted as a 505(b)(1) application and Teva has obtained right of reference to NDA 20716 (Vicoprofen). Vicoprofen is labeled for an acute indication. This product is an ER opioid and will be used chronically.

The Applicant has assessed the genetic toxicology, carcinogenic potential and reproductive and developmental toxicology of HC bitartrate. Additionally, qualification of multiple drug substance/drug product impurities and degradants and justification of novel excipients was provided.

In lieu of the chronic toxicology study in rodent, the applicant was given the opportunity to review their rat carcinogenicity study to determine if the study could be used to define a NOAEL for chronic drug treatment, assuming that an interim sacrifice and other additional endpoints to evaluate the chronic toxicology of HC were assessed. Upon preliminary review, the submitted rat carcinogenicity study does not contain an interim sacrifice and all appropriate endpoints were not included in the study design to be able to fully evaluate the potential for chronic toxicology.

Late in the review cycle, the Applicant submitted a request for a waiver of the pharmacology, ADME (absorption, distribution, metabolism, and excretion) studies, and chronic toxicology studies with HC. Given the timing of the waiver request, this review does not include a detailed assessment of the waiver request. The waiver request is formally reviewed in the secondary pharmacology toxicology review of this NDA by Dr. Daniel Mellon. I concur with Dr. Mellon's assessment of the waiver request. If the waiver request is granted by the Division, the NDA may be approved from a nonclinical pharmacology perspective.

1.2 Brief Discussion of Nonclinical Findings

All excipients in this product are commonly used and can be found in either previously approved products or have otherwise been adequately justified for safety and are considered acceptable when this product is consumed up to the current maximum theoretical daily dose (MTDD) of HC (3 grams/day).

Specifications for several drug substance impurities and one drug product degradant exceed the ICH Q3A/B qualification thresholds. Impurities and degradants were adequately qualified and the specifications are considered acceptable.

The standard ICH battery of genetic toxicology studies was conducted with HC. Hydrocodone tested negative in the in vitro bacterial reverse mutation assay and the in vivo mouse micronucleus assay. In contrast, HC tested positive for clastogenic activity in the in vitro chromosome aberration assay. Hydrocodone is considered to have clastogenic potential. A fourth genetic toxicology test would typically be required to fully characterize the clastogenic potential. However, regardless of the outcome of a fourth genetic toxicology study, a carcinogenicity assessment would provide the definitive answer as to the genotoxic potential of HC. Teva submitted carcinogenicity studies in mouse and rat via right of reference and HC was found negative for carcinogenic potential in both rat and mouse. These studies will be described in the product labeling.

A full battery of developmental and reproductive toxicology studies with oral administration of HC has been submitted by Teva. The fertility and early embryo-fetal development study in rats showed no effects on overall mating performance (NOAEL 3.2-times the human daily dose of 180 mg based on body surface area). However, hydrocodone treatment decreased absolute epididymides weight (3.2 times the human daily dose of 180 mg) and increased latency to mate in males (1 times the human daily dose). Hydrocodone decreased uterine weights and implantation sites in females (3.2 times the human daily dose) and decreased the number of corpora lutea (1 times the human daily dose).

Embryo-fetal development studies in rats and rabbits with oral administration of HC were submitted by Teva. Although no teratogenicity was observed in either species, embryo-fetal toxicities were noted in rats. Increases in post-implantation loss and non-viable litters were observed. In a pre- and post-natal development study in rats with oral administration of HC, increased post-implantation loss in the F0 dams and reduced survival of the F1 pups were observed. Reduced body weights from birth through the lactation phase were observed in the F1 generation pups. The toxicities observed in these studies are consistent with other opioids and will be described in the product labeling.

Two 13-week repeat-dose toxicity studies in rats and mice with HC were submitted by Teva. These studies were designed as dose-range finding studies in support of dose selection for carcinogenicity studies. Therefore, the studies used doses designed to define a maximum tolerated dose and predict dosing that will permit survival out to 2 years. They were not designed to characterize the chronic toxicity of HC or define a NOAEL. Although pharmacologic effects of HC were observed (decreases in body weights and food consumption) no findings considered adverse were noted and no target organs were identified. The studies are not of adequate duration or design to serve as support for the chronic use of HC for this product.

1.3 Recommendations

1.3.1 Approvability

Nonclinical pharmacology/toxicology recommends approval for NDA 207975 with no post-marketing requirements.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The table below contains the draft labeling submitted by the Applicant, the changes proposed by the reviewer and the rationale for the proposed changes. For the final version of the label, please refer to the Action Letter. Note: The recommended changes from the proposed labeling are in bold red (additions) or strikeout font.

Applicant's proposed labeling	Reviewer's proposed changes	Rationale for changes
INDICATIONS AND USAGE VANTRELA ER is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	INDICATIONS AND USAGE VANTRELA ER is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.	This section contains the Established Pharmacologic Class and is acceptable.
USE IN SPECIFIC POPULATIONS 8.1 Pregnancy Prolonged use of opioid analgesics during pregnancy	USE IN SPECIFIC POPULATIONS 8.1 Pregnancy <i>Risk Summary</i> Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see <i>Warnings and Precautions (5.3)</i>]. There are no available data on VANTRELA ER use in pregnant women to inform any drug associated risks. In animal toxicology studies, hydrocodone administered to pregnant rats during the period of organogenesis resulted in embryo-fetal toxicities including increased post-implantation loss and non-viable litters at doses approximately 2-fold the human hydrocodone dose of 180 mg/day. In another study, decreases in survival were seen in the offspring	Green Text added by PMHT Green text added by PMHT The format has been changed to comply with the Pregnancy and Lactation Labeling Rule. To

	(b) (4) <p>of rats administered hydrocodone during gestation and lactation at doses equivalent to the human dose of 180 mg/day. Additionally, in these rats increased post-implantation loss and decreased body weights of the pups from birth through weaning was seen at doses of hydrocodone 3-fold the human hydrocodone dose of 180 mg/day. No teratogenicity was observed in the offspring of rats and rabbits administered oral hydrocodone during the period of organogenesis at doses in both species 5-fold the human dose of 180 mg/day. Based on animal data, advise pregnant women of the potential risks to a fetus.</p> <p>The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.</p>	<p>The PMHT will add the appropriate language for the labor and delivery data.</p> <p>Exposure comparisons were based on body surface area comparisons with the human dose of 180 mg which is the highest strength of this product (90 mg) used as labeled (BID).</p> <p>This section is based on the applicant's data.</p>
	<p><i>Clinical Considerations</i></p> <p><u>Fetal/neonatal adverse reactions</u></p> <p>Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.</p>	(b) (4) Class labeling for NOWS.

(b) (4)
(b) (4)

Animal Data

Oral doses of hydrocodone were administered to pregnant rats and rabbits during the period of organogenesis. In rats, embryo-fetal toxicities including increased post-implantation loss and non-viable litters were observed at doses of 33 mg/kg and above (approximately 2-fold the human hydrocodone dose of 180 mg/day based on body surface area comparisons). Maternal toxicity (body weight loss) was present in the study at all doses. In rabbits, no adverse effects on embryo-fetal development were observed at doses up to 48 mg/kg (approximately 5-fold the human hydrocodone dose of 180 mg/day based on body surface area comparisons). No evidence of teratogenicity was observed in either study at doses up to 100 mg/kg in rat and 48 mg/kg in rabbit (approximately 5-fold for both rats and rabbits the human hydrocodone dose of 180 mg/day based on body surface area exposure comparisons).

Hydrocodone was administered

This section is based on the applicant's data.

	<p>orally to female rats during gestation and lactation in a pre- and post-natal development study. Decreases in pup survival at doses of 20 mg/kg and above (equivalent to the human hydrocodone dose of 180 mg/day, based on body surface area comparisons). Increased post-implantation loss and decreased body weights of the F1 generation pups from birth through weaning was seen at 60 mg/kg/day (3-fold the human hydrocodone dose of 180 mg/day, based on body surface area comparisons). Maternally toxic decreases in body weight were also observed at these doses.</p>	
	<p>8.3 Females and Males of Reproductive Potential In animal studies, male rats treated with hydrocodone bitartrate at 3.2-times the human daily dose of 180 mg demonstrated decreased epididymides weights and male rats treated with 1-times the human daily dose demonstrated decreased latency to mating. Female rats treated with 1-times the human daily dose of 180 mg demonstrated decreased corpora lutea and at 3.2-times the human daily dose of 180 mg decreased implantation sites [see (b) (4) (13.1)].</p>	<p>As per PLLR if there are adverse effects in animals on fertility, a summary statement to that effect should be included in 8.3 with full details in 13.1. This section is based on the applicant's data.</p>
11 Description Hydrocodone bitartrate is a white to slightly yellow-white crystalline powder...	11 Description Hydrocodone bitartrate is a white to slightly yellow-white crystalline powder...	This section contains the Established Pharmacologic Class and is acceptable.
12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action Hydrocodone is a opioid agonist with relative	12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action Hydrocodone is a opioid agonist. The precise	The Applicant did not submit any pharmacology

<p>selectivity for the mu-opioid (μ) receptor, although it can interact with other opioid receptors at higher doses.</p> <p>(b) (4)</p> <p>[REDACTED]</p>	<p>mechanism of action of hydrocodone and other opioids is not known, although it is believed to relate to the existence of opioid receptors in the central nervous system.</p> <p>(b) (4)</p> <p>[REDACTED]</p>	<p>studies. The Applicant has a right of reference to Vicoprofen.</p>
<p>13 NON-CLINICAL TOXICOLOGY</p> <p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p><i>Carcinogenesis</i></p> <p>(b) (4)</p> <p>[REDACTED]</p> <p><i>Mutagenesis</i></p> <p>(b) (4)</p> <p>[REDACTED]</p>	<p>13 NON-CLINICAL TOXICOLOGY</p> <p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p><i>Carcinogenesis</i></p> <p>(b) (4)</p> <p>[REDACTED]</p> <p style="color: red;">Hydrocodone was evaluated for carcinogenic potential in rats and mice. In a two-year bioassay in rats, doses up to 30 mg/kg in males and 100 mg/kg in females were administered orally and no treatment-related neoplasms were observed (exposure is equivalent to 0.06 times and 0.4 times for males and females, respectively the human hydrocodone dose of 180 mg/day based on AUC exposure comparisons). In a two-year bioassay in mice, doses up to 100 mg/kg in males and females</p>	<p>The carcinogenicity studies with hydrocodone were made available through a right of reference.</p> <p>The data from the genetic toxicology battery conducted by the Applicant were added. Positive findings were placed first.</p> <p>Exposure comparisons were based on body</p>

	<p><u>Impairment of Fertility</u></p> <p>In a fertility and general reproductive performance study, rats were administered doses of 0 (vehicle), 7, 20 and 60 mg/kg/day (equivalent to approximately 0.4, 1.1 and 3.2 times an adult human dose of 180 mg/day on a mg/m² basis). Male and female rats were dosed prior to cohabitation (28 and 14 days, respectively), during cohabitation and through gestation day 6 (implantation). Females were treated for at least 20 days while males received at least 42 daily doses prior to necropsy. Treated males were mated with untreated females and treated females were mated with untreated males. Overall mating performance was unaffected by treatment with hydrocodone bitartrate, although the weights of male and female reproductive organs were decreased in males and females treated with 20 and 60 mg/kg. Additionally, the latency to mate was increased in the 20 and 60 mg/kg treated males. In the pregnant females, early embryonic development was not affected by treatment with hydrocodone bitartrate at doses up to 60 mg/kg (approximately 3.2 times the adult human daily dose of 180 mg/day on a mg/m² basis).</p>	<p>(b) (4)</p> <p>were administered orally and no treatment-related neoplasms were observed (exposure is equivalent to 0.6 times and 1.1 times, respectively, the human hydrocodone dose of 180 mg/day based on AUC exposure comparisons.</p> <p><u>Mutagenesis</u></p> <p>Clastogenicity was observed with hydrocodone in the chromosomal aberration assay in human lymphocytes. There was no evidence of genotoxic potential in an <i>in vitro</i> bacterial reverse mutation assay (<i>Salmonella typhimurium</i> and <i>Escherichia coli</i>) or in an <i>in vivo</i> assay for chromosomal aberrations (mouse bone marrow micronucleus assay).</p>	<p>surface area comparisons with the human dose of 180 mg which is the highest strength of this product (90 mg) used as labeled (BID).</p> <p>This section is based on the applicant's data.</p>
	<p><u>Impairment of Fertility</u></p> <p>In a fertility and general reproductive performance study, rats were administered doses of 0 (vehicle), 7, 20 and 60 mg/kg/day (equivalent to approximately 0.4, 1.1 and 3.2 times an adult human dose of 180 mg/day on a mg/m² basis). Male and female rats were dosed prior to cohabitation (28 and 14 days, respectively), during cohabitation and through gestation day 6 (implantation). Females were treated for at least 20 days while males received at least 42 daily doses prior to necropsy. Treated males were mated with untreated females and treated females were mated with untreated males. Overall mating performance was unaffected by treatment with hydrocodone bitartrate, although</p>		

	<p>the weights of male and female reproductive organs were decreased in males and females treated with 20 and 60 mg/kg. Additionally, the latency to mate was increased in the 20 and 60 mg/kg treated males. In the pregnant females, early embryonic development was not affected by treatment with hydrocodone bitartrate at doses up to 60 mg/kg (approximately 3.2 times the adult human daily dose of 180 mg/day on a mg/m² basis).</p>	
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2 Drug Information

2.1 Drug

CAS Registry Number: 34195-34-1 (hydrate)

Generic Name: Hydrocodone bitartrate

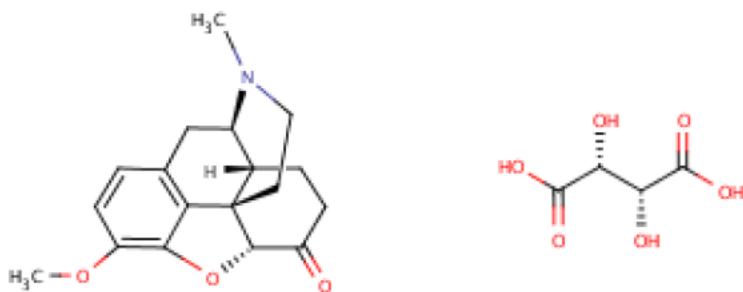
Code Names: CEP-33237

Chemical Name: 4,5-Dihydro-17-Methyl-4-methoxy-3H-1,2-dihydro-5H-pyrrolidin-2-one Tartrate (1:1) Hydrate (2:5)

Molecular Formula/Molecular Weight: C₁₈H₂₁NO₃•C₄H₆O₆•2.5H₂O / 494.90 (hydrate)

Structure:

Figure 1. Structure of Hydrocodone Bitartrate



Pharmacologic Class: Opioid Agonist (EPC)

2.2 Relevant INDs, NDAs, BLAs and DMFs

<i>IND/NDA/DMF</i>	<i>Drug/compound</i>	<i>Sponsor</i>	<i>Division/Office</i>	<i>status</i>
IND 105587	Hydrocodone ER	Teva	DAAAP	active
NDA 20716	Vicoprofen	Abbvie	DAAAP	approved
DMF		(b) (4)	ONDQA	adequate

2.3 Drug Formulation

The drug product is formulated as an oral tablet intended for BID dosing and will be manufactured in five strengths (15, 30, 45, 60, and 90 mg). The formulation is intended to provide abuse-deterrent properties and be resistant to alcohol-induced dose dumping.

The quantitative composition of the drug product formulation is depicted in the table below:

Table 1. Composition of VANTRELA ER capsules (reproduced from NDA)

Component	Reference to Standard	Function	15 mg (Light Red)	30 mg (Yellow)	45 mg (White)	60 mg (Light Blue)	90 mg (Light Green)
			mg/tablet	mg/tablet	mg/tablet	mg/tablet	mg/tablet
Hydrocodone bitartrate ^a [REDACTED]	USP	Active ingredient [REDACTED]	15.00	30.00	45.00	60.00	90.00 [REDACTED]
[REDACTED] lactose monohydrate	NF						
Ethyl cellulose, [REDACTED]	NF						
Hypromellose [REDACTED]	USP						
Glyceryl behenate	NF						
Magnesium stearate [REDACTED] [REDACTED]	NF						
Red ferric oxide	NF						
Yellow ferric oxide	NF						
FD&C Blue #2 aluminum lake [REDACTED]	FD&C [REDACTED]						
	USP/NF						
Total Weight / Tablet			575	575	575	1150	1150

NA: Not Applicable

^a Active ingredient quantities listed are of hydrocodone bitartrate hemipentahydrate, as described in 3.2.S.1.2.^b [REDACTED]

2.4 Comments on Novel Excipients

As with any single-entity opioid drug product approved for chronic use, there is no maximum daily dose listed in the labeling due to the development of tolerance. The development of tolerance necessitates increased doses with time in order to obtain the same desired effect. To establish the safety of the product for opioid-tolerant individuals, the Division has employed a “maximum theoretical daily dose” (MTDD) based on clinical use data. As there are limited clinical use data on single-entity HC

drug products, the Division elected to employ a rough potency comparison to morphine in order to estimate the MTDD and has established 3 grams per day as the MTDD for single-entity HC drug products.¹ The table below summarizes the MTDD of the excipients in this drug product and assumes that if these levels were to be reached, it would be via use of the highest dosage strength.

The quantitative composition of the 90 mg tablet and the amount of each inactive ingredient at the MTDD of HC is presented in the table below. With the exception of the glyceryl behenate, all of the excipients in this formulation are commonly used and can be found in previously approved chronic use products at higher levels and do not present any unique toxicologic concerns in this product.

Glyceryl Behenate

(b) (4)

Glyceryl behenate is the glycerol ester of behenic acid, with the diester fraction being predominant (40-60%). Behenic acid is a carboxylic acid with the formula C₂₁H₄₃COOH. It is found in dietary sources including rapeseed (canola) oil and peanut oil. At the MTDD of HC (b) (4) of glyceryl behenate would be consumed. Since estimates of the consumption of all added mono- and diglycerides in the diet approximately between 1 to 10 g per person per day, the amount of glyceryl behenate in this product is considered acceptable. We note that this conclusion is consistent with the Select Committee on GRAS Substances (SCOGS) opinion which came to a Type of Conclusion: 1 for mono- and diglycerides of edible fat-forming fatty acids. A Type of Conclusion: 1 states that there is no evidence in the available information that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or might reasonably be expected in the future. The rationale for the SCOGS opinion is below (indented text).

Mono- and diglycerides of edible fat-forming fatty acids (SCOGS Report #30, ID code 56-81-5 1975)

Although mono- and diglycerides of edible fat-forming fatty acids are found naturally, those that are used as food additives are usually prepared synthetically. Mono-, di- and triglycerides are metabolized by the same mechanisms. The biological effects of glycerides are either those of the entire molecule or of the metabolic products, fatty acids and glycerin. Triglyceride fats are a major source of calories in the diet of many people. Mono- and diglycerides are minor components of natural fats. They are intermediate metabolic products of ingested triglycerides. There is no evidence that the mono- and diglycerides of edible fat-forming fatty acids behave differently from triglycerides upon ingestion.

¹ The MTDD of HC (3 grams/day) has been applied to HC products to date. FDA is considering whether a lower MTDD would be appropriate for HC products. However, Teva's proposed product has been adequately qualified using the MTDD of 3 grams/day and it was not necessary to consider whether it would be appropriate to apply a lower MTDD for this application.

There is evidence that ingestion of excesses of saturated fats and cholesterol promotes arteriosclerosis and cardiovascular disease. Continuation of research in this area may refine relationships of the various fatty acids to the point where harmfulness may become an impelling consideration. However, because a reasonable estimate of the consumption of all added mono- and diglycerides is of the order of 1 to 10 g per person per day, only a fraction of which contains saturated fatty acids, it can hardly be concluded that they make a sufficient contribution to any hazard associated with normal ingestion of saturated fatty acids in fatty foods to justify limitation of the level of their current use.

Figure 2. Structure of Glyceryl Behenate

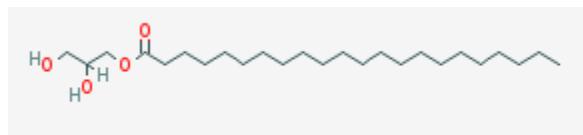


Table 2. Acceptability of Levels of Inactive Ingredients in the 90 mg Capsule at the MTDD of Hydrocodone

Inactive Ingredient	Total dosage via single 90 mg tablet, mg	Total Dose at MTDD (33 pills), mg	Rationale
Lactose monohydrate		(b) (4)	Acceptable: IIG
Ethyl cellulose			Acceptable: IIG
Hypromellose (b) (4)			Acceptable: IIG
Glyceryl behenate (b) (4)			Acceptable: See rationale above
Magnesium stearate			Acceptable: IIG
Yellow ferric oxide			Acceptable: IIG
FD&C Blue #2 aluminum lake			Acceptable: IIG

IIG: FDA Inactive Ingredients Guide

2.5 Comments on Impurities/Degradants of Concern

Drug Substance Impurities.

The qualification threshold according to the ICH Q3A(R2) guideline for impurities in the drug substance for a maximum daily dose (MDD) of drug substance > 2 g/day is 0.05%. For this product, the clinical team determined that the MTDD of hydrocodone is 3 g. The Applicant is obtaining the HC drug substance from (b) (4) (DMF (b) (4)). The drug substance specifications are outlined in the table below. Several other impurities exceed ICH Q3A(R2) qualification thresholds. Adequate qualification has been provided and details are discussed below. All drug substance impurity specifications are considered acceptable from a pharmacology toxicology perspective.

Table 3. Drug Substance Specifications of Hydrocodone Drug Substance

Degradant	Proposed Specification	ICH Q3B(R2) Qualification Thresholds or Limits	Comments
(b) (4)	NMT (b) (4)%	NMT (b) (4)%	Acceptable: meets ICH Q3A(R2) specification
	NMT (b) (4)%	NMT (b) (4)%	Acceptable: drug substance in approved products
	NMT (b) (4)%	NMT (b) (4)%	Acceptable: see qualification below
	NMT (b) (4)%	NMT (b) (4)%	Acceptable: see qualification below
	NMT (b) (4)%	NMT (b) (4)%	Acceptable: see qualification below
	NMT (b) (4)%	NMT (b) (4)%	Acceptable: Contains (b) (4) structural alert but qualified by DMF holder as a nongenotoxic impurity
	NMT (b) (4)%	NMT (b) (4)%	Acceptable: see qualification below

(b) (4) contains a structural alert for mutagenicity and (b) (4) has adequately qualified it for genotoxic potential. It was found to be negative for genotoxic potential and can therefore be regulated as a typical non-genotoxic drug substance impurity according to ICH Q3A(R2) thresholds for qualification. The proposed specification of (b) (4)% is acceptable.

(b) (4) (b) (4)
Specifications for (b) (4) are set in both the drug substance ((b) (4)%) and drug product ((b) (4)%). In both cases, ICH specifications for qualification are exceeded. For qualification of (b) (4) at the proposed specifications, the Applicant has conducted the standard battery of genetic toxicology studies as well as a 13-week toxicology study with (b) (4).

(b) (4) tested negative in the in vitro bacterial reverse mutation assay, the in vivo mouse micronucleus assay, and the in vitro chromosome aberration assay. Additionally, (b) (4) was predicted to be non-mutagenic by both the Derek and Sarah platforms. The 13-week toxicology study in rat had a NOEL of (b) (4) mg/kg, the highest dose tested. At the MTDD of HC (3 g), (b) (4) of (b) (4) would be consumed at the

proposed specification of (b) (4)% (the higher of the two specifications). Additionally, in a 90-day oral toxicity study in dogs, the NOEL of (b) (4) mg/kg (b) (4) mg/m²) provides approximately a 2-fold safety margin over the (b) (4) mg/kg; (b) (4) mg/m²) human dose. The proposed specifications for (b) (4) in the drug substance and drug product are considered acceptable.

(b) (4) and (b) (4)
Drug substance impurity specifications for (b) (4) and (b) (4) exceed ICH Q3A(R2) thresholds for qualification. For qualification at the proposed drug substance specification of (b) (4)%, the Applicant has conducted the standard battery of genetic toxicology studies as well as a 13-week toxicology study with a cocktail of three impurities ((b) (4) and (b) (4)) and (b) (4).

Both impurities tested negative in the in vitro bacterial reverse mutation assay, the in vivo mouse micronucleus assay, and the in vitro chromosome aberration assay. Additionally, both were predicted to be non-mutagenic by both the Derek and Sarah platforms. The 13-week toxicology study in rat had a NOEL of (b) (4) mg/kg for each of the three impurities, which was the highest dose tested. At the MTDD of HC (3 g), at the proposed specification of (b) (4)%, (b) (4) mg of each impurity would be consumed. The NOEL of (b) (4) mg/kg (b) (4) mg/m²) in rat provides a 1.3-fold safety margin over the (b) (4) mg ((b) (4) mg/kg; (b) (4) mg/m²) human dose based on BSA. The proposed specifications of (b) (4)% for (b) (4) and (b) (4) in the drug substance are considered acceptable.

(b) (4) and (b) (4)
Drug substance impurity specifications for (b) (4) and (b) (4) exceed ICH Q3A(R2) thresholds for qualification. For qualification at the proposed drug substance specification of (b) (4)%, the Applicant has conducted multiple genetic toxicology studies as well as a 13-week toxicology study with a cocktail of three impurities ((b) (4) and (b) (4)) and (b) (4).

Two lots with differing purities (69.8% and 91.4%) were tested in the in vitro bacterial reverse mutation assay and the in vitro chromosome aberration assay. In the Ames assay, positive and equivocal results were obtained in the TA100 in both the presence and absence of S9. However, when the 91.4% pure lot was tested, a negative result was obtained. Additionally, (b) (4) was predicted to be non-mutagenic by both the Derek and Sarah platforms. In the in vitro chromosome aberration assay, positive results were obtained with both the 69.8% and 91.4% pure lots in both the presence and absence of S9. The 94.1% pure lot was also tested in the in vivo mouse micronucleus assay and comet assay. In both of these assays a negative result was obtained. Although some studies had positive results, the weight-of-evidence suggests that (b) (4) is negative for mutagenic and clastogenic activity. The 13-week toxicology study in rat had a NOEL of (b) (4) mg/kg for each of the three impurities, which was the highest dose tested. At the MTDD of HC (b) (4) g, at the proposed specification of (b) (4)%, (b) (4) mg of each impurity would be

consumed. The NOEL of [b] mg/kg ([b] mg/m²) in rat provides a 1.3-fold safety margin over the [b] mg ([b] mg/kg; [b] mg/m²) human dose based on BSA. The proposed specification of [b] % for [b] in the drug substance is considered acceptable.

Drug Product Degradants.

The qualification threshold according to the ICH Q3B(R2) guidance for impurities/degradants in the drug product for a MDD of drug substance > 2 g is 0.15%. For this product, DAAAP has determined that the MTDD of HC is 3 g. A specification of [b] % has been set for [b] as a drug product degradant and the specification exceeds ICH Q3B(R2) thresholds for qualification. Adequate qualification has been submitted by the Applicant and is discussed above. The [b] % specification for [b] in the drug product is considered acceptable.

Table 4. Drug Product Degradant Specifications

Degradant	Proposed Specification	ICH Q3B(R2) Qualification Thresholds or Limits	Comments
[b]	NMT [b] %	NMT 0.15%.	Acceptable: see qualification under drug substance

2.6 Proposed Clinical Population and Dosing Regimen

This extended-release HC product is planned to be marketed as 15, 30, 45, 60, and 90 mg strengths intended for q12h dosing in adults. The indication sought is management of pain severe enough to require daily around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. The ER formulation is intended to provide abuse-deterrant properties and be resistant to alcohol-induced dose dumping.

2.7 Regulatory Background

The Applicant is submitting NDA 207975 via the 505(b)(1) regulatory pathway. The Applicant has provided a letter of authorization for Vicoprofen (NDA 20716). IND 105587 was originally opened on September 29, 2009 by Cephalon, Inc.

3 Studies Submitted

3.1 Studies Reviewed

The studies in the table below are located in the EDR in eCTD format.

Study Title	Study #
In Vitro Metabolism of Hydrocodone Bitartrate (CEP-33237) in Liver S9 and Microsomal Fractions From Rat, Dog, Monkey and Human and in cDNA-expressed Human Enzymes and Metabolic Profiling in Plasma From Dogs	DM-2011-006

and Rats and in Urine, Bile and Feces From Rats Administered Oral Doses of Hydrocodone Bitartrate	
13-Week Oral Toxicity Study of Hydrocodone Bitartrate (CEP-33237) in Mice	DS-2011-013
13-Week Oral Toxicity Study of Hydrocodone Bitartrate (CEP-33237) in Rat	DS-2011-011
13-Week Oral Toxicity Study of (b) (4) and (b) (4) in Rat	DS-2011-038
90-Day Oral (Gavage) Toxicity Study of (b) (4) in Beagle Dogs	DS-2011-036
90-Day Oral (Gavage) Toxicity Study of Hydrocodone Bitartrate Extended Release Formulation Excipients in Beagle Dogs	DS-2011-037
Bacterial Reverse Mutation Test in Salmonella Typhimurium and Escherichia Coli (Hydrocodone Bitartrate)	DS-2011 -031
(b) (4) Bacterial Reverse Mutation Assay	DS-2014-072
(b) (4) Bacterial Reverse Mutation Assay	DS-2014-073
(b) (4) Bacterial Reverse Mutation Assay	DS-2014-074
(b) (4) Bacterial Reverse Mutation Assay	DS-2014-075
(b) (4) Bacterial Reverse Mutation Assay	DS-2014-098
Computational Mutagenicity Report for Impurities in Hydrocodone Bitartrate Extended Release (CEP-33237)	DS-2011-084
In Vitro Mammalian Chromosome Aberration Test in HPBL (Hydrocodone Bitartrate)	DS-2011-032
(b) (4) In Vitro Mammalian Chromosome Aberration Assay in HPBL	DS-2014-076
(b) (4) In Vitro Mammalian Chromosome Aberration Assay in HPBL	DS-2014-077
(b) (4) In Vitro Mammalian Chromosome Aberration Assay in HPBL	DS-2014-078
(b) (4) In Vitro Mammalian Chromosome Aberration Assay in HPBL	DS-2014-079
(b) (4) In Vitro Mammalian Chromosome Aberration Assay in HPBL	DS-2014-099
Mammalian Erythrocyte Micronucleus Test in Rat Bone Marrow (Hydrocodone Bitartrate)	DS-2011-033
Computational Mutagenicity Report for Impurities in Hydrocodone Bitartrate Extended Release (CEP 33237)	DS-2014-084
(b) (4) In Vitro Mammalian Erythrocyte Micronucleus Assay and Alkaline Comet Assay in Rats	DS-2015-002
Reproductive Toxicity Study (Segment I) of Orally Administered Hydrocodone Bitartrate (CEP-33237) in Rats	DS-2011-001
Definitive Oral Developmental Toxicity Study (Segment II) of Hydrocodone Bitartrate (CEP-33237) in Rats	DS-2011-009
Definitive Oral Developmental Toxicity Study (Segment II) of Hydrocodone Bitartrate (CEP-33237) in Rabbits	DS-2011-010

Oral Reproductive and Developmental Toxicity Study (Segment III) of Hydrocodone Bitartrate in Rats	DS-2010-042
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3.2 Studies Not Reviewed

All studies submitted in NDA 207975 were reviewed.

3.3 Previous Reviews Referenced

No previous reviews have been referenced.

4 Pharmacology

4.1 Primary Pharmacology

No new pharmacology studies were completed by Teva. There are no pharmacology studies described in the pharmacology toxicology review of the Vicoprofen NDA, likely because that NDA appears to have been approved as a line extension from Vicodin and Vicodin ES drug products. As per the Vicoprofen label:

Hydrocodone is a semisynthetic opioid analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opioids is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, opioids may produce drowsiness, changes in mood, and mental clouding.

Teva did submit a literature review of the pharmacology of hydrocodone; however, this literature was not formally reviewed for and was not relied on by the Agency for approval of this 505(b)(1) application. The Applicant submitted a waiver request for these studies which FDA has granted. The reader is referred to the secondary review by Dr. Mellon to discuss the waiver request and the basis for granting it.

4.2 Secondary Pharmacology

No new secondary pharmacology studies were completed by Teva. There are no secondary pharmacology studies described in the pharmacology toxicology review of the Vicoprofen NDA, likely because that NDA appears to have been approved as a line extension from Vicodin and Vicodin ES drug products. The Applicant submitted a waiver request for these studies which FDA has granted. The reader is referred to the secondary review by Dr. Mellon to discuss the waiver request and the basis for granting it.

4.3 Safety Pharmacology

No new safety pharmacology studies were completed by Teva. There are no safety pharmacology studies described in the pharmacology toxicology review of the

Vicoprofen NDA, likely because that NDA appears to have been approved as a line extension from Vicodin and Vicodin ES drug products. The Applicant submitted a waiver request for these studies which FDA has granted. The reader is referred to the secondary review by Dr. Mellon to discuss the waiver request and the basis for granting it.

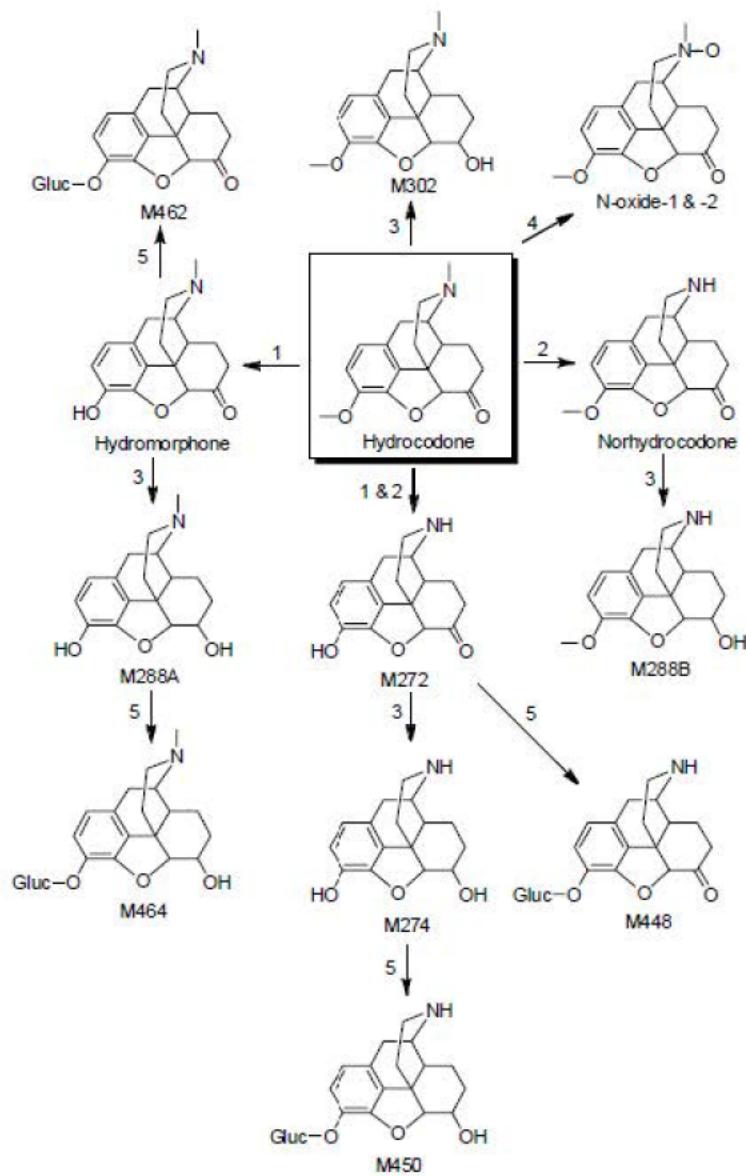
5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Teva conducted a single ADME study (Report Number DM-2011-006) titled “In Vitro Metabolism of Hydrocodone Bitartrate (CEP-33237) in Liver S9 and Microsomal Fractions From Rat, Dog, Monkey and Human and in cDNA-expressed Human Enzymes and Metabolic Profiling in Plasma From Dogs and Rats and in Urine, Bile and Feces From Rats Administered Oral Doses of Hydrocodone Bitartrate.” The study was conducted to assess the formation of hydrocodone N-oxide metabolites in these species.

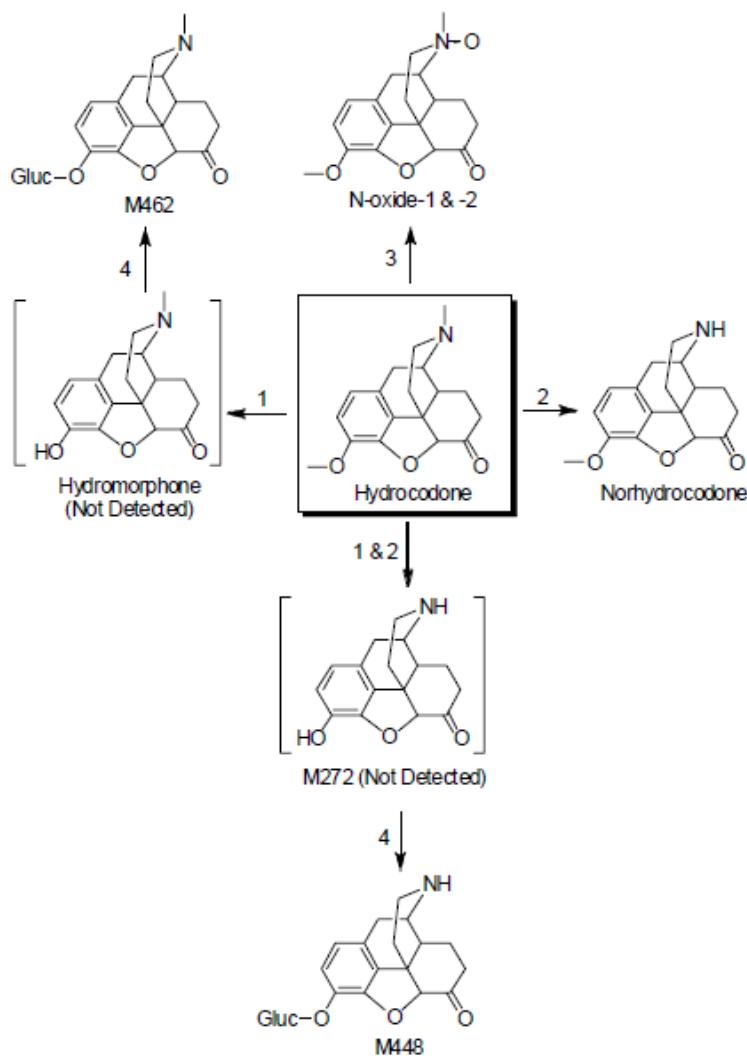
Hydrocodone was metabolized to norhydrocodone, and to a much lower extent, hydromorphone in human and dog microsomes. In monkey, comparable levels of these two metabolites were formed. Small amounts of hydrocodone N-oxide were detected in all species. Metabolism appears to be predominantly via CYP 3A4/5.

Hydrocodone is extensively metabolized by rats with 17 metabolites detected, whereas only three main metabolites were detected in dog. The Applicant’s proposed metabolic pathways for rats and dogs are depicted below.

Figure 4: Major Metabolic Pathways of Hydrocodone in Rat

1. *O*-demethylation; 2. *N*-demethylation; 3. ketone reduction; 4. *N*-oxidation;
 5. Phase II conjugation (glucuronidation).

* Minor metabolites M492, M298, M300 and M286 were not included in the pathway due to their ambiguous structure assignments.

Figure 5: Metabolic Pathways of Hydrocodone in Dog

1. *O*-demethylation; 2. *N*-demethylation; 3. *N*-oxidation; 4. Phase II conjugation (glucuronidation).

5.2 Toxicokinetics

Toxicokinetics are discussed in reviews of the individual toxicology studies.

6 General Toxicology

6.1 Single-Dose Toxicity

No single-dose toxicology studies were conducted.

6.2 Repeat-Dose Toxicity

Study title: 13-Week Oral Toxicity Study of Hydrocodone Bitartrate (CEP-33237) in Rats

Study no.: 11-623 (Sponsor DS-2011-011)
Study report location: EDR 4.2.3.2
Conducting laboratory and location: (b) (4)
Date of study initiation: April 13, 2011
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Hydrocodone bitartrate; Lot 1010000552;
100.2%

Key Study Findings

This study was conducted to determine high dose selection for a carcinogenicity study. Animals were dosed with 7, 20, 60 mg/kg (HD was increased to 100 mg/kg on Day 35) with the following key study findings:

- Males showed body weight decreases $\geq 10\%$ throughout the study in all dose groups and body weight gain decreases $\geq 10\%$ for the MD (18%), and HD (32%).
- Females at the HD showed a body weight gain decrease of 12%.
- Food consumption was decreased in both males and females throughout the study.
- Scabs were observed in males (LD: 1, MD: 4, HD: 2) and females (MD: 4, HD: 5).
- Tremors were observed in three females at the HD. Tremors in the absence of convulsions are not considered adverse.
- No significant adverse findings were identified in either males or females other than body weight gain decreases which are expected for an opioid, therefore the NOAEL is the HD for both sexes. Based on AUC, exposures for the HD males and females are 0.12-fold and 0.08-fold lower than a human dose of 90 mg HC.

Methods

Doses: 7, 20, 60 mg/kg (HD was increased to 100 mg/kg on Day 35)
Frequency of dosing: Daily
Route of administration: Oral gavage
Dose volume: 10 mL/kg
Formulation/Vehicle: Deionized water
Species/Strain: Rat, Sprague-Dawley
Number/Sex/Group: 15/sex/group
Age: 5 weeks
Weight: M: 85-120 g; F: 71-85 g
Satellite groups: TK: 3/sex/group for vehicle, 9/sex/group for treated
Unique study design: The high dose was increased to 100 mg/kg on

Day 35 presumably to allow higher dosing after the development of tolerance to the opioid. TK samples were collected but not analyzed.

Deviation from study protocol: None that affected the integrity of the study.

Observations and Results

Mortality

No mortalities were noted during the study.

Clinical Signs

A detailed clinical evaluation was performed weekly. Additionally, animals were evaluated daily during dosing for general appearance and signs of overt toxicity. Swollen limbs were seen in one male at the LD, one male and one female in the MD and two males and three females at the high dose. Scabs were noted at all doses in males (LD: 1, MD: 4, HD: 2) and in females at the mid and high doses (MD: 4, HD: 5). Tremors were seen in three females at the HD. In the absence of convulsions, the observation of tremors is not considered adverse. These clinical signs are attributed to hydrocodone but are not considered to contribute toward the MTD. Diarrhea was observed in one male at the MD and two males and two females at the HD. Other sporadic clinical signs were noted but not considered toxicologically relevant.

Body Weights

Animals were weighed weekly throughout the study. In males, statistically significant decreases in body weights were observed at all doses. Decreases of $\geq 10\%$ were seen throughout the study for the MD and HD. Group mean body weights for males are shown in the figure below. Males showed body weight gain decreases of 18% and 32% at the MD and HD, respectively (see table below). In females, no statistically significant decreases in body weights were observed at any dose. Group mean body weights for females are shown in the figure below. Females at the HD showed a body weight gain decrease of 12% (see table below).

Figure 3. Mean Body Weights in Male Rats, g, 13-Week Study

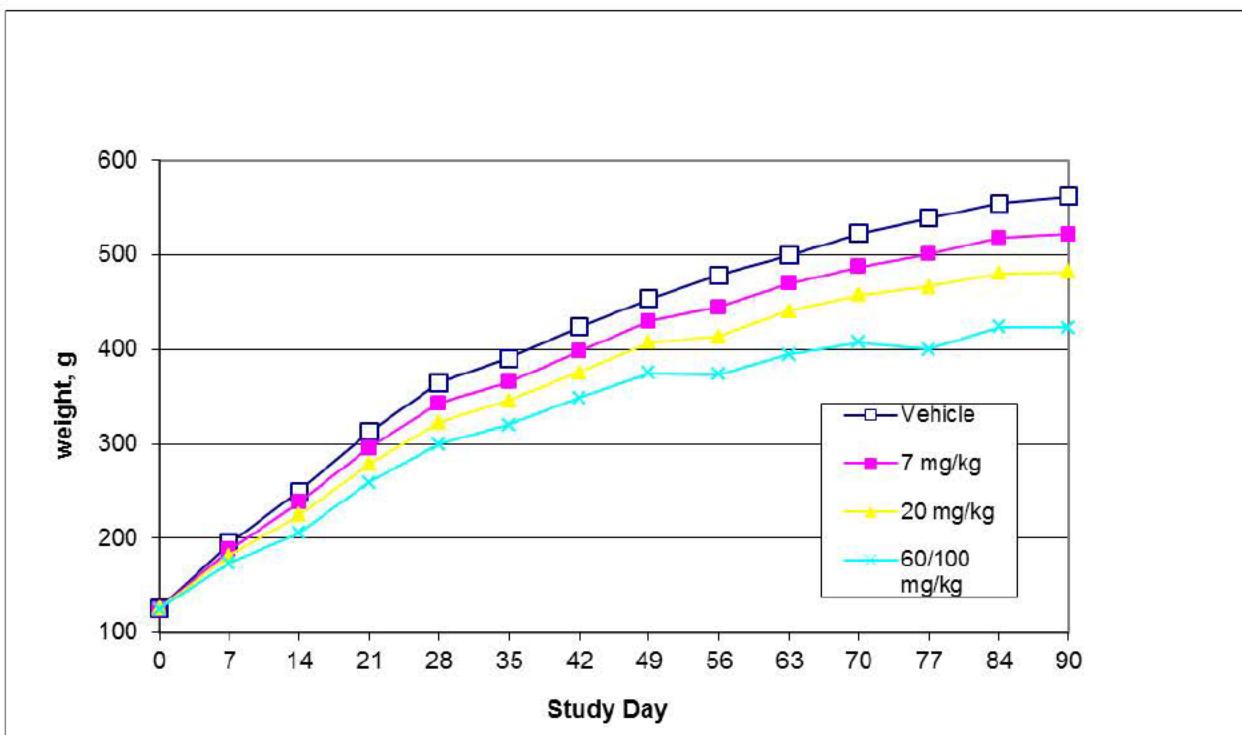


Figure 4. Mean Body Weights in Female Rats, g, 13-Week Study

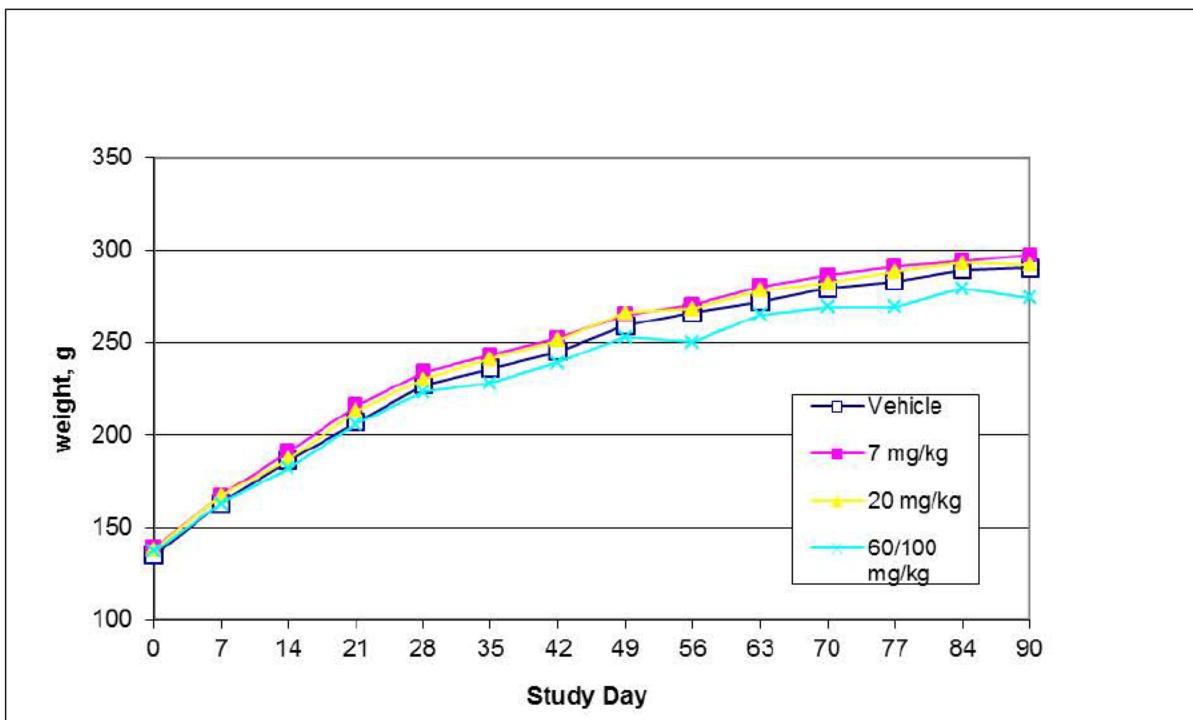


Table 5. Body Weight Gain in Rats, 13 Week Study

	<i>mg/kg</i>	<i>Body Weight (g), Day 0</i>	<i>Body Weight (g), Day 90</i>	<i>Body Weight Gain (BWG) (g), Day 0 to Day 91</i>	<i>BWG % Change from Control</i>
Male	0	126	562	436	-
	7	125	522	397	-9
	20	126	482	356	-18
	60/100	125	423	298	-32
Female	0	135	290	155	-
	7	139	297	158	2
	20	138	292	154	-1
	60/100	137	274	137	-12

bold denotes decreases >10%

Food Consumption

Food consumption was assessed weekly throughout the study. In males, decreases in food consumption were noted at all doses. Statistical significance was reached at a few time points for the low dose and at all time points from Day 7 through Day 90 for the mid and high dose groups. In females, decreases in food consumption were observed at the high dose with statistical significance being reached at several time points. For both males and females decreases in food consumption paralleled body weight decreases.

Ophthalmoscopy

Ophthalmologic analysis was performed pre-test and at the conclusion of the dosing period. No test article-related findings were observed.

ECG

ECG was not assessed in this study.

Hematology

The following hematological parameters were measured at Week 4 and Week 13:

Red Blood Cell Count
White Blood Cell Count
Hematocrit
Hemoglobin

Mean Corpuscular Volume
Mean Corpuscular Hemoglobin
Mean Corpuscular Hemoglobin Concentration
Platelet Count
Differential Leukocyte Count (abs and rel)
Red Cell Morphology
Reticulocyte Count (abs and rel)
Mean Platelet Volume

No changes in hematologic parameters that would contribute to the determination of the MTD were observed.

Clinical Chemistry

The following clinical chemistry parameters were measured at Week 4 and Week 13:

Alkaline Phosphatase	Glucose
Total Bilirubin	Total Cholesterol
Aspartate Aminotransferase	Sodium
Alanine Aminotransferase	Potassium
Lactate Dehydrogenase	Chloride
Blood Urea Nitrogen	Calcium
Creatinine	Phosphate
Total Protein	Creatinine Kinase
Albumin	Gamma-Glutamyl Transferase
Globulin	Triglycerides
Albumin/Globulin Ratio	

No changes in clinical chemistry parameters that would contribute to the determination of the MTD were observed.

Urinalysis

Urinalysis was not conducted.

Gross Pathology

No test article-related findings were noted.

Organ Weights

No test article-related findings were noted.

Histopathology

Adequate Battery: Yes

Peer Review: No

Histological Findings

No test article-related findings were noted.

Toxicokinetics

Toxicokinetic samples in this study were collected but not analyzed. The TK data from the male and female fertility study in Sprague-Dawley rats will be used to estimate exposure (see table below). Plasma samples were collected on Study Day 14 for females and Study Day 28 for males. The systemic exposures of HC are roughly equal for males and females. The human data are from Study C33237/1081 where 45 mg HC was dosed orally BID (AUC_{0-t} at steady state= 1330.1 h·ng/mL in males and females combined). All rat exposures of HC tested are well below human systemic exposure at the human daily dose of 90 mg. The exposures for the proposed doses are calculated based on extrapolation using linear regression analysis. The extrapolated exposures of HC at the doses proposed for the 2-year bioassay are all well below human systemic exposure at the human daily dose of 90 mg. Based on this extrapolation, an oral dose in rat of 850 mg/kg HC would be needed to reach equal systemic exposure to the 90 mg oral dose in humans.

Table 6. Summary of TK parameters for hydrocodone from the Segment 1 Fertility study Sprague-Dawley rat (Study DP-2011-058)

Dose mg/kg	Sex	Day	C _{max} ng/mL	t _{max} hr	λ _z 1/hr	t _{1/2} hr	AUC _{0-t} ng·hr/mL	AUC _{0-∞} ng·hr/mL	Extrap. %
7	F	1	2.28	0.5	0.371	1.87	5.1	5.9	12.8
	F	14	4.40	0.5	0.570	1.22	8.2	--	--
	M	1	3.82	0.5	0.483	1.44	7.1	7.5	5.8
	M	28	5.52	0.5	0.558	1.24	10.6	--	--
20	F	1	4.70	0.5	0.221	3.13	15.3	20.8	26.3
	F	14	13.64	1.0	0.597	1.16	31.3	--	--
	M	1	6.57	1.0	NC	NC	15.3	NC	NC
	M	28	19.20	1.0	0.451	1.54	42.8	--	--
60	F	1	9.62	0.5	0.074	9.39	74.8	87.5	14.5
	F	14	75.23	0.5	0.255	2.72	103.7	--	--
	M	1	10.36	0.5	0.092	7.50	64.6	71.8	10.1
	M	28	82.41	0.5	0.122	5.68	161.5	--	--

NC: Not calculable

Table 7. Exposure Ratios (Plasma Levels) Between Rat and Human for Hydrocodone

	<i>Dose, mg/kg</i>	<i>Rat/human*</i> <i>AUC_{0-t}</i>
Male	7	0.008
	20	0.032
	60/100	0.121
Female	7	0.006
	20	0.024
	60/100	0.078

*Human data from Study C33237/1081, AUC_{0-t} at steady state= 1330.1 h·ng/mL in males and females combined.

Table 8. Extrapolated Exposure Ratios Between Rat and Human for Hydrocodone: Doses for Carcinogenicity Study Proposed by Reviewer

	<i>Dose, mg/kg</i>	<i>Rat/human*</i> <i>AUC_{0-24h}</i>
Male	0.7	0.0008
	2	0.002
	7	0.008
Female	2	0.0002
	7	0.005
	20	0.02

*Human data from Study C33237/1081, AUC_{0-t} at steady state= 1330.1 h·ng/mL in males and females combined.

Dosing Solution Analysis

The concentration analyses were within an acceptable range.

Protein Binding

The extent of HC protein binding in human plasma is not known. However, it is expected to fall in the low-to-moderate range (19 to 45%), similar to that of other opioid agents (Vicoprofen package insert).

Study title: 13-Week Oral Toxicity Study of Hydrocodone Bitartrate (CEP-33237) in Mice

Study no.: 11-624 (Sponsor # DS-2011-013)
Study report location: EDR 4.2.3.2
Conducting laboratory and location: (b) (4)
Date of study initiation: April 13, 2011
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Hydrocodone bitartrate; Lot #
10103000114; 99.4%

Key Study Findings

This study was conducted to support dose selection for a carcinogenicity study. Mice were treated with 7, 20, 60 mg/kg (HD was increased to 100 mg/kg on Day 21) with the following key study findings:

- Males showed a body weight gain decrease of 17% at the high dose
- Females showed nonlinear body weight gain decreases at all doses: 25%, 16%, and 29% at the low, mid, and high doses, respectively
- Decreases in food consumption paralleled decreases in body weights in both males and females
- No other dose-limiting toxicities were observed in the study.
- No adverse findings were identified in either males or females, therefore the NOAEL is the HD for both sexes. Based on AUC, exposures for the HD males and females for the 60/100 mg/kg dose are 3.2/5.4-fold higher than a human dose of 90 mg HC based on body surface area.

Methods

Doses: 7, 20, 60 mg/kg (HD was increased to 100 mg/kg on Day 21)
Frequency of dosing: Daily
Route of administration: Oral gavage
Dose volume: 10 mL/kg
Formulation/Vehicle: Deionized water
Species/Strain: Mouse, CD-1
Number/Sex/Group: 15/sex/group
Age: 4 weeks
Weight: M: 20.9-24.6 g; F: 17.7-21.3 g
Satellite groups: TK: 12/sex/group for vehicle, 30/sex/group for treated
Unique study design: The high dose was increased to 100 mg/kg on Day 21 presumably to allow higher dosing after the development of tolerance to the opioid. TK samples were collected but not analyzed.

Deviation from study protocol: None that affected the integrity of the study.

Observations and Results

Mortality

No mortalities were noted during the study.

Clinical Signs

A detailed clinical evaluation was performed weekly. Additionally, animals were evaluated daily during dosing for general appearance and signs of overt toxicity. No treatment-related clinical signs were observed.

Body Weights

Animals were weighed weekly throughout the study. Minor decreases in body weights were observed in males at the high dose from approximately Study Day 49 to the end of the study. Group mean body weights for males are shown in Figure 3. Males showed body weight gain decreases of 17% at the high dose (Table 5). Slight decreases in body weights were observed in females at the low, mid and high doses from about Study Day 28 to the end of the study. Slightly larger decreases in body weights were observed in females at the high dose throughout the study. Group mean body weights for females are shown in Figure 4. Females showed body weight gain decreases of 25%, 16%, and 29% at the low, mid and high doses, respectively (Table 5).

Figure 5. Mean Body Weights in Male Mice, g, 13-Week Study

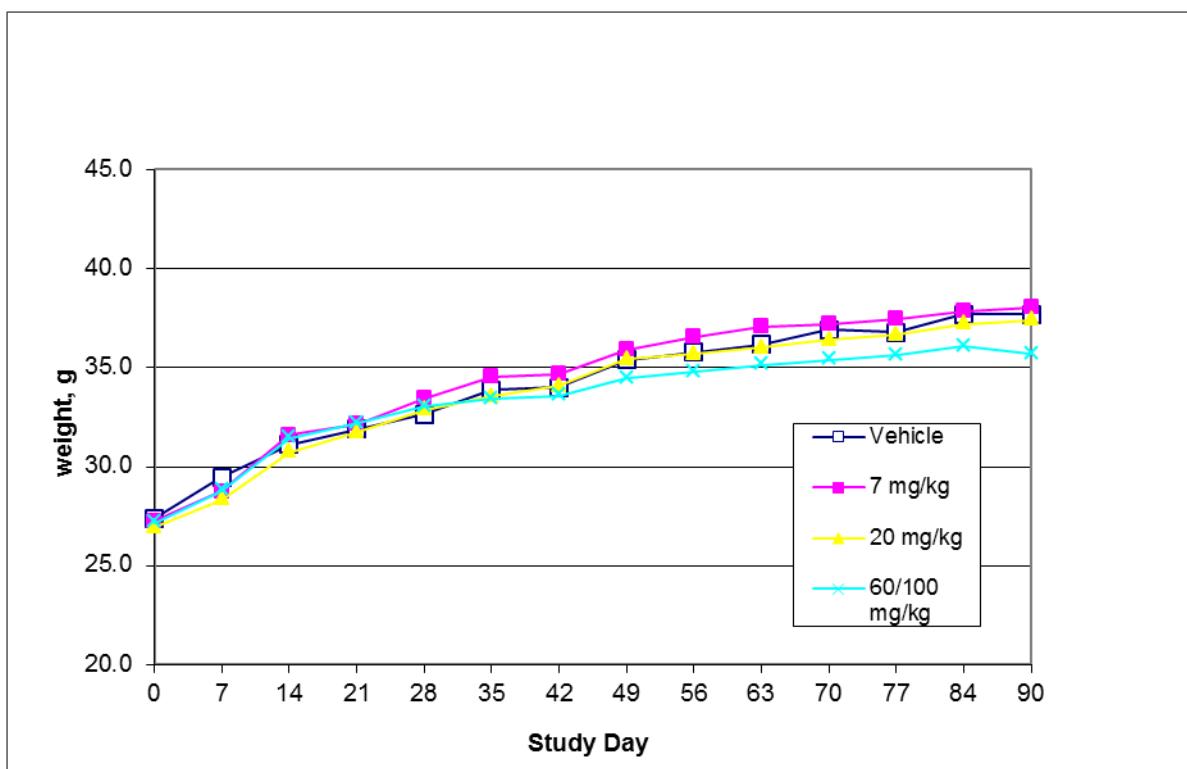


Figure 6. Mean Body Weights in Female Mice, g, 13-Week Study

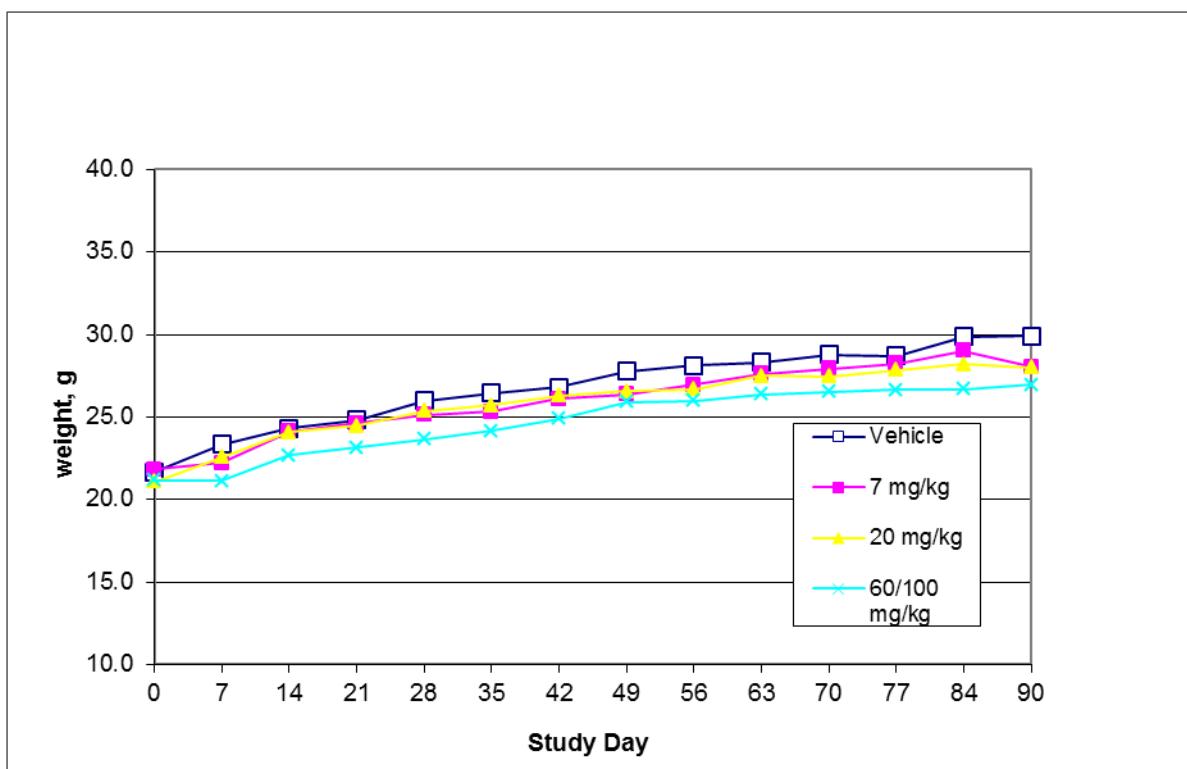


Table 9. Body Weight Gain in Mouse, 13-Week Study

	<i>mg/kg</i>	<i>Body Weight (g), Day 0</i>	<i>Body Weight (g), Day 90</i>	<i>Body Weight Gain (BWG) (g), Day 0 to Day 91</i>	<i>BWG % Change from Control</i>
Male	0	27.4	37.7	10.3	-
	7	27.3	38.0	10.8	5
	20	26.9	37.4	10.5	2
	60/100	27.2	35.7	8.5	-17
Female	0	21.7	29.9	8.2	-
	7	21.8	28.0	6.2	-25
	20	21.1	28.0	6.9	-16
	60/100	21.2	27.0	5.8	-29

Food Consumption

Food consumption was assessed weekly throughout the study. In males, small decreases in food consumption were noted at the high dose (Figure 5). In females, decreases in food consumption were observed at a few time points at the low and mid dose and most time points at the high dose (Figure 6). For both males and females decreases in food consumption paralleled body weight decreases.

Figure 7. Group Mean Food Consumption in Male Mice, g, 13-Week Study

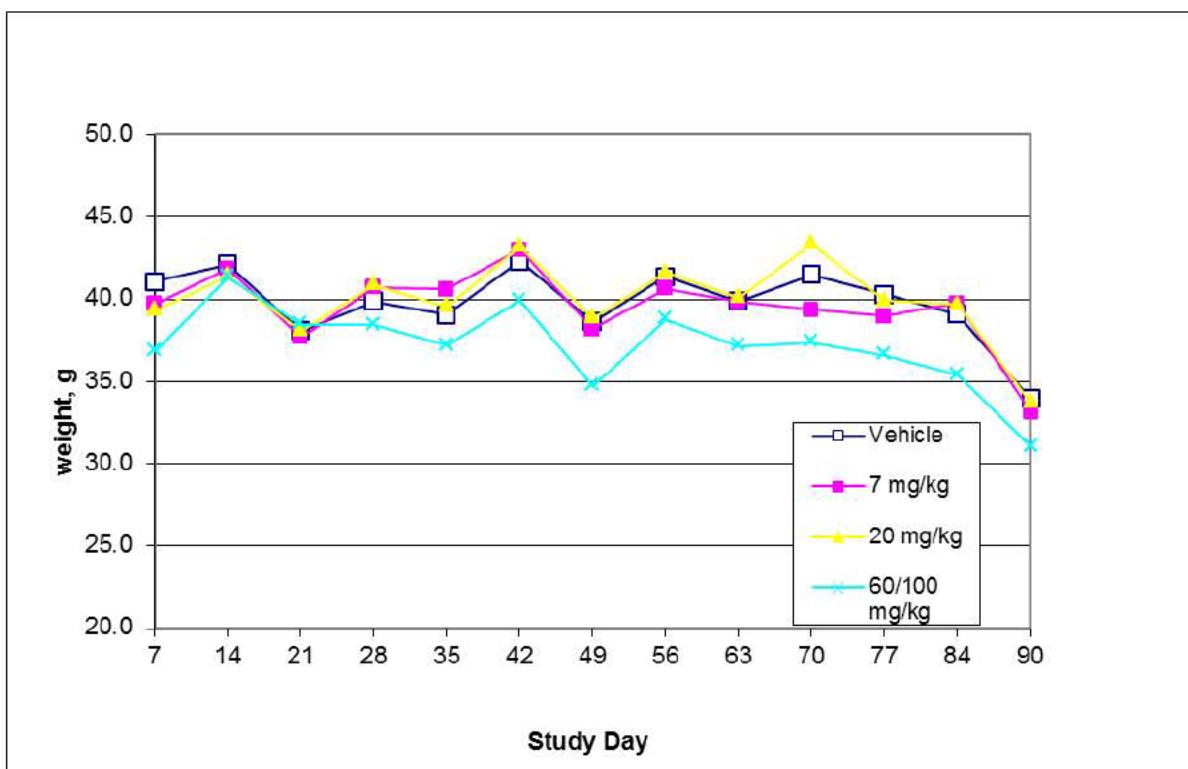
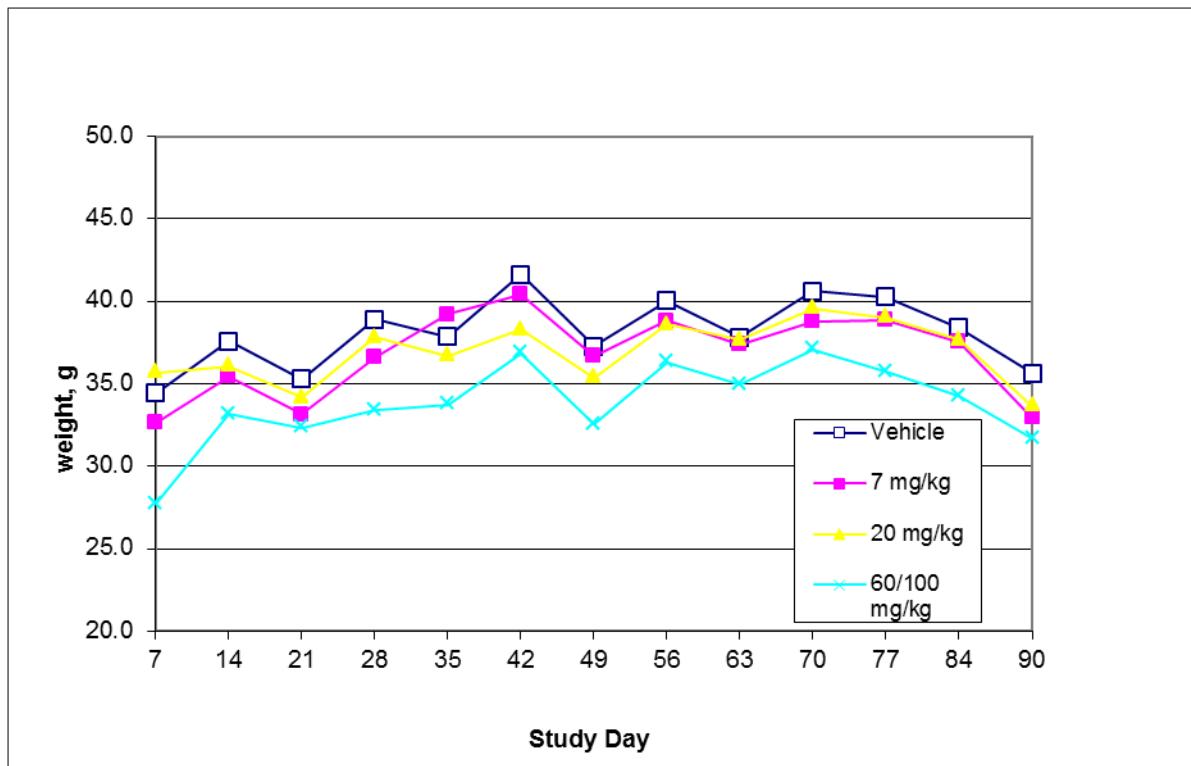


Figure 6. Group Mean Food Consumption in Female Mice, g

Figure 8. Group Mean Food Consumption in Female Mice, g, 13-Week Study

**Ophthalmoscopy**

Ophthalmologic analysis was not conducted.

ECG

ECG was not assessed in this study.

Hematology

The following hematological parameters were measured at Week 13:

Red Blood Cell Count
White Blood Cell Count
Hematocrit
Hemoglobin
Mean Corpuscular Volume
Mean Corpuscular Hemoglobin
Mean Corpuscular Hemoglobin Concentration
Platelet Count

Differential Leukocyte Count (abs and rel)
Red Cell Morphology
Reticulocyte Count (abs and rel)
Mean Platelet Volume

No treatment-related changes in hematology parameters were observed.

Clinical Chemistry

The following clinical chemistry parameters were measured at Week 13:

Alkaline Phosphatase	Glucose
Total Bilirubin	Total Cholesterol
Aspartate Aminotransferase	Sodium
Alanine Aminotransferase	Potassium
Lactate Dehydrogenase	Chloride
Blood Urea Nitrogen	Calcium
Creatinine	Phosphate
Total Protein	Creatinine Kinase
Albumin	Gamma-Glutamyl Transferase
Globulin	Triglycerides
Albumin/Globulin Ratio	

No treatment-related changes in clinical chemistry parameters were observed.

Urinalysis

Urinalysis was not conducted.

Gross Pathology

No test article-related findings were noted.

Organ Weights

No test article-related findings were noted.

Histopathology

Adequate Battery: Yes

Peer Review: No

Histological Findings

No test article-related findings were noted.

Toxicokinetics

Toxicokinetic samples in this study were collected but not analyzed. Exposure ratios were based on body surface area comparisons (Table 6). Exposure ratios based on body surface area comparisons were calculated using the human dose of 90 mg (Study

C33237/1081). The mid dose of the proposed doses for the 2-year bioassay would yield roughly equal exposure to the human daily dose of 90 mg based on body surface area comparisons (Table 7).

Table 10. Exposure Ratios (BSA) Between Mouse and Human for Hydrocodone, 13-Week Study

<i>Dose, mg/kg</i>	<i>Mouse/human*</i>
7	0.4x
20	1.1x
60/100	3.2/5.4x

*Human data from Study C33237/1081, 90 mg dose

Table 11. Exposure Ratios (BSA) Between Mouse and Human for Hydrocodone: Doses for Carcinogenicity Study Proposed by Reviewer

<i>Dose, mg/kg</i>	<i>Mouse/human*</i>
10	0.5x
30	1.6x
100	5.4x

*Human data from Study C33237/1081, 90 mg dose

Dosing Solution Analysis

The concentration analyses were within an acceptable range.

Protein Binding

The extent of hydrocodone protein binding in human plasma is not known. However, it is expected to fall in the low-to-moderate range (19 to 45%), similar to that of other opioid agents (Vicoprofen package insert).

Study title: 13-Week Oral Toxicity Study of Impurity 1 (b) (4)
 (b) (4) Impurity 2 (b) (4) and Impurity 3
 (b) (4) in Rats

Study no.: (b) (4)
 Study report location: EDR 4.2.3.7.6
 Conducting laboratory and location: (b) (4)
 Date of study initiation: December 13, 2011
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: See table below

Table 12. Compounds, Lot Numbers, and Purity

Compound	Lot	Purity
(b) (4)	(b) (4)	94.8%
(b) (4)	(b) (4)	95%
(b) (4)	(b) (4)	89.3%

Key Study Findings

- No treatment-related findings were observed
- The NOEL for the study is the highest dose tested of each impurity:
 - (b) (4) mg/kg
 - (b) (4) mg/kg
 - (b) (4) mg/kg
- At the MTDD of HC (3 g), at the proposed specification of (b) (4)%, (b) (4) mg of each impurity would be consumed. The NOEL of (b) (4) mg/kg, (b) (4) mg/m²) in rat provides a 1.3-fold safety margin over the (b) (4) mg, (b) (4) mg/kg; (b) (4) mg/m²) human dose based on BSA.

Methods

Doses: 0, 0.3, 0.6 mg/kg
Frequency of dosing: Daily (but see unique study design)
Route of administration: Oral gavage
Dose volume: 2 mL/kg
Formulation/Vehicle: Deionized water
Species/Strain: Rat, Sprague-Dawley
Number/Sex/Group: 10/sex/group
Age: 6-7 weeks
Weight: M: 94-106 g; F: 82-99 g
Satellite groups: None, blood for TK analysis was collected from main study rats following the last dose.
Unique study design: The vehicle group received a dose of the vehicle three times a day. The low dose and high dose groups received three consecutive doses of each individual impurity. The doses were separated by at least 15 minutes.
Deviation from study protocol: The TK evaluations were not GLP compliant. The Sponsor considered them "exploratory".

Observations and Results

Mortality

All animals were checked twice daily for moribundity and mortality. No test article-related moribundity or mortality was seen in this study.

Clinical Signs

Detailed clinical observations were conducted prior study initiation and weekly during treatment and recovery periods. No treatment-related clinical signs were noted.

Body Weights

Body weights were recorded prior to study initiation and weekly. No treatment-related changes in body weights in males or females were noted.

Food Consumption

Food consumption was recorded prior to study initiation and weekly. No test article-related changes were noted.

Ophthalmoscopy

Ophthalmoscopic examination was performed prior to study initiation and during the last week of the treatment period. No changes were noted in the ophthalmoscopic exams for any group.

Hematology, Clinical Chemistry, Gross Pathology, Organ Weights and Histopathology

Standard parameters were measured at termination of the treatment period. A few minor changes in clinical chemistry were noted but they were not dose-dependent and were within the historical control range. No toxicologically relevant changes in any parameters were observed.

Toxicokinetics

Although TK for all three compounds were conducted on Days 1 and 91, a large amount of variability was seen. This variability is most likely a result of the low levels tested and the measured values being close to the limit of detection of the assay. It can be concluded that exposure was demonstrated in this study, although exact TK values for the two impurities will not be calculated. Clinical levels of these impurities are not available and the exposure margins for the qualification of the proposed specification will be based on body surface area comparisons.

Dosing Solution Analysis

The solutions utilized in the study were analyzed and found to be within acceptable concentration ranges.

Study title: 90-Day Oral (Gavage) Toxicity Study of Hydrocodone Bitartrate Extended Release Formulation Excipients in Beagle Dogs

Study no.:	11-639 (DS-2011-037)
Study report location:	EDR 4.2.3.7.6
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 4, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	See table below for details on test article; Lot LB5226-71; no purity data was provided

Key Study Findings

- No test article-related findings were observed in this study.
- No TK or dosing analysis was conducted.
- The NOEL for this study is the highest dose tested, >1,145 mg/kg. Calculated for each excipient individually, exposure margins are 1-fold the amount in a human dose of 33 90 mg tablets of the clinical formulation, based on a mg/m² comparison.
- It should be noted that this 90-day study is not of adequate duration to serve as qualification for any excipients in this formulation. This drug product will be indicated for chronic use because it is an ER opioid formulation.

Methods

Doses: 0, 572.5, and 1,145 mg/kg (see table below for details of the formulation)

Frequency of dosing: Daily

Route of administration: Dietary (canned food)

Dose volume: NA

Formulation/Vehicle: Canned food without test article

Species/Strain: Dog: Beagle

Number/Sex/Group: 4/sex/group

Age: 5-6 months

Weight: M: 7.2-9.0 g; F: 6.6-8.4 g

Satellite groups: None

Unique study design: This study is testing a mixture of excipients which comprise the formulation of the drug product without the active ingredient. The high dose was based on the amount of the excipients a 60 kg human would ingest if they were to consume the drug product at the maximum theoretical daily dose of 3 g for hydrocodone.

Deviation from study protocol: None that affected the integrity of the study

Table 13. Test Article Formulation

Excipients	Maximum excipients quantity per tablet (mg)	Maximum tablets/day	Maximum excipient quantity in 3 g/day human HC dose (mg)	Per Day		
				mg/kg per 60 kg human	mg/m ² ^a	mg/kg dog ^b
Lactose Monohydrate *	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Ethyl Cellulose	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Hypromellose	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Glyceryl behenate	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Magnesium Stearate,	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Yellow Ferric Oxide†	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
FD&C Blue #2	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Aluminum Lake†	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Daily dose (mg)				per kg dog:		
*assuming 45 mg tablets, †assuming 45 mg tablets, ‡assuming 90 mg tablets.	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

At the maximum theoretical daily dose of 3 g for hydrocodone, (b) (4) 90 mg tablets of this formulation would be consumed. The Sponsor calculates the level of excipients for (b) (4) 45 mg tablets. (b) (4) (b) (4) (b) (4)

For each excipient tested, the high dose and low dose yield exposure margins of 1-fold and 0.5-fold, respectively, the human dose of (b) (4) 90 mg tablets based on a mg/m² comparison.

Observations and Results

Mortality

No mortality was observed in the study.

Clinical Signs

Clinical observations were made 1-2 h after daily dosing. A detailed examination was performed weekly. No treatment-related clinical signs were observed.

Body Weights

Body weights were recorded weekly. A minor transient decrease in body weights in all groups (including control) was observed in the first two weeks. The Sponsor stated that it was associated with insufficient caloric intake and supplemented the daily meal with dry dog food after consumption of the canned dog food. No test article-related changes in body weight or body weight gain were observed.

Food Consumption

Food consumption was recorded daily. Dogs consumed all of the canned food (either with or without the test article) daily. No treatment-related changes in food consumption were observed.

Ophthalmoscopy

Ophthalmoscopic parameters were measured pretest and at Week 13. No treatment-related findings were noted.

ECG

ECG was conducted pretest and at Week 13. No treatment-related findings were noted.

Hematology

Hematologic parameters were measured pretest and at Week 13. No treatment-related findings were noted.

Clinical Chemistry

Clinical chemistry parameters were measured pretest and at Week 13. No treatment-related findings were noted.

Urinalysis

Urinalysis was conducted at Week 13. No treatment-related findings were noted.

Gross Pathology

No treatment-related findings were noted.

Organ Weights

No treatment-related findings were noted.

Histopathology

Adequate Battery: Yes.

Peer Review: Yes

Histological Findings: No treatment-related findings were noted.

Special Evaluation

None

Toxicokinetics

Toxicokinetics were not conducted.

Dosing Solution Analysis

Dosing solution analysis was not conducted.

Study title: 90-Day Oral (Gavage) Toxicity and Toxicokinetic Study of [REDACTED] in Beagle Dogs

Study no.:	[REDACTED] [REDACTED]
Study report location:	EDR 4.2.3.7.6 [REDACTED] [REDACTED]
Conducting laboratory and location:	[REDACTED]
Date of study initiation:	October 13, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	[REDACTED] (b) (4) [REDACTED] (b) (4) Lot [REDACTED]; 99.1%

Key Study Findings

- No test article-related findings were observed in this study.
- The NOEL for this study is [REDACTED] mg/kg (highest dose tested).
- At the MTDD of HC (3 g), [REDACTED] mg of [REDACTED] (b) (4) would be consumed at the proposed specification of [REDACTED]%. The NOEL of [REDACTED] mg/kg [REDACTED] mg/m²) in dog provides approximately a 2-fold safety margin over the [REDACTED] (b) (4) mg ([REDACTED] mg/kg; [REDACTED] mg/m²) human dose.

Methods

Doses: 0, 0.5, and 1.0 mg/kg
Frequency of dosing: Daily
Route of administration: Oral (gavage)
Dose volume: 1.0 mL/kg
Formulation/Vehicle: Water
Species/Strain: Dog: Beagle
Number/Sex/Group: 4/sex/group
Age: 5-6 months
Weight: M: 7.5-8.8 g; F: 6.5-7.8 g
Satellite groups: TK
Unique study design: None
Deviation from study protocol: None that affected the integrity of the study

Observations and Results

Mortality

No mortality was observed in the study.

Clinical Signs

Clinical observations were made daily. A detailed examination was performed at weekly. No treatment-related clinical signs were observed.

Body Weights

Body weights were recorded weekly. No test article-related changes in body weight or body weight gain were observed.

Food Consumption

Food consumption was recorded weekly. No treatment-related changes in food consumption were observed.

Ophthalmoscopy

Ophthalmoscopic parameters were measured pretest and at Week 13. No treatment-related findings were noted.

ECG

ECG was conducted pretest and at Week 13. No treatment-related findings were noted.

Hematology

Hematologic parameters were measured pretest and at Week 13. No treatment-related findings were noted.

Clinical Chemistry

Clinical chemistry parameters were measured pretest and at Week 13. No treatment-related findings were noted.

Urinalysis

Urinalysis was conducted at Week 13. Specific gravity was significantly increased in low and high dose males as compared to controls. Increases were minor, not dose dependent and within normal ranges and will not be considered biologically relevant. No other treatment-related findings were noted.

Gross Pathology

No treatment-related findings were noted.

Organ Weights

No treatment-related findings were noted.

Histopathology

Adequate Battery: Yes.

Peer Review: Yes

Histological Findings: No treatment-related findings were noted.

Special Evaluation

None

Toxicokinetics

Toxicokinetics were measured on Day 1, Day 42, and Day 91. Hydrocodone and [REDACTED]^{(b) (4)} were measured. Systemic exposure was dose proportional and no sex differences or accumulation were observed. Elimination half-life ranged from 2-3.8 h. Approximately 50% of the [REDACTED]^{(b) (4)} was converted to HC.

Dosing Solution Analysis

Dosing solutions were analyzed and found to be acceptable.

7 Genetic Toxicology

7.1 In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Hydrocodone Bitartrate: Bacterial Reverse Mutation Assay

Study no.: 964183 (DS-2011-031)
Study report location: EDR 4.2.3.3.1
Conducting laboratory and location: [REDACTED] (b) (4)

Date of study initiation: December 22, 2011
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Hydrocodone bitartrate, E15660, 99.6%

Key Study Findings

- Hydrocodone bitartrate is not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 or *E. coli* strain WP2uvrA in either the presence or absence of S9 with both the plate incorporation and pre-incubation methods.

Methods

Strains: *Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 and *Escherichia coli*: WP2 uvrA
Concentrations in definitive study: 50, 158, 500, 1581, and 5000 mcg +/- S9
Basis of concentration selection: Initial study used 1.58 – 5000 mcg
Negative control: Sterile water
Positive control: See data tables
Formulation/Vehicle: Sterile water
Incubation & sampling time: Plate incorporation and pre-incubation: 65 h at 37°C

Study Validity

The study is valid. All strains were shown to contain the appropriate genetic markers. Suitable numbers of replicate plates and appropriate counting methods were utilized. The positive controls demonstrated clear increases in tester strain revertants while the vehicle control was within historical range for the tester strains for this vehicle.

Results

It is concluded that under conditions of the assays conducted, HC is not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 or *E. coli* strain WP2uvrA in either the presence or absence of S9. The results of the plate incorporation and pre-incubation assays are summarized in the tables below. No reduction in bacterial lawn

was observed at any concentration. For all strains, at least three concentrations of test article were able to be evaluated. All of the strains at all of the concentrations tested showed negative mutagenic responses in the presence and absence of exogenous metabolic activation with S9.

Table 14. Hydrocodone Bitartrate Plate Incorporation Ames Assay: Summary of Results in the Absence of S9

Strain	Conc. (μ g/plate)	S9	Number of revertants				Plate observations *			Fold response †	
			x_1	x_2	x_3	mean	SD	x_1	x_2	x_3	
TA1535	Water	0	22	21	22	22	1				1.0
	50	0	24	22	16	21	4				1.0
	158	0	23	24	23	23	1				1.1
	500	0	13	23	22	19	6				0.9
	1581	0	21	24	25	23	2				1.1
	5000	0	17	24	23	21	4				1.0
TA1537	Water	0	17	28	11	19	9				1.0
	50	0	9	17	8	11	5				0.6
	158	0	18	10	23	17	7				0.9
	500	0	19	10	11	13	5				0.7
	1581	0	25	19	14	19	6				1.0
	5000	0	26	17	16	20	6				1.1
TA98	Water	0	37	33	33	34	2				1.0
	50	0	33	44	20	32	12				0.9
	158	0	33	34	24	30	6				0.9
	500	0	28	30	29	29	1	CNOC			0.8
	1581	0	28	21	40	30	10				0.9
	5000	0	37	23	33	31	7				0.9
TA100	Water	0	134	143	160	146	13				1.0
	50	0	150	152	131	144	12				1.0
	158	0	138	151	142	144	7				1.0
	500	0	126	134	155	138	15				0.9
	1581	0	150	182	147	160	19				1.1
	5000	0	147	159	171	159	12				1.1
WP2 <i>uvrA</i>	Water	0	52	54	47	51	4				1.0
	50	0	56	41	51	49	8				1.0
	158	0	50	62	54	55	6				1.1
	500	0	55	58	37	50	11				1.0
	1581	0	50	56	42	49	7				1.0
	5000	0	39	47	60	49	11				1.0

* Comments on the plate or background lawn: Contamination did not obscure count (CNOC).

† Fold response in mean revertants compared to concurrent vehicle control.

SD Sample standard deviation.

Table 15. Hydrocodone Bitartrate Plate Incorporation Ames Assay: Summary of Results in the Presence of S9

Strain	Conc. ($\mu\text{g}/\text{plate}$)	S9	Number of revertants				Plate observations *			Fold response †
			x_1	x_2	x_3	mean	SD	x_1	x_2	
TA1535	Water	+	24	18	23	22	3			1.0
	50	+	24	21	26	24	3			1.1
	158	+	23	28	26	26	3			1.2
	500	+	36	16	19	24	11			1.1
	1581	+	25	22	22	23	2	CNOC		1.1
	5000	+	18	28	23	23	5			1.1
	Water	+	16	16	24	19	5			1.0
TA1537	50	+	18	19	18	18	1			1.0
	158	+	33	19	21	24	8			1.3
	500	+	23	21	25	23	2			1.2
	1581	+	21	18	22	20	2			1.1
	5000	+	27	18	13	19	7			1.0
TA98	Water	+	40	42	56	46	9			1.0
	50	+	53	51	32	45	12			1.0
	158	+	36	55	53	48	10			1.0
	500	+	41	41	47	43	3			0.9
	1581	+	45	48	46	46	2			1.0
	5000	+	48	36	37	40	7			0.9
TA100	Water	+	166	173	160	166	7			1.0
	50	+	172	151	156	160	11			1.0
	158	+	150	141	146	146	5			0.9
	500	+	160	159	160	160	1			1.0
	1581	+	154	159	186	166	17			1.0
	5000	+	170	164	157	164	7			1.0
WP2 <i>uvrA</i>	Water	+	58	58	65	60	4			1.0
	50	+	49	67	64	60	10			1.0
	158	+	48	52	61	54	7			0.9
	500	+	65	56	69	63	7			1.0
	1581	+	50	52	68	57	10			0.9
	5000	+	56	72	54	61	10			1.0

* Comments on the plate or background lawn: Contamination did not obscure count (CNOC).

† Fold response in mean revertants compared to concurrent vehicle control.

SD Sample standard deviation.

Table 16. Positive Controls in the Plate Incorporation Ames Assay: Summary of Results in the Absence and Presence of S9

Strain	Treatment	Conc. ($\mu\text{g}/\text{plate}$)	S9	Number of revertants				SD	Fold response †
				x_1	x_2	x_3	mean		
TA1535	NaAz	0.5	0	267	298	284	283	16	13
TA1537	9AC	50	0	463	385	463	437	45	23
TA98	2NF	1	0	297	267	233	266	32	7.7
TA100	NaAz	0.5	0	488	548	570	535	42	3.7
WP2 <i>uvrA</i>	NQO	0.5	0	248	256	258	254	5	5.0
TA1535	2AA	5	+	416	429	438	428	11	20
TA1537	BaP	5	+	103	109	104	105	3	5.6
TA98	BaP	5	+	339	391	339	356	30	7.7
TA100	BaP	5	+	860	764	778	801	52	4.8
WP2 <i>uvrA</i>	2AA	15	+	275	230	282	262	28	4.3

† Fold response in mean revertants compared to concurrent vehicle control.

SD Sample standard deviation.

Table 17. Hydrocodone Bitartrate Pre-Incubation Ames Assay: Summary of Results in the Absence of S9

Strain	Conc. (μ g/plate)	S9	Number of revertants				Plate observations *			Fold response †
			x_1	x_2	x_3	mean	SD	x_1	x_2	
TA1535	water	0	20	17	11	16	5			1.0
	50	0	15	14	24	18	6			1.1
	158	0	20	19	24	21	3			1.3
	500	0	24	17	21	21	4			1.3
	1581	0	24	20	26	23	3			1.5
	5000	0	32	14	25	24	9			1.5
TA1537	water	0	8	15	16	13	4			1.0
	50	0	12	14	18	15	3			1.1
	158	0	24	12	12	16	7			1.2
	500	0	3	12	12	9	5			0.7
	1581	0	16	9	10	12	4			0.9
	5000	0	13	18	16	16	3			1.2
TA98	water	0	33	28	25	29	4			1.0
	50	0	29	34	27	30	4			1.0
	158	0	23	33	18	25	8			0.9
	500	0	29	27	25	27	2			0.9
	1581	0	20	20	23	21	2			0.7
	5000	0	24	26	30	27	3			0.9
TA100	water	0	107	114	118	113	6			1.0
	50	0	122	134	114	123	10			1.1
	158	0	144	143	143	143	1			1.3
	500	0	126	124	121	124	3			1.1
	1581	0	166	142	157	155	12			1.4
	5000	0	144	139	136	140	4			1.2
WP2 <i>uvrA</i>	water	0	60	49	35	48	13			1.0
	50	0	35	51	37	41	9			0.9
	158	0	53	48	53	51	3			1.1
	500	0	38	56	38	44	10			0.9
	1581	0	45	43	54	47	6			1.0
	5000	0	37	52	38	42	8			0.9

* Comments on the plate or background lawn: none.

† Fold response in mean revertants compared to concurrent vehicle control.

SD Sample standard deviation.

Table 18. Hydrocodone Bitartrate Pre-Incubation Ames Assay: Summary of Results in the Presence of S9

Strain	Conc. ($\mu\text{g}/\text{plate}$)	S9	Number of revertants					Plate observations *	Fold response †
			x_1	x_2	x_3	mean	SD		
TA1535	water	+	22	18	17	19	3		1.0
	50	+	17	25	20	21	4		1.1
	158	+	29	19	33	27	7		1.4
	500	+	17	28	18	21	6		1.1
	1581	+	20	18	25	21	4		1.1
	5000	+	26	26	26	26	0		1.4
	TA1537	water	+	21	15	17	18	3	1.0
TA98	50	+	15	28	18	20	7		1.2
	158	+	14	9	36	20	14		1.1
	500	+	16	16	15	16	1		0.9
	1581	+	10	18	23	17	7		1.0
	5000	+	14	17	19	17	3		0.9
	TA100	water	+	40	47	50	46	5	1.0
	50	+	43	45	41	43	2		0.9
WP2 <i>uvrA</i>	158	+	36	51	39	42	8		0.9
	500	+	50	37	34	40	9		0.9
	1581	+	44	39	47	43	4		0.9
	5000	+	39	36	27	34	6		0.7
	water	+	154	156	167	159	7		1.0
	50	+	151	143	132	142	10		0.9
	158	+	157	141	150	149	8		0.9
TA100	500	+	158	132	179	156	24		1.0
	1581	+	165	152	157	158	7		1.0
	5000	+	161	158	192	170	19		1.1
	WP2 <i>uvrA</i>	+	47	51	53	50	3		1.0
	50	+	42	41	54	46	7		0.9
	158	+	61	42	50	51	10		1.0
	500	+	44	61	56	54	9		1.1
TA98	1581	+	48	44	43	45	3	CNOC	0.9
	5000	+	50	63	55	56	7		1.1

* Comments on the plate or background lawn: Contamination did not obscure count (CNOC).

† Fold response in mean revertants compared to concurrent vehicle control.

SD Sample standard deviation.

Table 19. Positive Controls in the Pre-Incubation Ames Assay: Summary of Results in the Absence and Presence of S9

Strain	Treatment	Conc. ($\mu\text{g}/\text{plate}$)	S9	Number of revertants					Fold response †
				x_1	x_2	x_3	mean	SD	
TA1535	NaAz	0.5	0	303	287	316	302	15	19
TA1537	9AC	50	0	220	570	415	402	175	31
TA98	2NF	1	0	171	168	143	161	15	5.6
TA100	NaAz	0.5	0	534	521	559	538	19	4.8
WP2 <i>uvrA</i>	NQO	0.5	0	1577	1543	1521	1547	28	32
TA1535	2AA	5	+	299	304	323	309	13	16
TA1537	BaP	5	+	97	115	76	96	20	5.4
TA98	BaP	5	+	209	233	240	227	16	5.0
TA100	BaP	5	+	891	881	882	885	6	5.6
WP2 <i>uvrA</i>	2AA	15	+	313	338	321	324	13	6.4

† Fold response in mean revertants compared to concurrent vehicle control.

SD Sample standard deviation.

Study title:

(b) (4)

Bacterial Reverse Mutation Assay

Study no.: AE03NA.502ICH.BTL (DS-2014-075)

Study report location: EDR 4.2.3.3.1

Conducting laboratory and location:

(b) (4)

September 3, 2014

Date of study initiation:

Yes

GLP compliance:

Yes

QA statement:

Drug, lot #, and % purity:

(b) (4) DRM-3337-185-

P1, 88.4%

Key Study Findings

- (b) (4) is not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 or *E. coli* strain WP2uvrA in either the presence or absence of S9.

Methods

Strains: *Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 and *Escherichia coli*: WP2 uvrA

Concentrations in definitive study: 50, 150, 500, 1500, and 5000 mcg +/- S9

Basis of concentration selection: Initial study used 6.7 – 5000 mcg

Negative control: DMSO

Positive control: See table below

Formulation/Vehicle: DMSO

Incubation & sampling time: 48-72 h at 37°C

Table 20. Ames Assay Positive Controls

Strain	S9 Activation	Positive Control	Concentration (µg/plate)
TA98, TA1535	Rat	2-aminoanthracene (b) (4)	1.0
TA100, TA1537		Lot No. STBB1901V Exp. Date 31-Oct-2014 CAS No. 613-13-8 Purity 97.5%	2.0
WP2 uvrA		2-nitrofluorene (b) (4)	15
TA98	None	Lot No. S43858V Exp. Date 31-Mar-2016 CAS No. 607-57-8 Purity 99.4%	1.0

TA100, TA1535	sodium azide Lot No. MKBH5113V Exp. Date 30-Jun-2016 CAS No. 26628-22-8 Purity 99.6%	(b) (4)	1.0
TA1537	9-aminoacridine Lot No. 09820CEV Exp. Date 31-Mar-2016 CAS No. 52417-22-8 Purity 99.4%	(b) (4)	75
WP2 <i>uvrA</i>	methyl methanesulfonate Lot No. MKBG0368V Exp. Date 31-Oct-2014 CAS No. 66-27-3 Purity 99.9%	(b) (4)	1,000

Study Validity

The study is valid. All strains were shown to contain the appropriate genetic markers. Suitable numbers of replicate plates and appropriate counting methods were utilized. The positive controls demonstrated clear increases in tester strain revertants while the vehicle control was within historical range for the tester strains for this vehicle.

Results

It is concluded that under conditions of the assays conducted, (b) (4) is not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 or *E. coli* strain WP2*uvrA* in either the presence or absence of S9. The results of the confirmatory assay are summarized in the table below. No reduction in bacterial lawn was observed at any concentration. For all strains, at least three concentrations of test article were able to be evaluated. All of the strains at all of the concentrations tested showed negative mutagenic responses in the presence and absence of exogenous metabolic activation with S9.

Table 21. ^{(b) (4)} Ames Confirmatory Assay Summary of Results

Metabolic Activation	Test Article	Dose Level ($\mu\text{g}/\text{plate}$)	Mutagenicity Assay Revertant Colony Counts (Mean \pm SD)				
			TA98	TA100	TA1535	TA1537	WP2uvrA
Without Activation	DMSO Hydrocodone N-Oxide	50 $\mu\text{L}/\text{plate}$	14 \pm 5	83 \pm 1	13 \pm 8	6 \pm 1	25 \pm 5
		50	16 \pm 4	77 \pm 12	17 \pm 2	6 \pm 3	19 \pm 6
		150	14 \pm 4	85 \pm 11	8 \pm 2	10 \pm 1	26 \pm 3
		500	12 \pm 2	83 \pm 6	11 \pm 6	8 \pm 2	26 \pm 10
		1500	12 \pm 2	84 \pm 15	9 \pm 3	9 \pm 2	29 \pm 5
		5000	16 \pm 3	84 \pm 7	11 \pm 4	8 \pm 2	28 \pm 4
		2NF	1.0	106 \pm 18			
		SA	1.0		723 \pm 71	480 \pm 31	
		9AAD	75				321 \pm 33
		MMS	1000				389 \pm 12
With Activation	DMSO Hydrocodone N-Oxide	50 $\mu\text{L}/\text{plate}$	23 \pm 6	104 \pm 12	11 \pm 4	9 \pm 1	28 \pm 10
		50	29 \pm 6	116 \pm 16	14 \pm 4	7 \pm 2	33 \pm 5
		150	22 \pm 6	99 \pm 3	10 \pm 3	7 \pm 0	28 \pm 5
		500	23 \pm 9	111 \pm 14	11 \pm 3	9 \pm 6	30 \pm 4
		1500	25 \pm 4	94 \pm 4	13 \pm 1	9 \pm 5	29 \pm 3
		5000	23 \pm 1	98 \pm 9	17 \pm 5	5 \pm 3	30 \pm 7
		2AA	1.0	234 \pm 17		85 \pm 40	
		2AA	2.0		525 \pm 229		92 \pm 34
		2AA	15				396 \pm 47

Key to Positive Controls

SA sodium azide
 2AA 2-aminoanthracene
 9AAD 9-Aminoacridine
 2NF 2-nitrofluorene
 MMS methyl methanesulfonate

Study title: ^{(b) (4)} Bacterial Reverse Mutation Assay

Study no.: AE03MY.502ICH.BTL (DS-2014-073)

EDR 4.2.3.3.1

Conducting laboratory and location:

^{(b) (4)}

September 3, 2014

Date of study initiation:

Yes

GLP compliance:

Yes

QA statement:

(b) (4)

Drug, lot #, and % purity:

DRM3424-062-P2, 93.1%

Key Study Findings

- ^{(b) (4)} is not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 or *E. coli* strain WP2uvrA in either the presence or absence of S9.

Methods

Strains: *Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 and *Escherichia coli*: WP2 *uvrA*

Concentrations in definitive study: 50, 150, 500, 1500, and 5000 mcg +/- S9

Basis of concentration selection: Initial study used 6.7 – 5000 mcg

Negative control: DMSO

Positive control: See table below

Formulation/Vehicle: DMSO

Incubation & sampling time: 48-72 h at 37°C

Table 22. Ames Assay Positive Controls

Strain	S9 Activation	Positive Control	Concentration (µg/plate)
TA98, TA1535	Rat	2-aminoanthracene (b) (4)	1.0
TA100, TA1537		Lot No. STBB1901V Exp. Date 31-Oct-2014 CAS No. 613-13-8 Purity 97.5%	2.0
WP2 <i>uvrA</i>		2-nitrofluorene (b) (4) Lot No. S43858V Exp. Date 31-Mar-2016 CAS No. 607-57-8 Purity 99.4%	15
TA98	None	sodium azide (b) (4) Lot No. MKBH5113V Exp. Date 30-Jun-2016 CAS No. 26628-22-8 Purity 99.6%	1.0
TA100, TA1535		9-aminoacridine (b) (4) Lot No. 09820CEV Exp. Date 31-Mar-2016 CAS No. 52417-22-8 Purity 99.4%	75
TA1537		methyl methanesulfonate (b) (4) Lot No. MKBGU508V Exp. Date 31-Oct-2014 CAS No. 66-27-3 Purity 99.9%	1,000
WP2 <i>uvrA</i>			

Study Validity

The study is valid. All strains were shown to contain the appropriate genetic markers. Suitable numbers of replicate plates and appropriate counting methods were utilized. The positive controls demonstrated clear increases in tester strain revertants while the vehicle control was within historical range for the tester strains for this vehicle.

Results

It is concluded that under conditions of the assays conducted, (b) (4) is not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 or *E. coli* strain WP2uvrA in either the presence or absence of S9. The results of the confirmative assay are summarized in the table below. Slight and moderate reduction of the bacterial lawn occurred in the absence and presence of S9, respectively, in strain TA100 at the 5000 mcg concentration. In strain TA1535, slight reduction in the bacterial lawn was observed in the presence of S9 at the 5000 mcg concentration. No other reductions in bacterial lawn were observed for any other condition. For all strains, at least three concentrations of test article were able to be evaluated. All of the strains at all of the concentrations tested showed negative mutagenic responses in the presence and absence of exogenous metabolic activation with S9.

Table 23. (b) (4) Ames Confirmatory Assay in the Absence of S9: Summary of Results

(b) (4)
(b) (4)



(b) (4)

Table 24. Ames Confirmatory Assay in the Presence of S9: Summary of Results



Study title: (b) (4) **Bacterial Reverse Mutation Assay**

Study no.: AE03MZ.502ICH.BTL (DS-2014-074)

Study report location: EDR 4.2.3.3.1

Conducting laboratory and location: (b) (4)

Date of study initiation: September 3, 2014

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: (b) (4)

as per
Certificate of Analysis), 87.2%

Key Study Findings

- There was an apparent concentration-dependent increase in revertants in Strain TA100 and the report concludes that the results are equivocal. The results were within the historical control range and were <2-fold increase. Therefore, (b) (4) is negative for mutagenicity in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2uvrA in both the presence and absence of S9.

Methods

Strains: *Salmonella typhimurium*: TA98, TA100,
TA1535, TA1537 and *Escherichia coli*:
WP2 uvrA

Concentrations in definitive study: TA 100: 30,100, 300, 450, 600, 750, 1000,
1200, 1400, 1500 and 5000 mcg +/-
S9; all other strains: 30,100, 300, 600,
1500, and 5000 mcg +/- S9

Basis of concentration selection: Initial study used 6.7 – 5000 mcg

Negative control: DMSO

Positive control: See table below

Formulation/Vehicle: DMSO

Incubation & sampling time: 48-72 h at 37°C

Table 25. Ames Assay Positive Controls

Strain	S9 Activation	Positive Control	Concentration (µg/plate)
TA98, TA1535	Rat	2-aminoanthracene Lot No. STBB1901V Exp. Date 31-Oct-2014 CAS No. 613-13-8 Purity 97.5%	1.0 2.0
TA100, TA1537		(b) (4)	
WP2 <i>uvrA</i>		2-nitrofluorene Lot No. S43858V Exp. Date 31-Mar-2016 CAS No. 607-57-8 Purity 99.4% sodium azide Lot No. MKBH5113V Exp. Date 30-Jun-2016 CAS No. 26628-22-8 Purity 99.6%	15 1.0
TA98	None	0-aminoacridine Lot No. 09820CEV Exp. Date 31-Mar-2016 CAS No. 52417-22-8 Purity 99.4%	75
TA100, TA1535		methyl methanesulfonate Lot No. MKBG0368V Exp. Date 31-Oct-2014 CAS No. 66-27-3 Purity 99.9%	1,000
TA1537		(b) (4)	
WP2 <i>uvrA</i>		(b) (4)	

Study Validity

The study is valid. All strains were shown to contain the appropriate genetic markers. Suitable numbers of replicate plates and appropriate counting methods were utilized. The positive controls demonstrated clear increases in tester strain revertants while the vehicle control was within historical range for the tester strains for this vehicle.

Results

There was an apparent concentration-dependent increase in revertants in Strain TA100 and the report concludes that the results are equivocal. The results were within the historical control range and were < 2-fold increase. It is concluded that under conditions of the assays conducted, (b) (4) is not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 or *E. coli* strain WP2*uvrA* in either the presence or absence of S9.

No precipitate was observed in any condition. The higher doses in most strains showed signs of toxicity. For all strains, at least three concentrations of test article were able to be evaluated.

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Study title: (b) (4) **Bacterial Reverse Mutation Assay**

Study no.: AE03MX.502ICH.BTL (DS-2014-072)
Study report location: EDR 4.2.3.3.1
Conducting laboratory and location: (b) (4)
Date of study initiation: September 3, 2014
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: (b) (4) (b) (4) 69.8%

Key Study Findings

- (b) (4) yielded the following results in this assay:
- Positive for mutagenicity in *S. typhimurium* strain TA100 in the absence of S9 and equivocal for mutagenicity in the presence of S9
- Equivocal for mutagenicity in *S. typhimurium* strain TA98 in the absence of S9
- Negative for mutagenicity in *S. typhimurium* strains TA1535, and TA1537

and *E. coli* strain WP2uvrA in either the presence or absence of S9 and TA98 in the presence of S9

Methods

Strains: *Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 and *Escherichia coli*: WP2 uvrA

Concentrations in definitive study: TA 100: 500, 1500, 3000, 4000, and 5000 mcg +/- S9; all other strains: 50, 150, 500, 1500, and 5000 mcg +/- S9

Basis of concentration selection: Initial study used 6.7 – 5000 mcg

Negative control: DMSO, MTBE (repeat study)

Positive control: See table below

Formulation/Vehicle: DMSO, MTBE (repeat study)

Incubation & sampling time: 48-72 h at 37°C

Table 30. Ames assay: Positive Controls

Strain	S9 Activation	Positive Control	Concentration (µg/plate)
TA98, TA1535	Rat	2-aminoanthracene (b) (4)	1.0
TA100, TA1537		Lot No. STBB1901V Exp. Date 31-Oct-2014 CAS No. 613-13-8 Purity 97.5%	2.0
WP2 uvrA		2-nitrofluorene (b) (4) Lot NO. S45858V Exp. Date 31-Mar-2016 CAS No. 607-57-8 Purity 99.4%	15
TA98	None	sodium azide (b) (4) Lot No. MKBH5115V Exp. Date 30-Jun-2016 CAS No. 26628-22-8 Purity 99.6%	1.0
TA100, TA1535		9-aminoacridine (b) (4) Lot NO. U9820CEV Exp. Date 31-Mar-2016 CAS No. 52417-22-8 Purity 99.4%	75
TA1537		methyl methanesulfonate (b) (4) Lot No. MKBG0368V Exp. Date 31-Oct-2014 CAS No. 66-27-3 Purity 99.9%	1,000
WP2 uvrA			

Study Validity

The study is valid. All strains were shown to contain the appropriate genetic markers. Suitable numbers of replicate plates and appropriate counting methods were utilized. The positive controls demonstrated clear increases in tester strain revertants while the vehicle control was within historical range for the tester strains for this vehicle.

Results

It is concluded that under conditions of the assays conducted, (b) (4) (b) (4) is positive in *S. typhimurium* strain TA100 in the absence of S9 and equivocal in the presence of S9. Additionally, *S. typhimurium* strain TA98 is equivocal in the absence of S9. *S. typhimurium* strain TA 98 in the presence of S9 and TA1535, TA1537 and *E. coli* strain WP2uvrA in either the presence or absence of S9 were negative in this assay.

The data from the mutagenicity assay and the preliminary test with the strains TA98 and TA100 are presented in the summary tables below. As outlined in the study protocol, to be considered a positive response, a culture must demonstrate a dose-related increase in mean revertants that is greater than or equal to 2.0-times the mean vehicle control (for the TA98 and TA100 strains). Biologically relevant increase in revertant count that partially meets the criteria for a positive response would be considered an equivocal response. This could include a dose-responsive increase that does not meet the 2-fold threshold or a non dose-responsive increase that is equal to or greater than the 2-fold threshold. If a response is judged as neither positive nor equivocal, it is considered negative.

No precipitate or cytotoxicity was observed in any condition.

In the mutagenicity assay, non dose-related increases in revertants were observed in strain TA98 in the absence of S9, however, at the highest concentration tested, a 2.2-fold increase in revertant count over vehicle was observed. A preliminary toxicity assay (1 plate) did not show a dose-related increases and the highest increase in revertants was 1.3-fold. No relevant increases in revertant count were observed in the TA98 strain in the presence of S9. No confirmatory assay was conducted. The vehicle historical control values for the TA98 strain in the absence of S9 are 18 +/- 8 (3-64) [mean +/- SD (range)]. All of the increases in revertants, including the 2.2-fold increase at the high dose, were well within this range. Although the increase in revertants at the highest concentration evaluated was still within the historical range of the vehicle, the more relevant comparison is considered the concurrent controls. Treatment of strain TA98 in the absence of S9 with (b) (4) is concluded to be equivocal for mutagenicity.

In the mutagenicity assay, concentration-related increases in revertants were observed in strain TA100 in both the presence and absence of S9 at concentrations of 30 mcg-5000 mcg. At the highest concentration tested, 2.1- and 1.6-fold increases were seen in the absence and presence of S9, respectively. In the preliminary assay (1 plate) similar trends in dose-related increases and at the highest concentration tested, 2.2- and 2.4-fold increases were seen in the absence and presence of S9, respectively. No confirmatory assay was conducted. The vehicle historical control values for the TA100 strain in the absence and presence of S9 are 98 +/- 18 (50-251) and 110 +/- 23 (55-247), respectively [mean +/- SD (range)]. All of the increases in revertants were well within this range. Although the increases in revertants at the highest concentrations evaluated were still within the historical range of the vehicle, the more relevant comparison is considered the concurrent controls. The dose-related increases above

concurrent controls were reproducible and the data were fairly tight. Treatment of strain TA100 with [REDACTED] ^{(b) (4)} in the absence and presence of S9 is concluded to be positive and equivocal for mutagenicity, respectively.

Table 31.

^{(b) (4)} Ames Assay Results Without S9 Activation^{(b) (4)}

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Table 34. (b) (4) Preliminary Toxicity Ames Assay Results With S9 Activation for Strain TA100



Study title: (b) (4) **Bacterial Reverse Mutation Assay (Second Assay)**

Study no.: AE03MX, AE10GV.502ICHR.BTL (DS-2014-098)

EDR 4.2.3.3.1

Conducting laboratory and location:

(b) (4)

Date of study initiation:

November 17, 2014

GLP compliance:

Yes

QA statement:

Yes

Drug, lot #, and % purity:

(b) (4) 91.4% and (b) (4)
(b) (4) 69.8% (b) (4)

Key Study Findings

- It is concluded that under the conditions of the assay conducted, (b) (4) (Lot (b) (4)) with a purity of 69.8% is positive for mutagenicity in *S. typhimurium* strain TA100 in the absence and presence of S9. It is negative for mutagenicity in strain TA98 in both the presence and absence of S9.
- It is concluded that under the conditions of the assay conducted, (b) (4) (Lot (b) (4)) with a purity of 91.4% is negative for mutagenicity in *S. typhimurium* strains TA98, TA100,

TA1535, and TA1537 and *E. coli* strain WP2uvrA in the absence and presence of S9.

Reviewer's note:

Methods

Strains: **Assay 1** (Study AE03MX): Lot [REDACTED] (b) (4)
 [REDACTED] *Salmonella typhimurium*:
Salmonella typhimurium: TA98 and
 TA100

Assay 2 (Study AE10GV.502ICHR.BTL) :
 Lot # [REDACTED] (b) (4) TA98, TA100,
 TA1535, TA1537 and *Escherichia coli*: WP2 uvrA

Concentrations in definitive study: 150, 500, 1500, 3000, 4000, and 5000 mcg
 +/- S9

Basis of concentration selection: Initial study used 6.7 – 5000 mcg

Negative control: DMSO

Positive control: See table below

Formulation/Vehicle: DMSO

Incubation & sampling time: 48-72 h at 37°C

Table 35. Ames assay: Positive Controls

Strain	S9 Activation	Positive Control	Concentration (µg/plate)
TA98, TA1535	Rat	2-aminoanthracene (b) (4)	1.0
TA100, TA1537		Lot No. STBB1901V Exp. Date 31-Oct-2014 CAS No. 613-13-8 Purity 97.5%	2.0
WP2 uvrA		2-nitrofluorene (b) (4) Lot No. S43858V Exp. Date 31-Mar-2016 CAS No. 607-57-8 Purity 99.4%	15
TA98	None	sodium azide (b) (4) Lot No. MKBH1113V Exp. Date 30-Jun-2016 CAS No. 26628-22-8 Purity 99.6%	1.0
TA100, TA1535		9-aminoacridine (b) (4) LOT NO. 09820CEV Exp. Date 31-Mar-2016 CAS No. 52417-22-8 Purity 99.4%	75
TA1537		methyl methanesulfonate (b) (4) Lot No. MKBG0368V Exp. Date 31-Oct-2014 CAS No. 66-27-3 Purity 99.9%	1,000
WP2 uvrA			

Study Validity

The study is valid. All strains were shown to contain the appropriate genetic markers. Suitable numbers of replicate plates and appropriate counting methods were utilized. The positive controls demonstrated clear increases in tester strain revertants while the vehicle control was within historical range for the tester strains for this vehicle.

Results

Assay 1: Lot [REDACTED] (b) (4) (b) (4)

It is concluded that under conditions of the assay conducted, [REDACTED] (b) (4) (Lot [REDACTED] (b) (4) (b) (4)) is positive in *S. typhimurium* strain TA100 in the absence and presence of S9. It is negative in strain TA98 in both the presence and absence of S9.

The data from Assay 1 with the strains TA98 and TA100 are presented in the summary tables below. As outlined in the study protocol, to be considered a positive response, a culture must demonstrate a dose-related increase in mean revertants that is greater than or equal to 2.0-times the mean vehicle control (for the TA98 and TA100 strains). Biologically relevant increase in revertant count that partially meets the criteria for a positive response would be considered an equivocal response. This could include a dose-responsive increase that does not meet the 2-fold threshold or a non dose-responsive increase that is equal to or greater than the 2-fold threshold. If a response is judged as neither positive nor equivocal, it is considered negative.

No precipitate or cytotoxicity was observed in any condition. [REDACTED] (b) (4) (Lot [REDACTED] (b) (4) (b) (4)) was tested up to the limit dose of 5000 mcg. No clear dose-related increases or increases in mutant counts equal to or greater than 2-fold the vehicle were observed in either the presence or absence of S9. Treatment of strain TA98 in the absence and presence of S9 with [REDACTED] (b) (4) (Lot [REDACTED] (b) (4) (b) (4)) is concluded to be negative for mutagenicity in this assay.

Concentration-related increases in revertants were observed in strain TA100 in both the absence and presence of S9 at concentrations of 150 mcg-5000 mcg. In the absence of S9, the three highest concentrations tested (3000, 4000, and 5000 mcg) showed 2.0, 2.6- and 2.8-fold increases, respectively. In the presence of S9, the two highest concentrations tested (4000, and 5000 mcg) showed 2.1, and 2.2-fold increases, respectively. Treatment of strain TA100 with [REDACTED] (b) (4) (Lot [REDACTED] (b) (4) (b) (4)) in the absence and presence of S9 is concluded to be positive for mutagenicity.

Assay 2: Lot [REDACTED] (b) (4)

It is concluded that under conditions of the assay conducted, [REDACTED] (b) (4) (Lot [REDACTED] (b) (4)) is negative in all strains tested.

No precipitate or cytotoxicity was observed in any condition. [REDACTED] (b) (4) (Lot [REDACTED] (b) (4)) was tested up to the limit dose of 5000 mcg. The data from Assay 2 are presented in the summary tables below. No clear dose-related increases or increases in mutant counts equal to or greater than 2-fold (for strains TA98, TA100 and WP2 *uvrA*) or 3-fold (for strains TA1535 and TA 1537) the vehicle were observed in either the presence or absence of S9. In *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2_{uvrA} in the absence and presence of S9, [REDACTED] (b) (4) (Lot [REDACTED] (b) (4)) is concluded to be negative for mutagenicity in this assay.



(b) (4)

7.2 *In Vitro Assays in Mammalian Cells*

Study title: Hydrocodone Bitartrate In Vitro Mammalian Chromosome Aberration in Human Peripheral blood Lymphocytes

Study no.: DS-2001-032
Study report location: EDR 4.2.3.3.1
Conducting laboratory and location: [REDACTED] (b) (4)
Date of study initiation: December 13, 2011
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: Hydrocodone bitartrate, Lot E15660,
99.6%

Key Findings

- It is concluded that hydrocodone bitartrate is clastogenic in the in vitro chromosomal aberration assay in HPBLs in the absence of metabolic activation with a 21 h incubation. Hydrocodone bitartrate did not produce structural aberrations in the presence or absence of metabolic activation with 4 h incubation and did not produce numerical aberrations in either the presence or absence of metabolic activation.

Methods

Cell line: Human peripheral blood lymphocytes
Concentrations in definitive study: 1236.4, 2473.5, 4945 mcg/L
Basis of concentration selection: A preliminary toxicity test using concentrations 9.7-4945 mcg/mL was conducted.
Negative control: Sterile water for injection
Positive control: -S9: Mitomycin C; +S9: Cyclophosphamide
Formulation/Vehicle: Sterile water for injection
Incubation & sampling time: 4 h +/- S9, 21 h -S9

Study Validity

The study appears to be valid for the following reasons: 1) The appropriate positive controls were employed according to FDA/CFSAN Redbook guidelines and produced expected results. 2) The appropriate number of cells was evaluated and two replicates of each test concentrations were tested which is in accordance with the current practice. 3) Metaphase cells with 46 centromeres were examined under oil immersion. Whenever possible, a minimum of 200 metaphase spreads (100 per duplicate treatment condition) were examined and scored for chromatid-type and chromosome-type aberrations. The counting method was in compliance with the currently accepted procedure and therefore considered valid. 4) According to the protocol a test article was considered to induce a positive response when the percentage of cells with aberrations (minus gaps) was increased in a concentration-responsive manner with one or more concentrations being statistically elevated relative to the solvent control group. A reproducibly statistically significant increase at the high concentration only or one other concentration only with no concentration-response was considered positive. The criteria for the evaluation of the positive results were considered valid. 5) The conditions of the assays were appropriate given the use of the limit dose for 4 h incubations and toxicity measured in the 21 h incubation (FDA/CFSAN Redbook guidelines). The dose selection based upon mitotic index was acceptable.

Results

Significant increases in structural aberrations were observed with hydrocodone under non-activated conditions at the 21 h time point. No increases in structural aberrations were observed at the 4 h time point in either the absence or presence of S9. For the 20 h incubation, increases in structural aberrations were observed with hydrocodone at the highest concentrations (Veh= 0.0%, 4955 mcg/mL= 12.0%). This is the same magnitude as the positive control (MMC 0.05 mcg/mL= 12%). Additionally, a large increase in the incidental finding of "chromatid break, exchange or gap" was observed at the 21 h (Veh= 0, 4955 mcg/mL= 55). The concentration of 4955 mcg/mL HC inhibited mitosis by 51% relative to controls but is still considered an acceptable level of cytotoxicity for cytogenetic analysis. The positive controls yielded appropriate increases in structural aberrations under both activated and non-activated conditions. It is

concluded that hydrocodone produces structural aberrations in the in vitro chromosomal aberration assay in HPBLs in the absence of metabolic activation at 21 h.

Table 40. Summary of Cytogenetic Analysis Results with Hydrocodone Bitartrate

Treatment	Conc. (μ g/mL)	MI (%)	RMI (%)	No. Cells Examined	% Aberrant	No. of Aberrations				Incidental Observations \dagger			
						b	e	B	E other	(g	G	P	C)
<i>4 hours treatment in the absence of S9 (-S9)</i>													
Water	-	8.7	100	200	1.5	1	2	1	0	0	8	0	0
Test Item	1236.4	5.1	58	200	0.5	1	0	0	0	0	4	0	0
	2472.5	5.3	61	200	2.0	4	0	0	0	0	3	0	0
	4945	5.1	59	200	0.5	1	0	0	0	0	2	0	1
MMC	0.10	5.6	64	200	11.5**	15	3	5	0	0	17	2	0
<i>4 hours treatment in the presence of S9 (+S9)</i>													
Water	-	7.6	100	200	1.0	1	0	0	1	0	1	0	1
Test Item	1236.4	7.5	99	200	0.5	1	0	0	0	0	5	0	0
	2472.5	5.6	74	200	2.0	3	0	0	0	1	6	0	0
	4945	5.4	71	200	0.5	1	0	0	0	0	4	0	0
CP	6.0	4.5	59	200	18.5**	29	15	4	0	0	25	2	0
<i>21 hours treatment in the absence of S9 (-S9)</i>													
Water	-	5.1	100	200	0.0	0	0	0	0	0	2	0	2
Test Item	618.6	3.9	77	200	0.5	0	0	1	0	0	7	0	0
	1236.4	2.7	53	200	0.0	0	0	0	0	0	8	1	0
	2472.5	2.5	49	200	12.0**	(23	0	9	0	0	55	0	1
MMC	0.05	3.9	77	200	12.0**	13	8	5	0	0	13	0	0

MI, RMI Mitotic Index, Relative Mitotic Index (vehicle = 100%)

b, e, g Chromatid break, exchange, gap

B, E, G Chromosome break, exchange, gap

other Includes pulverized chromosomes and cells with > 8 aberrations

P Polyploidy and endoreduplication

C Centromeric disruption

\dagger g, G, P and C are excluded from the calculation of % aberrant cells

a statistically significant but not dose dependant and observed at a toxic dose level

Results of statistical analysis using one-tailed Fisher's exact test

* $p \leq 0.01$ (significant)

** $p \leq 0.001$ (highly significant)

Otherwise, $p > 0.01$ (not significant)

Study title: (b) (4) **In Vitro Mammalian Chromosome Aberration in Human Peripheral blood Lymphocytes**

Study no.: AE03NA.341ICH.BTL (DS-2014-079)
Study report location: EDR 4.2.3.3.1
Conducting laboratory and location: (b) (4)
Date of study initiation: September 5, 2014
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: (b) (4) Lot DRM-3337-
185-P1, 88.4%

Key Findings

- Under the conditions of the assay, (b) (4) is concluded to be negative for clastogenicity in the *in vitro* chromosomal aberration assay with human peripheral blood lymphocytes.

Methods

Cell line: Human peripheral blood lymphocytes
Concentrations in definitive study: 50, 100, 200, and 316 mcg/L
Basis of concentration selection: A preliminary toxicity test using concentrations 0.0316-316 mcg/mL was conducted.
Negative control: DMSO
Positive control: -S9: Mitomycin C; +S9: Cyclophosphamide
Formulation/Vehicle: DMSO
Incubation & sampling time: 4 h +/- S9, 20 h -S9

Study Validity

The study appears to be valid for the following reasons: 1) The appropriate positive controls were employed according to FDA/CFSAN Redbook guidelines and produced expected results. 2) The appropriate number of cells was evaluated and two replicates of each test concentrations were tested which is in accordance with the current practice. 3) Metaphase cells with 46 centromeres were examined under oil immersion.

Whenever possible, a minimum of 200 metaphase spreads (100 per duplicate treatment condition) were examined and scored for chromatid-type and chromosome-type aberrations. The counting method was in compliance with the currently accepted procedure and therefore considered valid. 4) According to the protocol a test article was considered to induce a positive response when the percentage of cells with aberrations (minus gaps) was increased in a concentration-responsive manner with one or more concentrations being statistically elevated relative to the solvent control group. A reproducibly statistically significant increase at the high concentration only or one other concentration only with no concentration-response was considered positive. The

criteria for the evaluation of the positive results were considered valid. 5) The conditions of the assays were appropriate given the use of the limit dose for 4 h incubations and toxicity measured in the 20 h incubation (FDA/CFSAN Redbook guidelines). The dose selection based upon mitotic index was acceptable.

Results

No treatment-related increases in structural or numerical aberrations were seen. The results are summarized in the table below. Under the conditions of the assay, (b) (4) is negative for clastogenicity in the *in vitro* chromosomal aberration assay with human peripheral blood lymphocytes.

Table 41. Summary of Cytogenetic Analysis Results with (b) (4)

(b) (4)
(b) (4)

Study title: (b) (4) **In Vitro Mammalian Chromosome Aberration in Human Peripheral blood Lymphocytes**

Study no.: AE03MY.341ICH.BTL (DS-2014-077)
Study report location: EDR 4.2.3.3.1
Conducting laboratory and location: (b) (4)
Date of study initiation: September 5, 2014
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: (b) (4) Lot
DRM3424-062-P2, 93.1%

Key Findings

- Under the conditions of the assay, (b) (4) is concluded to be negative for clastogenicity in the *in vitro* chromosomal aberration assay with human peripheral blood lymphocytes in both the presence and absence of S9.

Methods

Cell line: Human peripheral blood lymphocytes
Concentrations in definitive study: -S9 4 h: 20, 60, and 100 mcg/L; +S9 4 h: 100, 300, and 450 mcg/mL; -S9 20h: 10, 20, and 40 mcg/mL
Basis of concentration selection: A preliminary toxicity test using concentrations 0.05-500 mcg/mL was conducted.
Negative control: DMSO
Positive control: -S9: Mitomycin C; +S9: Cyclophosphamide
Formulation/Vehicle: DMSO
Incubation & sampling time: 4 h +/- S9, 20 h -S9

Study Validity

The study appears to be valid for the following reasons: 1) The appropriate positive controls were employed according to FDA/CFSAN Redbook guidelines and produced expected results. 2) The appropriate number of cells was evaluated and two replicates of each test concentrations were tested which is in accordance with the current practice. 3) Metaphase cells with 46 centromeres were examined under oil immersion.

Whenever possible, a minimum of 200 metaphase spreads (100 per duplicate treatment condition) were examined and scored for chromatid-type and chromosome-type aberrations. The counting method was in compliance with the currently accepted procedure and therefore considered valid. 4) According to the protocol a test article was considered to induce a positive response when the percentage of cells with aberrations (minus gaps) was increased in a concentration-responsive manner with one or more concentrations being statistically elevated relative to the solvent control group.

A reproducibly statistically significant increase at the high concentration only or one other concentration only with no concentration-response was considered positive. The criteria for the evaluation of the positive results were considered valid. 5) The conditions of the assays were appropriate given the use of the limit dose for 4 h incubations and toxicity measured in the 20 h incubation (FDA/CFSAN Redbook guidelines). The dose selection based upon mitotic index was acceptable.

Results

Significant cytotoxicity was observed. Mitotic inhibition at the highest dose selected for each condition ranged between 46-48%, relative to control. No changes in pH or osmolality were observed in the study. No treatment-related increases in structural or numerical aberrations were seen. The results are summarized in the table below. Under the conditions of the assay, [REDACTED] (b) (4) is negative for clastogenicity in the *in vitro* chromosomal aberration assay with human peripheral blood lymphocytes.

Table 42. Summary of Cytogenetic Analysis Results with [REDACTED]

(b) (4)

[REDACTED]
(b) (4)

Study title: (b) (4) **In Vitro Mammalian Chromosome Aberration in Human Peripheral blood Lymphocytes**

Study no.:	AE03MZ.341ICH.BTL (DS-2014-078)
Study report location:	EDR 4.2.3.3.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 5, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	(b) (4) Lot YW3712-284-column 3-2, 87.2%

Key Findings

- Under the conditions of the assay, (b) (4) is concluded to be negative for clastogenicity in the *in vitro* chromosomal aberration assay with human peripheral blood lymphocytes in both the presence and absence of S9.

Methods

Cell line:	Human peripheral blood lymphocytes
Concentrations in definitive study:	-S9 4 h: 100, 200, and 250 mcg/L; +S9 4 h: 100, 200, and 250 mcg/L; -S9 20h: 30, 50, and 80 mcg/L
Basis of concentration selection:	A preliminary toxicity test using concentrations 0.038-380 mcg/mL was conducted.
Negative control:	DMSO
Positive control:	-S9: Mitomycin C; +S9: Cyclophosphamide
Formulation/Vehicle:	DMSO
Incubation & sampling time:	4 h +/- S9, 20 h -S9

Study Validity

The study appears to be valid for the following reasons: 1) The appropriate positive controls were employed according to FDA/CFSAN Redbook guidelines and produced expected results. 2) The appropriate number of cells was evaluated and two replicates of each test concentrations were tested which is in accordance with the current practice. 3) Metaphase cells with 46 centromeres were examined under oil immersion. Whenever possible, a minimum of 200 metaphase spreads (100 per duplicate treatment condition) were examined and scored for chromatid-type and chromosome-type aberrations. The counting method was in compliance with the currently accepted procedure and therefore considered valid. 4) According to the protocol a test article was considered to induce a positive response when the percentage of cells with aberrations (minus gaps) was increased in a concentration-responsive manner with one or more concentrations being statistically elevated relative to the solvent control group.

A reproducibly statistically significant increase at the high concentration only or one other concentration only with no concentration-response was considered positive. The criteria for the evaluation of the positive results were considered valid. 5) The conditions of the assays were appropriate given the use of the limit dose for 4 h incubations and toxicity measured in the 20 h incubation (FDA/CFSAN Redbook guidelines). The dose selection based upon mitotic index was acceptable.

Results

No treatment-related increases in structural or numerical aberrations were observed in either the presence or absence of S9. The results are summarized in the table below. Under the conditions of the assay, [REDACTED] ^{(b) (4)} is negative for clastogenicity in the *in vitro* chromosomal aberration assay with human peripheral blood lymphocytes.

Table 43. Summary of Cytogenetic Analysis Results with [REDACTED]

(b) (4)

(b) (4)

Study title: (b) (4) **In Vitro Mammalian Chromosome Aberration in Human Peripheral blood Lymphocytes**

Study no.: AE03MX.341ICH.BTL (DS-2014-076)
Study report location: EDR 4.2.3.3.1
Conducting laboratory and location: (b) (4)
Date of study initiation: September 5, 2014
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: (b) (4) Lot (b) (4) (b) (4) 69.8%

Key Findings

- It is concluded that under conditions of the assay conducted, both lots of (b) (4) (Lot (b) (4) (b) (4)) produced structural aberrations in the in vitro chromosomal aberration assay in HPBLs in the presence and absence of metabolic activation for 4h and in the absence of metabolic activation with 20 h incubation.

Methods

Cell line: Human peripheral blood lymphocytes
Concentrations in definitive study: -S9 4 h: 100, 200, and 250 mcg/L; +S9 4 h: 100, 200, and 250 mcg/L; -S9 20h: 30, 50, and 80 mcg/L
Basis of concentration selection: A preliminary toxicity test using concentrations 0.05-500 mcg/mL was conducted.
Negative control: DMSO
Positive control: -S9: Mitomycin C; +S9: Cyclophosphamide
Formulation/Vehicle: DMSO
Incubation & sampling time: 4 h +/- S9, 20 h -S9

Study Validity

The study appears to be valid for the following reasons: 1) The appropriate positive controls were employed according to FDA/CFSAN Redbook guidelines and produced expected results. 2) The appropriate number of cells was evaluated and two replicates of each test concentrations were tested which is in accordance with the current practice. 3) Metaphase cells with 46 centromeres were examined under oil immersion. Whenever possible, a minimum of 200 metaphase spreads (100 per duplicate treatment condition) were examined and scored for chromatid-type and chromosome-type aberrations. The counting method was in compliance with the currently accepted procedure and therefore considered valid. 4) According to the protocol a test article was considered to induce a positive response when the percentage of cells with

aberrations (minus gaps) was increased in a concentration-responsive manner with one or more concentrations being statistically elevated relative to the solvent control group. A reproducibly statistically significant increase at the high concentration only or one other concentration only with no concentration-response was considered positive. The criteria for the evaluation of the positive results were considered valid. 5) The conditions of the assays were appropriate given the use of the limit dose for 4 h incubations and toxicity measured in the 20 h incubation (FDA/CFSAN Redbook guidelines). The dose selection based upon mitotic index was acceptable.

Results

Significant increases in structural aberrations were observed with [REDACTED] (b) (4)
[REDACTED] (b) (4) Lot [REDACTED] (b) (4) (b) (4) at the highest dose tested under both S9-activated and non-activated conditions with 4 h incubation time points. Additionally, a significant increase in structural aberrations was observed at the 20 h time point in the absence of S9. The data are presented in the tables below. It is concluded that under conditions of the assay conducted, [REDACTED] (b) (4) Lot [REDACTED] (b) (4) (b) (4) produces structural aberrations in the in vitro chromosomal aberration assay in HPBLLs in the presence and absence of metabolic activation with a 4h incubation and absence of metabolic activation with a 20 h incubation.

Table 44. Summary of Cytogenetic Analysis Results with [REDACTED] (b) (4)
[REDACTED]

Parameter	Value
Test Item	[REDACTED] (b) (4)
Concentration	[REDACTED] (b) (4)
Incubation Time	[REDACTED] (b) (4)
Activation	[REDACTED] (b) (4)
Aberration Type	[REDACTED] (b) (4)
Number of Cells	[REDACTED] (b) (4)
Percent Aberrant	[REDACTED] (b) (4)
Significance	[REDACTED] (b) (4)



Study title: (b) (4) (Lots (b) (4) (b) (4) and
In Vitro Mammalian Chromosome Aberration in Human
Peripheral blood Lymphocytes

Study no.: AE03MX, AE10GV.341ICHR.BTL (DS-
2014-099)

Study report location:
EDR 4.2.3.3.1

Conducting laboratory and location:
(b) (4)

Date of study initiation:
November 18, 2015

GLP compliance:
Yes

QA statement:
Yes

Drug, lot #, and % purity:
(b) (4)
69.8% and (b) (4)
91.4%

Key Findings

- It is concluded that under conditions of the assay conducted, both lots of (b) (4) (Lots (b) (4) (b) (4) (b) (4) and (b) (4) produced structural aberrations in the in vitro chromosomal aberration assay in HPBLs in the presence and absence of metabolic activation for 4h.

Reviewer's note:

This assay re-tests the relatively low purity (b) (4) (Lot (b) (4) (b) (4) 69.8%) which yielded positive results in an in vitro chromosomal assay. This assay also tests a more purified batch of (b) (4) (Lot (b) (4) 91.4%). Refer to review of Study DS-2014-076 above for details on the low purity batch results.

Methods

Cell line: Human peripheral blood lymphocytes
Concentrations in definitive study: +/- S9 4 h: 100, 200, and 500 mcg/L; -S9 20h: 25, 50, and 100 mcg/L
Basis of concentration selection: A preliminary toxicity test using concentrations 50-500 mcg/mL was conducted.
Negative control: DMSO
Positive control: -S9: Mitomycin C; +S9: Cyclophosphamide
Formulation/Vehicle: DMSO
Incubation & sampling time: 4 h +/- S9, 20 h -S9

Study Validity

The study appears to be valid for the following reasons: 1) The appropriate positive controls were employed according to FDA/CFSAN Redbook guidelines and produced expected results. 2) The appropriate number of cells was evaluated and two replicates of each test concentrations were tested which is in accordance with the current practice. 3) Metaphase cells with 46 centromeres were examined under oil immersion.

Whenever possible, a minimum of 200 metaphase spreads (100 per duplicate treatment condition) were examined and scored for chromatid-type and chromosome-type aberrations. The counting method was in compliance with the currently accepted procedure and therefore considered valid. 4) According to the protocol a test article was considered to induce a positive response when the percentage of cells with aberrations (minus gaps) was increased in a concentration-responsive manner with one or more concentrations being statistically elevated relative to the solvent control group. A reproducibly statistically significant increase at the high concentration only or one other concentration only with no concentration-response was considered positive. The criteria for the evaluation of the positive results were considered valid. 5) The conditions of the assays were appropriate given the use of the limit dose for 4 h incubations and toxicity measured in the 20 h incubation (FDA/CFSAN Redbook guidelines). The dose selection based upon mitotic index was acceptable.

Results

Lot [REDACTED] (b) (4) (b) (4)

Significant increases in structural aberrations were observed with [REDACTED] (b) (4) Lot [REDACTED] (b) (4) (b) (4) under both S9-activated and non-activated conditions with 4 h incubation time points. No increases in structural aberrations were observed at the 20 h time point in the absence of S9. The data are presented in the tables below. It is concluded that under conditions of the assay conducted,

[REDACTED] (b) (4) Lot [REDACTED] (b) (4) (b) (4) produces structural aberrations in the in vitro chromosomal aberration assay in HPBLs in the presence and absence of metabolic activation for 4h. This study partially replicates the findings for the same lot of test article in which increases of structural aberrations were observed in the presence and absence of metabolic activation for 4h and in the absence of metabolic activation with 20 h incubation (see review of Study DS-2014-076).

Lot (b) (4)

Significant increases in structural aberrations were observed with (b) (4) (b) (4) under both S9-activated and non-activated conditions (b) (4) Lot (b) (4) with 4 h incubation time points. No increases in structural aberrations were observed at the 20 h time point in the absence of S9. The data are presented in the tables below. It is concluded that under conditions of the assay conducted, (b) (4) (b) (4) Lot (b) (4) produces structural aberrations in the in vitro chromosomal aberration assay in HPBLs in the presence and absence of metabolic activation for 4h.

Table 45. Summary of Cytogenetic Analysis Results with (b) (4)

Lot (b) (4) (b) (4)

(b) (4)

(b) (4)

Table 46. Summary of Cytogenetic Analysis Results with (b) (4)

(b) (4)
Lot

(b) (4)



7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: Hydrocodone Mammalian Erythrocyte Micronucleus Test in Rat Bone Marrow

Study no: 980050 (DS-2011-033)

Study report location: EDR 4.2.3.3.2

Conducting laboratory and location:

(b) (4)

Date of study initiation: December 13, 2011

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: Hydrocodone bitartrate, Lot E15660,
99.6%

Key Study Findings

- Hydrocodone bitartrate was found to be negative in the in vivo micronucleus assay in rat bone marrow.

Methods

Doses in definitive study: 10, 33, and 100 mg/kg
Frequency of dosing: Two doses 24 h apart
Route of administration: Oral gavage
Dose volume: 10 mL/kg
Formulation/Vehicle: Water
Species/Strain: Rat, Sprague Dawley
Number/Sex/Group: Main study: Vehicle, low and mid dose: 5 M/group, high dose: 5 M and 5 F, positive control 3 M
Satellite groups: TK: 3 M/group, high dose: 3 M and 3 F
Basis of dose selection: MTD from 90-day toxicity study
Negative control: Water
Positive control: Cyclophosphamide

Study Validity

The study was deemed valid for the following reasons:

- Previous pharmacokinetic assessments demonstrated systemic exposure.
- Dosing appeared to be adequate based upon the results of the dose-ranging study.
- Preparation and administration of the test substance was acceptable.
- The species and number of animals/sex/group were acceptable.
- Tissue sampling and analysis was acceptable.
- Positive controls exhibited appropriate responses.

Results

At all three doses, sedation was observed in males. Activity was increased at the mid and high dose in males. In females at the high dose, increases in activity as well as sedation were observed. Rats treated with hydrocodone bitartrate showed a proportion of immature erythrocytes that was similar to controls in both males and females indicating the lack of bone marrow toxicity. Group mean incidences of micronucleated immature and mature erythrocytes were similar to controls. Micronucleus data are summarized in the table below. Based on the results of this study, hydrocodone bitartrate did not induce an increase in micronucleated erythrocytes in the bone marrow in either males or females. Hydrocodone bitartrate can be considered negative the in vivo micronucleus assay in rat bone marrow.

Table 47. Summary of Results in Micronucleus Assay with Hydrocodone Bitartrate

Sampling Time - 24 Hours

Group 1 - Vehicle control
 Group 2 - Hydrocodone 10 mg/kg/day^a
 Group 3 - Hydrocodone 33 mg/kg/day^a
 Group 4 - Hydrocodone 100 mg/kg/day^a
 Group 5 - Cyclophosphamide 20 mg/kg^b

Group	% IE/(IE+ME) Males	% IE/(IE+ME) Females	% IE/(IE+ME) Males & Females	Incidence MIE Males	Incidence MIE Females	Incidence MIE Males & Females	Incidence MME Males	Incidence MME Females	Incidence MME Males & Females
1	36.4	N/a	N/a	1.2	N/a	N/a	0.0	N/a	N/a
2	40.1	N/a	N/a	2.0	N/a	N/a	0.0	N/a	N/a
3	36.9	N/a	N/a	3.2	N/a	N/a	0.0	N/a	N/a
4	37.2	36.8	37.0	1.4	1.6	1.5	0.0	0.0	0.0
5	39.3	N/a	N/a	44.3	N/a	N/a	0.0	N/a	N/a

%IE/(IE+ME) Proportion of immature erythrocytes

MIE Number of micronucleated cells observed per 2000 immature erythrocytes examined.

MME Number of micronucleated mature erythrocytes observed (mean value expressed per 2000 mature erythrocytes examined, see results for individual animals in appendices for actual numbers of cells examined).

a Two doses were administered 24 hours apart

b Positive control dosed once only, by oral gavage, 24 hours prior to sampling

N/a Not applicable

7.3 In Vivo Clastogenicity Assay in Rodent (Combined Micronucleus/Comet Assay)

Study title: (b) (4) (Lot (b) (4)) : In Vivo Mammalian Erythrocyte Micronucleus Assay and Mammalian Alkaline Comet Assay in Rats

Study no: AE10GV.433.BTL (DS-2015-002)

Study report location: EDR 4.2.3.3.2

Conducting laboratory and location:

(b) (4)

Date of study initiation:

February 12, 2015

GLP compliance:

Yes

QA statement:

Yes (August 28, 2015)

Drug, lot #, and % purity:

(b) (4)

Lot

(b) (4)

98.0%

Key Study Findings

- (b) (4) was found to be negative in the in vivo micronucleus assay using bone marrow.
- (b) (4) was found to be negative in the in vivo comet assay in liver.
- The results of the comet assay in duodenum showed excessive variability and the study was considered suboptimal. The comet assay in duodenum will not be used to support a regulatory decision.

Methods

Doses in definitive study: See table below
 Frequency of dosing: Daily for three days
 Route of administration: Oral gavage
 Dose volume: 10 mL/kg
 Formulation/Vehicle: water
 Species/Strain: Rat, Hsd:SD
 Number/Sex/Group: Main study: 6/sex/group, positive control:
 3/sex/group
 Satellite groups: None
 Basis of dose selection: Dose range-finding study
 Negative control: water
 Positive control: Ethyl methanesulfonate

Table 48. Study Design for the Comet/MN Assay with

(b) (4)

Group	Treatment	Dose Level (mg/kg/day)	Dose Volume (mL/kg/day)	Dose Route	Rats/ Sex	Euthanasia Time (Hrs after Treatment)
1	Vehicle	0	10	Oral Gavage	6	3-4
2	(b) (4)	10	10	Oral Gavage	6	3-4
3		30	10	Oral Gavage	6	3-4
4		100	10	Oral Gavage	6	3-4
5		300	10	Oral Gavage	6	3-4
6		1000	10	Oral Gavage	6	3-4
7	EMS	200 mg/kg	10 mL/kg	Oral Gavage	3	3-4

Study Validity

The micronucleus assay was deemed valid for the following reasons: 1) previous pharmacokinetic assessments demonstrated systemic exposure, 2) dosing appeared to be adequate based upon the results of the dose-ranging study, 3) preparation and administration of the test substance was acceptable, 4) the species and number of animals/sex/group were acceptable, 5) tissue sampling and analysis was acceptable, 6) positive controls exhibited appropriate responses, and 7) the proportion of immature erythrocytes among total erythrocytes was not less than 20% of the control value.

The comet assay in liver was deemed valid based on the OECD test guideline. The comet assay in duodenum is not considered valid because of the high degree of variability in % tail DNA for individual animals within a treatment group and excessive cytotoxicity in the sample. The overlap between the negative and positive historical control data also indicate substantial variability with the duodenum.

Results

Clinical signs

Mortality occurred in one male at the high dose (1000 mg/kg). All treated rats exhibited hyperactivity immediately after dosing. Piloerection, lethargy and prostration were observed in males at the high dose and piloerection and lethargy were observed in female rats at the high dose.

Micronucleus Assay

Mice treated with [REDACTED] ^{(b) (4)} showed a group mean %PCE that was similar to controls indicating the lack of bone marrow toxicity. Group mean frequencies of MN PCE were similar to controls and within historical control ranges for the vehicle. Micronucleus data are summarized in the table below.

Table 49. Summary of Results for Bone Marrow Micronucleus Assay with (b) (4)

						(b) (4)

Table 50. Historical Control Data for the Vehicle in the Micronucleus Assay

Negative Control¹

Parameter	%PCE (Individual Animals)		%MnPCE (Individual Animal)		%MnPCE (Studies)	
	Males	Females	Males	Females	Males	Females
Mean ³	52.1	51.8	0.04	0.04	0.04	0.04
Standard Deviation	6.3	6.1	0.05	0.04	0.03	0.02
95% Control Limits	39.5-64.7	39.6-63.9	0.00-0.14	0.00-0.11	0.00-0.11	0.00-0.08
Range ⁴	33.2-66.8	40.8-64.8	0.00-0.25	0.00-0.15	0.00-0.16	0.00-0.08

Comet Assay

Liver:

Small dose-related increases in the percent of clouds were observed in treated groups in the liver, indicating that the drug treatment did not cause excessive DNA damage that could have interfered with the comet analysis. With the exception of the high doses in males and females, % tail DNA values were similar to or less than the control groups. Although increases in the high dose groups for both males and females were statistically significant, no dose response was observed and the values fell within the historical negative control range. The comet assay in liver will be considered to be negative. The PTCC Genetic Toxicology Subcommittee was consulted and are in agreement with the conclusions in this review. Comet assay data are summarized in the tables below.

Duodenum:

The results of the comet assay using duodenum had a high degree of variability. In agreement with the analysis of the PTCC Genetic Toxicology Subcommittee, the study is suboptimal. The data will not be used to make a regulatory decision. The data are presented in the tables below.

Conclusions

(b) (4) is considered negative in the comet assay in liver of male mice following oral gavage administration at doses of 10, 30, 100, 300, and 1000 mg/kg/day. At these same doses, (b) (4) did not induce any increase in micronucleated polychromatic erythrocytes in the bone marrow. The results from the comet assay in duodenum showed excessive variability and the study is considered suboptimal. However, as summarized by the PTCC Genetic Toxicology Subcommittee (consult dated September 4, 2015) the assay in the duodenum is not needed to conclude the absence of genotoxic potential:

The negative micronucleus result addresses the possibility of a direct effect and the negative liver Comet result addresses potential of an effect dependent on metabolism. It is not clear that data for the duodenum is even needed. The weight of evidence indicates the impurity does not pose substantial clinical risk.

(b) (4) can be considered negative in the comet assay (in liver) and the in vivo micronucleus assay (in bone marrow).

Table 51. Summary of Results for the Comet Assay in Liver Cells from Males with
(b) (4)

Treatment (10 mL/kg/treatment)	Number of Animals	Group Mean % of Clouds	Tail DNA (%) ^A	
			Mean	± S.D.
Vehicle Control:				
Deionized water and 1N HCl (for adjusting pH to 2.1 ± 0.1)	6	0.0	0.021	± 0.018

(b) (4)

Table 52. Summary of Results for the Comet Assay in Liver Cells from Females with
(b) (4)

Treatment (10 mL/kg/treatment)	Number of Animals	Group Mean % of Clouds	Tail DNA (%) ^A	
			Mean	± S.D.
Vehicle Control:				
Deionized water and 1N HCl (for adjusting pH to 2.1 ± 0.1)	6	0.0	0.012	± 0.0027

(b) (4)

Table 53. Historical Control Data in Vehicle and Positive control for Liver Cells in the Comet Assay (Males)

Male Rat Historical Control Data⁵

2011 to 2013

Electrophoresis performed refrigerated (2 to 10°C), protected from light

Organs harvested at ~3 hour post last dose

VEHICLE (NEGATIVE) CONTROL¹

Organ	Parameter	Tail Moment	Tail Migration (μm)	% Tail DNA
		Males	Males	Males
Liver	Mean ³	0.16	20.82	0.69
	Standard Deviation	0.23	8.69	1.02
	Range ⁴	0.01	6.96	0.02
		1.29	53.04	5.84

POSITIVE CONTROL²

Organ	Parameter	Tail Moment	Tail Migration (μm)	% Tail DNA
		Males	Males	Males
Liver	Mean ³	4.45	46.30	21.43
	Standard Deviation	2.56	10.22	10.33
	Range ⁴	0.10	18.55	0.41
		15.56	76.48	56.62

¹Negative control articles: all vehicles used; Route of administration: oral gavage (PO), intraperitoneal (IP), subcutaneous (SC), or intravenous (IV)

²Positive control article: Ethyl methanesulfonate (200 mg/kg);

³Average (mean) of the median Comet Assay parameters measured per animal for the total number of animals used in studies during 2011 to 2013.

⁴Minimum and maximum range of Comet Assay measurements.

⁵Historical range includes data from nonGLP studies.

Table 54. Historical Control Data in Vehicle and Positive control for Liver Cells in the Comet Assay (Females)

**Female Rat Historical Control Data
2008 to 2013**

Electrophoresis performed refrigerated (2 to 10°C), protected from light

Organs harvested at ~3 hour post last dose

VEHICLE (NEGATIVE) CONTROL¹

Organ	Parameter	Tail Moment	Tail Migration (µm)	% Tail DNA
		Females	Females	Females
Liver	Mean ³	0.15	21.62	0.70
	Standard Deviation	0.17	8.74	0.79
	Range ⁴	0.00	1.85	0.02
		0.97	47.29	4.39

POSITIVE CONTROL²

Organ	Parameter	Tail Moment	Tail Migration (µm)	% Tail DNA
		Females	Females	Females
Liver	Mean ³	4.95	49.31	22.95
	Standard Deviation	3.34	11.67	12.22
	Range ⁴	1.24	30.14	6.46
		13.91	84.70	51.24

¹Negative control articles: all vehicles used; Route of administration: oral gavage (PO), intraperitoneal (IP), subcutaneous (SC), or intravenous (IV)

²Positive control article: Ethyl methanesulfonate (200 mg/kg);

³Average (mean) of the median Comet Assay parameters measured per animal for the total number of animals used in studies during 2008 to 2013.

⁴Minimum and maximum range of Comet Assay measurements.

⁵Historical range includes data from nonGLP studies.

Table 55. Summary of Results for the Comet Assay in Duodenal Cells from Males with
(b) (4)

Treatment (10 mL/kg/treatment)	Number of Animals	Group Mean % of Clouds	Tail DNA (%) ^A	
			Mean	± S.D.
Vehicle Control:				
Deionized water and 1N HCl (for adjusting pH to 2.1 ± 0.1)	6	0.3	0.016	± 0.014

(b) (4)

Table 56. Summary of Results for the Comet Assay in Duodenal Cells from Females
(b) (4)

Treatment (10 mL/kg/treatment)	Number of Animals	Group Mean % of Clouds	Tail DNA (%) ^A	
			Mean	± S.D.
Vehicle Control:				
Deionized water and 1N HCl (for adjusting pH to 2.1 ± 0.1)	6	7.0	0.028	± 0.043
(b) (4)				

Table 57. Historical Control Data in Vehicle and Positive control for Duodenal Cells in
the Comet Assay (Females)

Female Rat Historical Control Data⁵**2008 to 2013**

Electrophoresis performed refrigerated (2 to 10°C), protected from light

Organs harvested at ~3 hour post last dose

VEHICLE (NEGATIVE) CONTROL¹

Organ	Parameter	Tail Moment	Tail Migration (μm)	% Tail DNA
		Females	Females	Females
Duodenum	Mean ³	1.21	44.02	5.99
	Standard Deviation	0.78	8.81	4.12
	Range ⁴	0.14	23.65	0.71
		2.89	57.50	15.31

POSITIVE CONTROL²

Organ	Parameter	Tail Moment	Tail Migration (μm)	% Tail DNA
		Females	Females	Females
Duodenum	Mean ³	5.46	60.33	25.48
	Standard Deviation	1.92	12.16	6.50
	Range ⁴	2.80	45.90	15.94
		9.37	84.39	38.03

¹Negative control articles: all vehicles used; Route of administration: oral gavage (PO), intraperitoneal (IP), subcutaneous (SC), or intravenous (IV)

²Positive control article: Ethyl methanesulfonate (200 mg/kg);

³Average (mean) of the median Comet Assay parameters measured per animal for the total number of animals used in studies during 2008 to 2013.

⁴Minimum and maximum range of Comet Assay measurements.

⁵Historical range includes data from nonGLP studies.

7.4 Other Genetic Toxicity Studies

Computational Mutagenicity Report for Impurities in Hydrocodone Bitartrate Extended Release (CEP 33237; Study DS-2014-084)

Computational structure analysis for mutagenicity alerts was performed for four HC degradation products: (b) (4) and (b) (4). As per ICH M7, the

expert rule-based DEREK Nexus (version 4.05) and the statistical-based Sarah Nexus (version 1.1.2) were used. The structures of the compounds are shown in the figures below. All four compounds were predicted to be non-mutagenic by both the Derek and Sarah platforms.

Figure 9. Structure of [REDACTED]

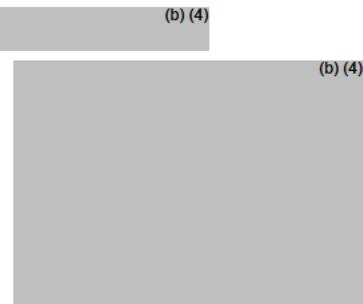


Figure 10. Structure of [REDACTED]

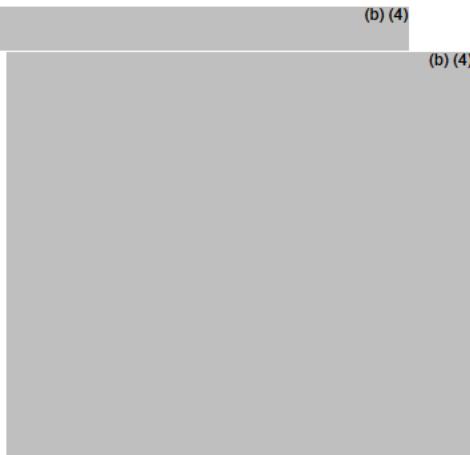


Figure 11. Structure of [REDACTED]

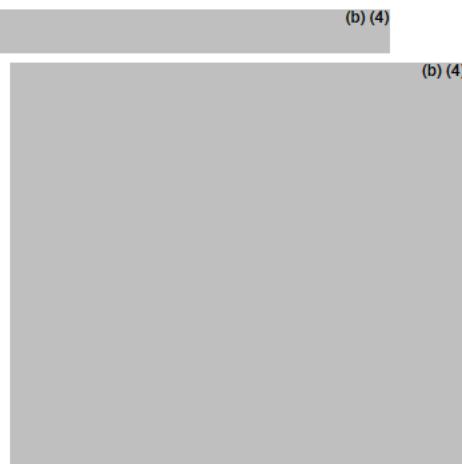


Figure 12. Structure of [REDACTED]



8 Carcinogenicity

Teva has obtained a right of reference for the mouse and rat carcinogenicity studies reviewed below.

8.1 Two-Year Rat Bioassay

Study title: 104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with Hydrocodone Bitartrate in Rats

Study no.:	8237255
Study report location:	EDR 4.2.3.4.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	January 10, 2012
GLP compliance:	Yes
QA statement:	Yes
Drug, lot # (% purity):	Hydrocodone Bitartrate (HC), Lot 1103001006; 99.9%

Key Study Findings

- A statistically significant positive dose-response relationship and a statistically significant pair-wise comparison (HD only) in benign fibromas of the skin were observed in males. Additionally, two malignant fibrosarcomas were observed in the control and the high dose males. When pooled, the dose response was statistically significant but the pairwise comparison was not. Therefore, the lesions are not considered treatment-related.
- This carcinogenicity study in rat is valid and no hydrocodone-related neoplasms were observed in either sex.
- Statistically, survival in both males and females was comparable to controls.
- The NOEL for relevant neoplastic lesions is the high dose in both male (30 mg/kg) and female (100 mg/kg) rats which provide 0.06 and 0.4 fold exposure margins, respectively, as compared to the clinical dose of 180 mg/day.

Adequacy of Carcinogenicity Study

The study was conducted with doses chosen based on a 90-day dose range-finding study in Fisher-344 rats. The SPA was presented to the ECAC and doses for the carcinogenicity study were recommended. This study employed an appropriate rat strain, an adequate number of animals per sex for each dose and concurrent control groups, and the clinically relevant route of administration. Animals were individually housed, provided appropriate food and care, and were administered test article or vehicle control for 104 weeks. The study is considered adequate.

Appropriateness of Test Models

The rat is an appropriate model for a 2-year bioassay and the strain, Fisher-344, is acceptable.

Evaluation of Tumor Findings

No HC-mediated increases in neoplastic lesions were observed in this study. A statistically significant positive dose-response relationship and a statistically significant pair-wise comparison (HD only) in benign fibromas of the skin were observed in males. Additionally, in males two malignant fibrosarcomas were observed in the control and the high dose. When pooled, the dose response was statistically significant but the pairwise comparison was not. Therefore, the lesions are not considered significant. Several treatment-related decreases in tumor incidences were seen. Decreased incidences in tumors in the thyroid (males) and adrenal cortex (females) were observed. The significance of these decreases is unknown. Statistical analysis of the data was conducted by Dr. Feng Zhou of the Division of Biostatistics VI. Tumors were combined for statistical analysis according to McConnell, et al, 1986 (McConnell EE, et al., 1986). No tumor types were considered to have a statistically significant positive dose-response relationship and a statistically significant pair-wise comparison for either males or females.

Methods

Doses:	M: 3, 10, 30 mg/kg; F: 10, 30, 100 mg/kg
Frequency of dosing:	Daily
Dose volume:	10 mL/kg
Route of administration:	Gavage
Formulation/Vehicle:	Distilled water
Basis of dose selection:	The ECAC recommended the high dose based on the determination of an MTD (body weight gain decrements) in a 90-day study in Fisher-344 rats (see ECAC meeting minutes dated March 1, 2011).
Species/Strain:	Rat; Fisher-344
Number/Sex/Group:	50/sex/group (Table 1)
Age:	6-7 weeks
Animal housing:	Individually housed in stainless steel cages
Paradigm for dietary restriction:	None
Dual control employed:	No
Interim sacrifice:	No
Satellite groups:	TK, 12/sex/group for treated TK
Deviation from study protocol:	None that affected the integrity of the study

Table 58. Study Design

Group	Subgroup	No. of Animals		Hydrocodone Bitartrate Dose Level (mg/kg/day)		Dose Concentration (mg/mL)	
		Male	Female	Male	Female	Male	Female
1 (Control) ^a	1 (Carcinogenicity)	50	50	0	0	0	0
2 (Low)	1 (Carcinogenicity)	50	50	3	10	0.3	1
	2 (Toxicokinetic)	12	12	3	10	0.3	1
3 (Mid)	1 (Carcinogenicity)	50	50	10	30	1	3
	2 (Toxicokinetic)	12	12	10	30	1	3
4 (High)	1 (Carcinogenicity)	50	50	30	100	3	10
	2 (Toxicokinetic)	12	12	30	100	3	10

a Group 1 received vehicle control article (reverse osmosis water) only.

Observations and Results

Mortality

Cage-side observations were made twice daily. Any rats euthanized *in extremis* were examined *post mortem*. Any rats found dead were examined as soon as possible after death. Statistically, no treatment-related effect on mortality was observed.

Figure 13. Survival in Males

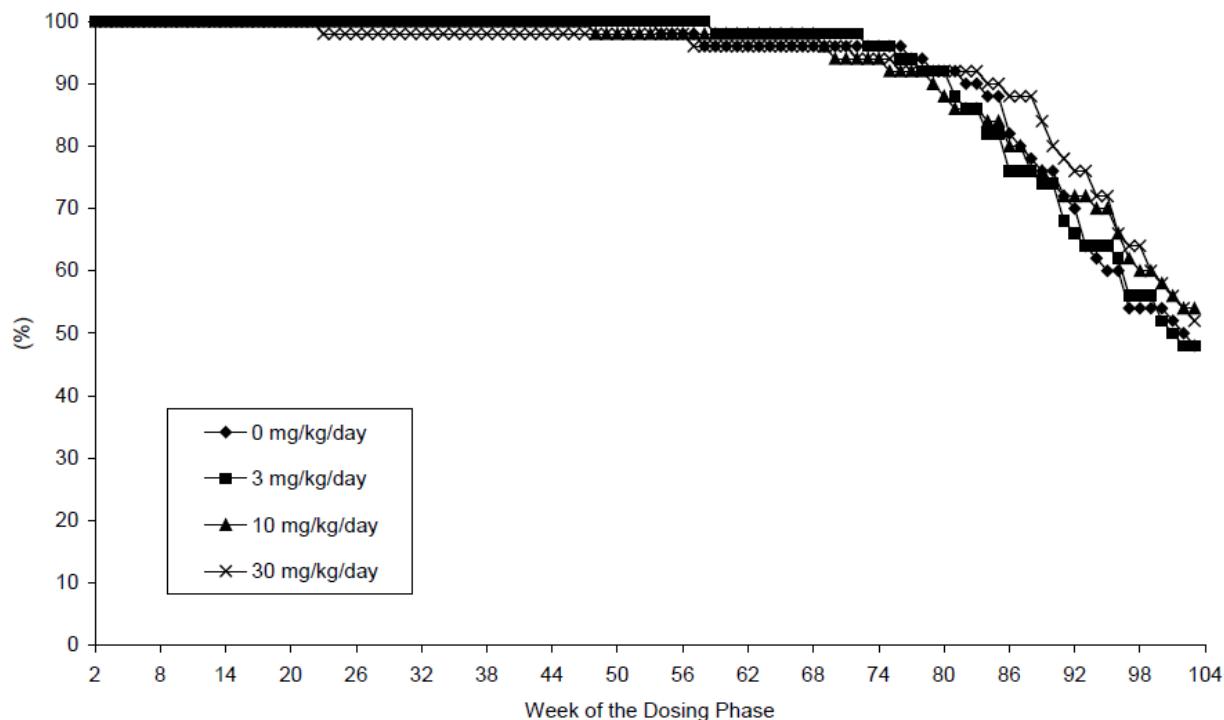
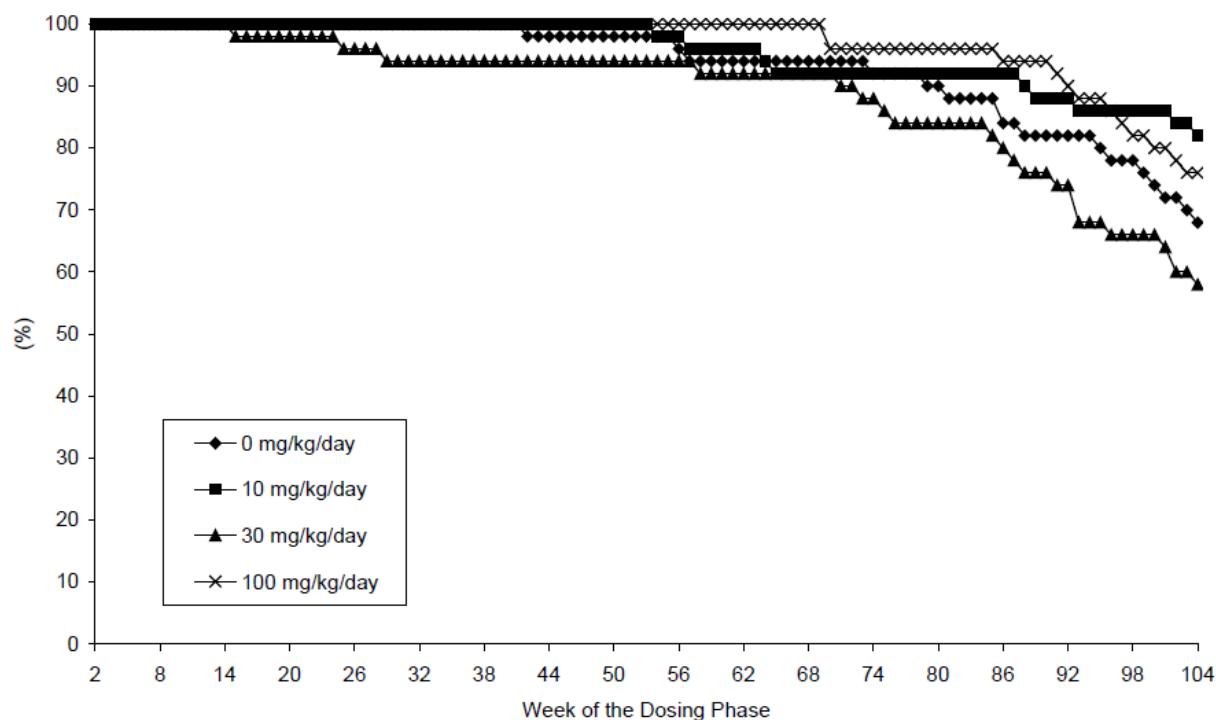


Figure 14. Survival in Females



Food Consumption

Food consumption was recorded one week prior to treatment, weekly through Week 13 and every four weeks thereafter. With the exception of the high dose groups in males and females, controls and treated groups showed similar food consumption.

Throughout the study, high dose groups of both sexes showed higher food consumption than control groups. At no point in the study were the changes in food consumption considered aversive.

Body Weights

Body weights were recorded prior to treatment, weekly through Week 13, and every four weeks thereafter. All rats were weighed immediately prior to termination. In males, throughout most of the study treatment with HC was associated with dose-dependent decreases in body weights. In females, body weights in all treated groups were consistently lower throughout the study than controls. Decreased body weights are expected pharmacologic effects of opioid agonists and at no point in the study were they considered to be adverse. Body weights are presented in the table and figures below.

Figure 15. Body Weights in Males

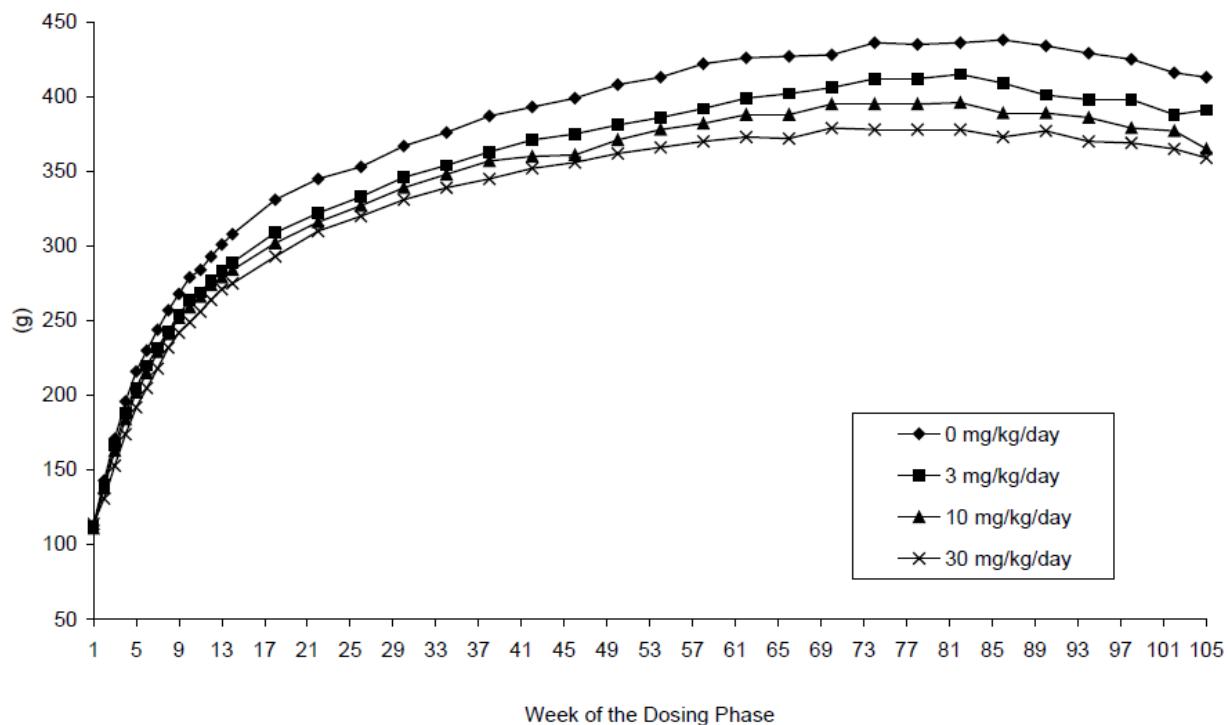
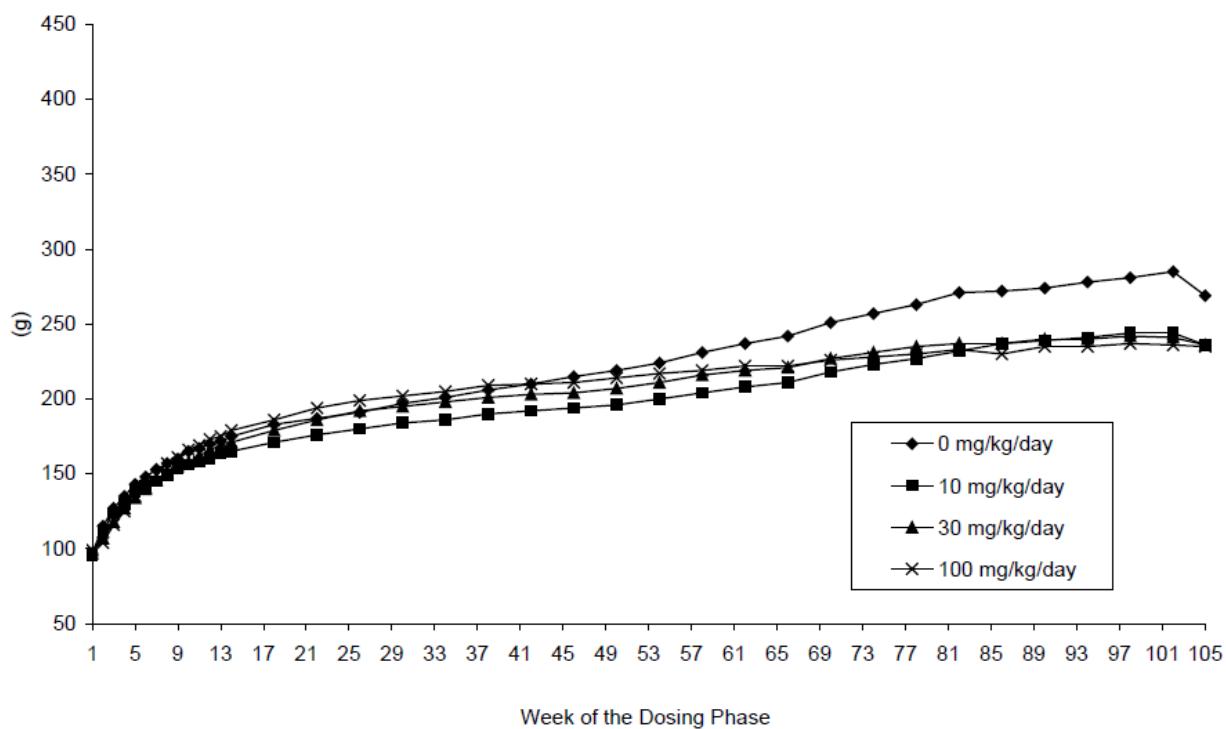


Figure 16. Body Weights in Females



Clinical Signs

Cage-side observations included recording of any changes in clinical condition or behavior and were made twice daily. A detailed examination was performed at least weekly. The rats in the drug-treated groups showed increases over control groups including sores and scabs (on paws, limbs, mouth, tail), thin haircoat, rough haircoat and hunched posture. Age-related signs were observed in all groups were not considered drug-related.

Ophthalmoscopy

Ophthalmic observations were conducted prior to treatment and during Week 52. No treatment-related ophthalmic findings were observed.

Hematology

Samples for hematology were collected on the day of scheduled sacrifice. The parameters in the table below were measured.

Erythrocyte cell count
Leukocyte cell count
Differential blood cell count
Blood smear

No test article-related hematology changes were observed.

Gross Pathology

Test article-related macroscopic findings included dose-dependent increases in the number of scabs observed in both males and females. In males, these sores mostly occurred on the paws and were referred to as pododermatitis by the pathologist. No further analysis was conducted to determine whether the cause of the pododermatitis was bacterial or fungal. Chronic use of opioids can lead to immunosuppression which could be an explanation for the increased incidence and severity of the observed dermatitis, if the dermatitis is due to overgrowth of endogenous skin flora. Alternatively, some opioids, including HC, have been reported to lead to histamine release in a non-opioid receptor mediated manner. This could result in increased scratching and dermatitis.

Histopathology

Peer Review: Yes

<i>Histopathology Inventory</i>			
Study Number	8237255		
Species	Rat		
Organ	assessed	Organ	assessed
Adrenal	X	Nasopharynx	
Aorta	X	Optic nerve	X
Brain	X	Ovary	X
Cecum	X	Pancreas	X
Cervix	X	Preputial gland	
Clitoral gland	X	Pituitary	X
Colon	X	Prostate	X
Duodenum	X	Rectum	X
Epididymis	X	Salivary gland	X
Eye	X	Seminal vesicles	X
Esophagus	X	Skin	X
Femur with bone marrow	X	Spinal cord	X
Gross lesions	X	Spleen	X
Harderian gland	X	Sternum	X
Heart	X	Stomach	X
Ileum	X	Testes	X
Jejunum	X	Thymus	X
Kidney	X	Thyroid with parathyroid	X
Lacrimal gland	X	Tongue	X
Larynx	X	Trachea	X
Liver	X	Urinary bladder	X
Lungs with large bronchi	X	Ureters	
Lymph nodes, mesenteric	X	Vagina	X
Mammary gland	X	Voluntary muscle	X
Nerve, sciatic	X		

Neoplastic

Incidences of benign and malignant neoplastic lesions were evaluated separately and combined where appropriate as per the work of McConnell, et al (McConnell EE, et al., 1986). No HC-mediated increases in neoplastic lesions in females were observed in this study.

A statistically significant trend for increase and pairwise comparison at the high dose was observed in males for benign fibroma in the skin (Table 3). Additionally, in males two malignant fibrosarcomas were observed in the control and the high dose. For statistical analysis, fibromas and fibrosarcomas are pooled. Since the control incidence is $\geq 1\%$ for the pooled tumors, it is considered a common tumor and the necessary P-value to reach statistical significance is <0.01 . The dose response of the pooled tumors is significant with a P-value of 0.003 but the pairwise comparison is not significant

(Table 3). Therefore, the lesion will not be considered treatment-related. Several treatment-related decreases in tumor incidences were seen. In males at the high dose, decreased incidences in tumors in the thyroid (benign adenoma and malignant carcinoma combined C-cell) were observed. In females at the low dose, a significant decrease benign adenoma of the adrenal cortex was observed.

Various neoplasms or pre-neoplastic lesions were observed in the treated groups with incidences similar to controls. None of these tumors were considered to be treatment-related.

Table 59. Selected Neoplastic Lesions

Tissue	Tumor type	Incidence (observed/examined)			
		Males, mg/kg			
		0	3	10	30
Skin/ subcutis	Fibroma (benign)	0/50 0%	1/50 2%	2/50 4%	5/50 10%
	Fibrosarcoma (malignant)	1/50 1/50	0/50 1/50	0/50 2/50	2/50 7/50
	combined				

Table 60. P-values for male fibromas, fibrosarcomas and combined lesions (from statistical analysis by Dr Feng Zhou)

Organ Name	Tumor Name	0	3	10	30	Dose Response	P-Value		
		mg/kg/day VC N=50	mg/kg/day LD N=50	mg/kg/day MD N=50	mg/kg/day HD N=50		VC vs. LD	VC vs. MD	VC vs. HD
Skin/Subcutis	B-Fibroma	0	1	2	5	0.0076*	0.5000	0.2531	0.0312*
	M-Fibrosarcoma	1	0	0	2	0.1632	1.0000	1.0000	0.5185
	C_Fibroma_M+B	1	1	2	7	0.0030*	0.7532	0.5094	0.0336

Non Neoplastic

A higher incidence of bilateral retinal atrophy (minimal to severe) was observed in all female treated rats and males at the two highest doses. Lens degeneration (minimal to marked) was seen in all rats, including controls, with a slightly higher incidence in the two highest doses in males and females. An increase above control animals in granulomatous inflammation of the lung was observed non-dose-dependently in both males and females. Dose-dependent inflammation of the tail in males and females and inflammation of the tail vessel in males only were observed. Additionally, increased incidence of thrombus in the tail was observed both sexes at the mid and high doses. In treated males, dose-dependent increases in pododermatitis were observed. One low dose female and one high dose female also showed pododermatitis.

Toxicokinetics

Twelve rats/sex for treated groups were bled for toxicokinetics on Day 1 and Day 176. Toxicokinetic parameters of HC are detailed in the table below. Exposure to HC generally increased with increasing dose in males from 3 to 30 mg/kg and at all dose levels in females. Increases in HC C_{max} and AUC₀₋₂₄ were generally dose proportional on Day 1 and greater than dose proportional on Day 176. Exposure to HC was similar in males and females.

In order to calculate the exposure margins for the highest strength of the product when dosed as labeled (90 mg BID), the Division requested that the Applicant submit human PK data. The Applicant submitted data from study C33237/1091. The sampling scheme in this study was designed to characterize the PK over a dosing interval (12 hours) at steady state. The AUC₀₋₂₄ was calculated by doubling the AUC₀₋₁₂ values on the sixth day of BID dosing at 90 mg which yielded a mean a mean AUC of 2563 ng·hr/ml. This strategy is considered acceptable and the value was used for systemic exposure comparisons with rat in the table below. The high doses in male and female mice provide 0.06 and 0.4 fold exposure margins, respectively, as compared to the clinical dose of 180 mg/day. All rat exposures of HC in this study are below the systemic exposure at the human dose of 180 mg. The pharmacologic effects of opioids limit the dosing and typically multiples of human clinical exposures are not achieved in rat studies.

Table 61. Toxicokinetic Parameters of Hydrocodone in Rat Plasma

Interval	Group	Hydrocodone Bitartrate		Sex	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng·hr/mL)
		Dose Level (mg/kg/day)				
Day 1	2	3		M	2.63	5.28
		10		F	8.78	22.7
		3	10	M	6.34	16.9
	4	30		F	17.4	71.7
		30		M	13.7	68.5
		100		F	66.6	248
Day 176	2	3		M	5.01	8.23
		10		F	32.5	59.9
	3	10		M	26.8	37.9
		30		F	116	205
	4	30		M	116	165
		100		F	495	1050

F = Female; M = Male.

Table 62. Exposure Comparisons Between Rat and Human

	<i>Dose, mg/kg</i>	<i>Rat/human* AUC₀₋₂₄</i>
Male	3	0.003
	10	0.015
	30	0.064
Female	10	0.023
	30	0.080
	100	0.410

Extrapolated values for 180 mg/day human $AUC_{0-24h} = 2563 \text{ ng.h/mL}$ (Study C33237/1091)

Dosing Solution Analysis

The homogeneity of samples and the sample concentrations were both within an acceptable range of the respective target concentrations for HC.

8.1 Two-Year Mouse Bioassay

Study title: 104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with Hydrocodone Bitartrate in Mice

Study no.: 8237254
 Study report location: EDR 4.2.3.4.1
 Conducting laboratory and location: (b) (4)
 Date of study initiation: January 10, 2012
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: Hydrocodone bitartrate (HC), Lot 1103001006, 99.9%

Key Study Findings

- This carcinogenicity study in mice is valid and no hydrocodone-related neoplasms were observed in either sex.
- Statistically, survival in both males and females was comparable to controls.
- The NOEL for neoplastic lesions is the high dose in both male (100 mg/kg) and female (100 mg/kg) mice which provide 0.6 and 1.14 fold exposure margins, respectively, as compared to the clinical dose of 180 mg/day.

Adequacy of Carcinogenicity Study

The study was conducted with doses chosen based on a 90-day dose range-finding study in CD-1 mice. The SPA was presented to the ECAC and doses for the carcinogenicity study were recommended. This study employed an appropriate mouse strain, an adequate number of animals per sex for each dose and concurrent control groups, and the clinically relevant route of administration. Animals were housed appropriately, provided appropriate food and care, and were administered test article or vehicle control for an appropriate duration. The study is considered adequate.

Appropriateness of Test Models

The mouse is an appropriate model for a 2-year bioassay and the strain, Crl:CD-1 (ICR), is acceptable.

Evaluation of Tumor Findings

No HC-mediated increases in neoplastic lesions were observed in this study. Various neoplasms or pre-neoplastic lesions were observed in the treated groups with incidences similar to controls and/or similar to levels observed in the historical controls. None of these tumors were considered to be treatment-related. Statistical analysis of the data was conducted by Dr. Feng Zhou of the Division of Biostatistics VI. Tumors were combined for statistical analysis according to McConnell, et al, 1986 (McConnell EE, et al., 1986). According to Dr. Zhou's review, no tumor types were considered to have a statistically significant positive dose-response relationship and a statistically significant pair-wise comparison for either males or females.

Methods

Doses: M: 10, 30, 100 mg/kg; F: 10 (25), 30 (75), 100 (150) mg/kg; Note: Due to high mortality, on Day 50 of the study the dose in females was reduced, with concurrence from the ECAC.

Frequency of dosing: Daily

Dose volume: 10 mL/kg

Route of administration: Oral gavage

Formulation/Vehicle: Distilled water

Basis of dose selection: The ECAC recommended the high dose based on the determination of an MTD (reductions in body weight gain) in a 90-day study in the mouse (see ECAC meeting minutes dated March 1, 2011).

Species/Strain: Mouse, Crl:CD-1 (ICR)

Number/Sex/Group: See table below

Age: 6-7 weeks

Animal housing: Individually housed in stainless steel cages

Paradigm for dietary restriction: No

Dual control employed: No

Interim sacrifice: No

Satellite groups: Yes, TK groups, see table below

Deviation from study protocol: None that affected the integrity of the study.

Table 63. Study Design

Group	Subgroup	No. of Animals		Dose Level ^a (mg/kg/day)		Dose Concentration ^a (mg/mL)	
		Male	Female	Male	Female	Male	Female
1 (Control) ^b	1 (Carcinogenicity)	60	60	0	0	0	0
2 (Low)	1 (Carcinogenicity)	60	60	10	25 (10)	1	2.5 (1.0)
	2 (Toxicokinetic)	30	30	10	25 (10)	1	2.5 (1.0)
3 (Mid)	1 (Carcinogenicity)	60	60	30	75 (30)	3	7.5 (3.0)
	2 (Toxicokinetic)	30	30	30	75 (30)	3	7.5 (3.0)
4 (High)	1 (Carcinogenicity)	60	60	100	150 (100)	10	15 (10)
	2 (Toxicokinetic)	30	30	100	150 (100)	10	15 (10)

^a For 49 days, females from Groups 2, 3, and 4 were dosed at dose levels of 25, 75, and 150 mg/kg/day, respectively. Starting on Day 50, dose levels for females were reduced for Groups 2, 3, and 4 to 10, 30, and 100 mg/kg/day, respectively.

^b Group 1 was given vehicle control article only.

Observations and Results

Mortality

Mice were checked twice daily for moribundity and mortality. Survival at the termination of the study is detailed in the table below. No differences in survival for either sex were noted between control and treated groups. In Week 6 of this study, the Sponsor contacted the Agency with a request to decrease the dosing for the females due to mortality observed in the high dose group. In consultation with the ECAC, the Division recommended that the Sponsor decrease the dosing of the female groups to 10, 30, and 100 mg/kg. Refer to the review by Dr. Elizabeth Bolan (dated March 8, 2012) for details. Due to high mortality in the female high-dose group, all females were sacrificed at Week 98. Males were sacrificed as scheduled at Week 104. Throughout the study, an increase in moribundity or mortality attributed to ulcerative dermatitis was noted, in both males and females. No dose-response was noted and the condition was not considered treatment-related. Ulcerative dermatitis is an idiopathic, progressive, debilitating syndrome of laboratory mice, especially common in aged mice. Prevalence rates between 4.1% and 21% have been reported (Hampton, et al., 2012). Although the prevalence rates in this study are higher than those cited, and a significant amount of mortality occurred, the study will not be considered compromised. The numbers of mice did not drop below acceptable levels for analysis of neoplastic endpoints. See the tables below for mortality data.

Table 64. Survival at the Conclusion of the Study

Group	Male Surviving/total	Female Surviving/total
Control	23/60 (38%)	19/60 (32%)
Low dose	23/60 (38%)	21/60 (35%)
Mid dose	25/60 (42%)	21/60 (35%)
High dose	27/60 (45%)	21/60 (35%)

Table 65. Unscheduled Sacrifice as a Result of Ulcerative Dermatitis

Group	Male Deaths	Female Deaths
Control	4 (11%)	10 (24%)
Low dose	15 (41%)	6 (15%)
Mid dose	7 (20%)	4 (10%)
High dose	11 (33%)	3 (8%)

Figure 17. Survival in Males

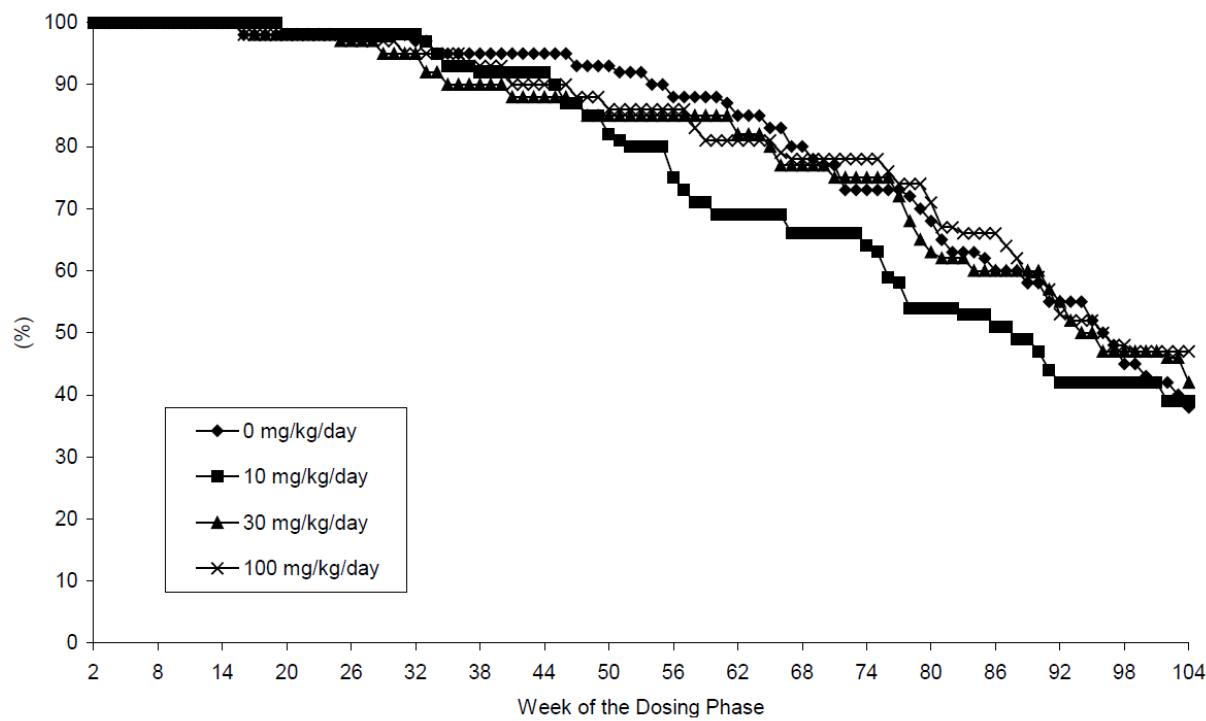
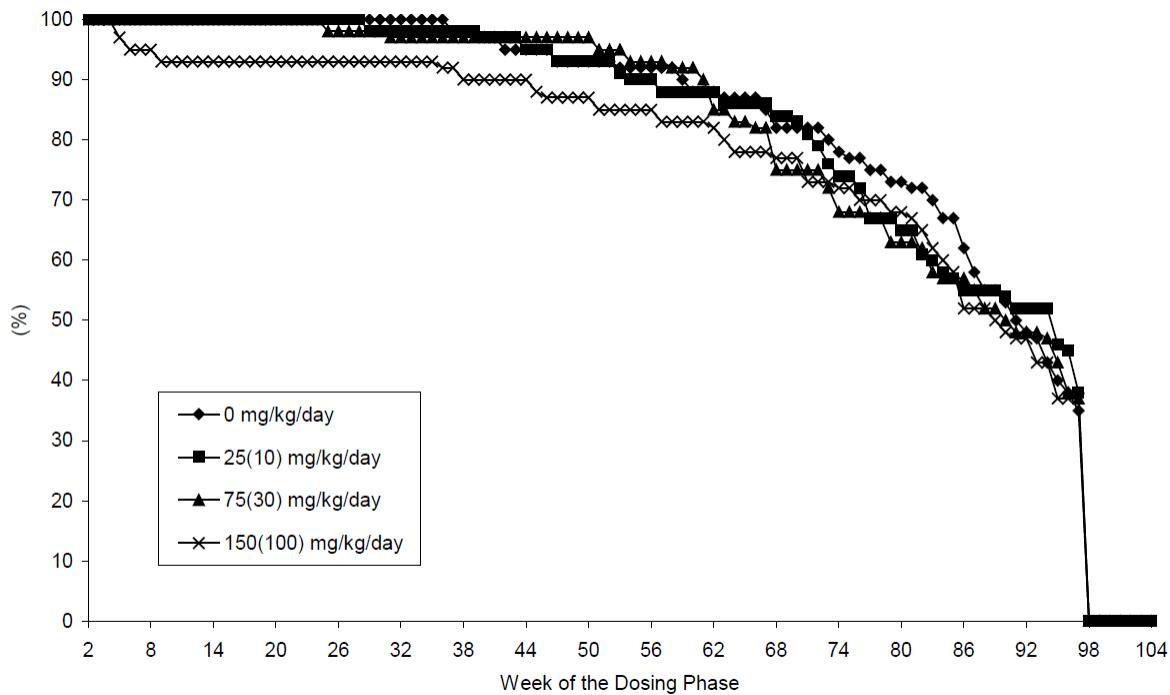


Figure 18. Survival in Females



Clinical Signs

Detailed clinical observations were conducted once weekly. Ulcerative dermatitis was noted in all groups with a higher incidence in males. The finding was not dose-dependent or considered treatment-related. Several clinical signs were noted in the treated mice including rough hair coat, sores, and scabs. In males and females, hunched posture was observed at higher incidences in the treated groups.

Food Consumption

Food consumption was recorded one week prior to treatment, weekly through Week 13 and every four weeks thereafter. Throughout the study, both male and female treated groups (all doses) showed consistently lower food consumption than controls. Concomitant decreases in body weight in both sexes of treated groups were observed. Decreased food consumption and body weights are expected pharmacologic effects of opioid agonists and at no point in the study were either considered to be adverse.

Body Weights

Body weights were recorded prior to treatment, weekly through Week 13, every four weeks for Weeks 14 through Week 66 and weekly beginning on Week 67. All rats were weighed immediately prior to termination. In males, throughout most of the study treatment with HC was associated with dose-dependent decreases in body weights. In females, body weights in all treated groups were lower throughout the study than controls. At terminal sacrifice, both male and female body weights were considerably lower than controls. Concomitant decreased food consumption was observed. Decreased food consumption and body weights are expected pharmacologic effects of opioid agonists and at no point in the study were either considered to be adverse. Hydrocodone-related body weight decrements were not considered to affect the integrity of the study because there were no associated increases in survival in either treated males or females. Body weights are presented in the table and figures below.

Table 9. Body Weights at the Conclusion of Dosing

	<i>Group, mg/kg</i>	<i>Body weight difference: Treated - control at last time point, g</i>	<i>Percent change from control at last time point, %</i>
Male	10	-11	-31
	30	-9	-43
	100	-6	-64
Female	10	-10	-32
	30	-10	-34
	100	-9	-42

Figure 19. Body Weights in Males

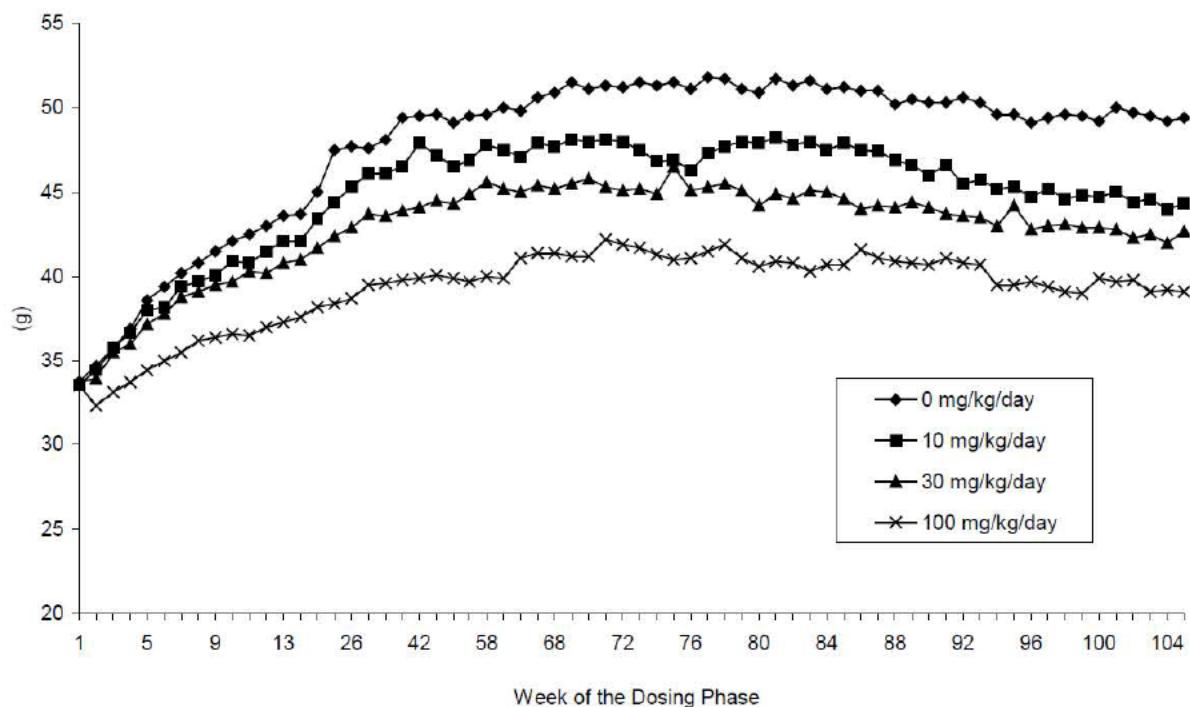
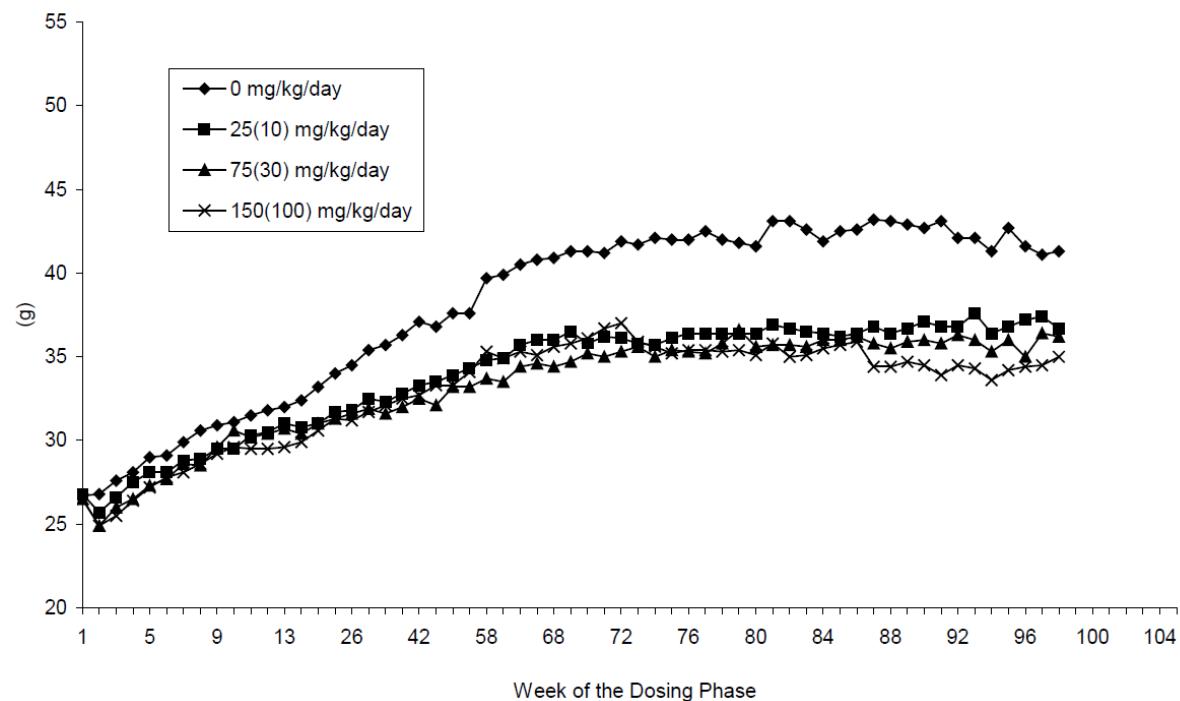


Figure 20. Body Weights in Females

Gross Pathology

Macroscopic observations in the mandibular lymph node, thymus, and spleen of both sexes and liver in females were observed; however, the findings correlated microscopically with lymphosarcoma and were not considered treatment-related. No other treatment-related gross pathology findings were observed.

Histopathology

Peer Review: Yes

<i>Histopathology Inventory</i>			
Study Number	8237254		
Species	Mouse		
Organ	assessed	Organ	assessed
Adrenal	X	Nasal turbinates with paranasal sinus	
Aorta	X	Nasopharynx	
Brain	X	Ovary with oviduct	X
Cecum	X	Pancreas	X
Cervix	X	Preputial gland	
Clitoral gland		Pituitary	X
Colon	X	Prostate	X
Duodenum	X	Rectum	X
Epididymis	X	Salivary gland	X
Eye	X	Seminal vesicles	X
Esophagus	X	Skeletal muscle (biceps)	X
Femur	X	Skin	X
Gallbladder	X	Spinal cord	X
Gross lesions	X	Spleen	X
Harderian gland	X	Sternum with bone marrow	X
Heart	X	Stomach	X
Ileum	X	Testes	X
Jejunum	X	Thymus	X
Kidney	X	Thyroid with parathyroid	X
Lacrimal gland	X	Tongue	X
Larynx	X	Trachea	X
Liver	X	Urinary bladder	X
Lungs with bronchi	X	Ureters	
Lymph nodes, mesenteric	X	Vagina	X
Mammary gland	X	Voluntary muscle	
Nerve, sciatic	X	Zymbal gland	

Neoplastic

Incidence of benign and malignant neoplastic lesions were evaluated separately and combined where appropriate as per the work of McConnell, et al (McConnell EE, et al., 1986). No statistically significant trends for increase or pairwise comparisons were noted in the study. Increases in lymphosarcoma in females were observed but the increase was not statistically significant and was within historical control ranges. The lesion will not be considered treatment-related.

Several treatment-related decreases in tumor incidences were seen. Various neoplasms in the lung, Harderian gland, liver, and pituitary had lower incidences in treated mice. Decreased body weights were observed in this study and have been

shown in long-term studies to be associated with decreased incidences of pituitary tumors in rats and mice (Haseman, et al., 1997). The significance of these findings is unknown.

Other neoplasms or pre-neoplastic lesions were observed in the treated groups with incidences similar to controls. None of these tumors were considered to be treatment-related.

Table 66. Selected Neoplasms in Mice

Tissue	Tumor type	<i>Incidence (observed/examined)</i>							
		<i>Males, mg/kg</i>				<i>Females, mg/kg</i>			
		0	3	10	30	0	10	30	100
Body cavity	lymphosarcoma (malignant)	9/60 15%	4/60 7%	4/60 7%	1/60 2%	17/60 28%	19/60 32%	15/60 25%	22/60 37%

Non Neoplastic

Microscopic findings of erosion/ulcer, mixed cell inflammation and/or acanthosis/hyperkeratosis and loss of dermis and epidermis was seen in all groups. These findings correlated with the macroscopic observation of sores/scabs and ulcerative dermatitis. As noted in the rat study review, chronic use of opioids can lead to immunosuppression which could explain the increased incidence and severity of the observed dermatitis if the dermatitis is due to overgrowth of endogenous skin flora. Alternatively, some opioids, including HC, have been reported to lead to histamine release in a non-opioid receptor mediated manner. Histamine release could result in increased scratching and dermatitis. No other treatment-related non neoplastic findings were observed.

Toxicokinetics

Thirty mice/sex for treated groups were bled for toxicokinetics on Day 20 and Day 176. The Applicant notes that due to the limited number of time points at 24 h on Day 20, the TK conclusions focused on Day 176. Toxicokinetic parameters of HC are detailed in the table below.

In males, increases in HC C_{max} and AUC_{0-24} were greater than dose proportional from 10 to 30 mg/kg and less than dose proportional from 30 to 100 mg/kg. In females, increases in HC C_{max} and AUC_{0-24} were generally dose proportional. Exposure to HC was similar (not greater than a factor of two) in male and female mice at all doses.

In order to calculate the exposure margins for the highest strength of the product when dosed as labeled (90 mg BID), the Division requested that the Applicant submit human PK data. The Applicant submitted data from study C33237/1091. The sampling scheme in this study was designed to characterize the PK over a dosing interval (12 hours) at steady state. The AUC_{0-24} was calculated by doubling the AUC_{0-12} values on the sixth day of BID dosing at 90 mg which yielded a mean a mean AUC of 2563 ng*hr/ml. This strategy is considered acceptable and the value was used for systemic

exposure comparisons with mouse in the table below. The high doses in male and female mice provide 0.6 and 1.1 fold exposure margins, respectively, as compared to the clinical dose of 180 mg/day.

Table 67. Toxicokinetic Parameters of Hydrocodone in Mouse Plasma

Interval Day 176	Group 2	Hydrocodone Bitartrate Dose Level (mg/kg/day)		Sex	C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)
		10				
	3	30		M	78.9	207
				F	96.3	224
	4	100		M	893	1250
				F	306	863
	4	100		M	570	1510
				F	1160	2910

F = Female; M = Male; NR = Not reported.

Note: AUC NR when less than three measurable mean concentrations were observed.

Table 68. Exposure Comparisons Between Mouse and Human

	Dose, mg/kg	Mouse/human AUC_{0-24}
Male	10	0.08
	30	0.49
	100	0.59
Female	10	0.09
	30	0.03
	100	1.14

Extrapolated values for 180 mg/day human $AUC_{0-24h} = 2563 \text{ ng.h/mL}$ (Study C33237/1091)

Dosing Solution Analysis

The homogeneity of samples and the sample concentrations were both within an acceptable range of the respective target concentrations for HC.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

The following study was reviewed by Dr. Huiqing Hao.

Study title: Reproductive Toxicity Study (Segment I) of Orally Administered Hydrocodone Bitartrate (CEP-33237) in Rats

Study no.:	DS-2011-001
Study report location:	EDR 4.2.3.5.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	02/16/2011
GLP compliance:	Yes, a signed GLP compliance statement was included in the report
QA statement:	Yes
Drug, lot #, and % purity:	Hydrocodone bitartrate, Lot 1010000552, 100.2% w/w

Key Study Findings

Male and female rats were administered hydrocodone bitartrate orally (7, 20, and 60 mg/kg). Male rats were treated for 4 weeks prior to mating and during mating with untreated females. Female rats were treated for 2 weeks prior to mating, during mating and through gestation (GD6). Treated females were mated untreated males.

- In males, hydrocodone decreased body weight gain, reduced food consumption, reduced epididymal weight, increased latency to mate
- In females, hydrocodone treatment reduced number of corpora lutea and implantation sites.
- These findings were mainly observed at the mid dose and/or high dose, and the reproductive system findings were attributed to hydrocodone-induced decreased libido or decreased body weights.
- Male and female mating performances, female estrus cyclicity, male reproductive function (epididymal sperm density, sperm morphology, sperm motility), and pre- and post-implantation loss were not affected by the treatment.
- The NOAEL for male and female reproductive function is 7 mg/kg as defined by small changes in reproductive organ weights, and latency to mate in males and reduced uterus weights and corpora lutea and implantation sites in females. This dose corresponds to a human equivalent dose of 68 mg/60 kg person (0.4-times the daily dose of 180 mg).
- Based on absence of treatment-related changes in rat reproductive outcome (successful pregnancy) in this study, the high dose of 60 mg/kg (AUC_{0-t} of 133 ng.h/mL) was considered to be the NOAEL for overall reproductive outcome.

This dose corresponds to a human equivalent dose of 580 mg/60 kg person (3.2-times the daily dose of 180 mg).

Methods

Doses: 0, 7, 20, and 60 mg/kg
 Frequency of dosing: Daily
 Dose volume: 10 mL/kg
 Route of administration: Oral
 Formulation/Vehicle: De-ionized water
 Species/Strain: Sprague-Dawley CD (Crl:CD[SD]) Rats
 Number/Sex/Group: 25/sex/group
 Satellite groups: 6/sex for TK study
 Study design: Males were dosed for 4 weeks prior to and during mating and until their scheduled necropsy; Females were dosed for 2 weeks prior to mating, during mating and through Gestation Day 6 (i.e., implantation) and sacrificed at Day 13 of gestation. Treated females were mated with naïve males, and treated males were mated with naïve females, and their mating performance was compared to the vehicle control animals as the vehicle control males were mated with the vehicle control females.

Cross-Over Mating Design:	
Vehicle Control ♂ X	Vehicle Control ♀
Low Dose ♂ X Naïve ♀	Naïve ♂ X Low Dose ♀
Mid Dose ♂ X Naïve ♀	Naïve ♂ X Mid Dose ♀
High Dose ♂ X Naïve ♀	Naïve ♂ X High Dose ♀

Deviation from study protocol: No significant deviation from protocol that affects result interpretation

Observations and Results

Mortality

No treatment related mortality

Clinical Signs

Signs of irritation (e.g. alopecia, swollen, scab, trauma) of the fore- and hind-limbs and paws were noted primarily in the treated rats.

Body Weight

For males, treatment-related reduced body weight gain was most significant during the first week of treatment. Over time, the effect became less significant. By week 6, percent body weight gain relative to Day 0 was 74%, 61%, 56% and 38% for control, LD, MD and HD, respectively.

For females, dose-related reduced body weight gain was observed in the premating period of 14 days (percent body weight gain from Day 0 was 6%, 4%, 1% and -2% for control, LD, MD and HD, respectively). Reduced body weight gain was also seen in pregnant females when treatment was continued (for the control, LD, MD and HD groups, body weight gain was 10%, 9%, 9% and 8% during the first week of gestation with maintained treatment); after treatment was terminated, body weight gain rebounded in the pregnant females (during Gestation Days 7-13, body weight gain was 12%, 16%, 16% and 12% for the LD, MD and HD, respectively).

Food Consumption

Food consumption was reduced in all treatment groups in a dose-related manner during treatment period (in average, 22- 27% reduction in HD males; 11-27% reduction in HD females during premating period of two weeks; 3-13% reduction in HD females during the first 6 days of gestation when treatment was maintained); after treatment termination, food consumption was rebounded in pregnant females (9%, 15%, 16% higher than control for the LD, MD and HD females on Gestation Day 12).

Estrus cycling and latency to mate

The length of estrous cycle was not affected by hydrocodone based on the observation during the 14-day treatment prior to mating (3.1-3.4 estrus cycles in the 14 days). The latency to mate was similar across female groups, but was slightly delayed in males at 20 and 60 mg/kg (3.8 days versus 2.7 days). The Sponsor considered this delay to be related to sedative effect of hydrocodone on libido. As the overall mating result was unaffected, the significance of delayed onset of mating is minimal. The table below presents a summary of mating performance data.

Table 69. Summary of Mating Parameters

	0	7 mg/kg	20 mg/kg	60 mg/kg
Treated dams x naïve males				
No. of estrus cycle /14 days	3.4	3.4	3.3	3.1
Latency to mate (days)	2.7	2.7	2.6	2.8
Mating index	100%	100%	100%	100%
Treated males x naïve dams				
Latency to mate (days)	2.7	2.7	3.8*	3.8*
Mating index	100%	95%	92%	92%

* p<0.05 compared to control

Toxicokinetics

Following oral administration, systemic exposures (C_{max} and AUC) to hydrocodone were generally dose proportional. The high dose of 60 mg/kg was associated with significantly longer plasma $T_{1/2}$ which might be related to hydrocodone-induced slowing gastrointestinal motility and increased absorption of hydrocodone. Over the treatment

of 4 weeks in males and 2 weeks in females, systemic dose accumulated (1.5- to 2.5-fold AUC) at 20 and 60 mg/kg.

Systemic exposures to hydromorphone, a metabolite of hydrocodone, were also proportional to the hydrocodone dose. Accumulation of hydromorphone was negligible in most groups, but was approximately 2-fold in the mid- and high-dose males after 4 weeks of treatment. Compared to hydrocodone, hydromorphone $T_{1/2}$ and systemic exposures are significantly higher.

For both hydrocodone and hydromorphone, there were no sex-related TK findings.

Table 70. TK parameters for hydrocodone and hydromorphone in rats following oral hydrocodone administration

		T_{max}, h	$C_{max}, ng/mL$	$AUC_{0-t}, ng.h/mL$	$T_{1/2}, h$
Hydrocodone bitartrate					
7 mg/kg	M	Day 1	0.5	3.82	7.1
		Day 28		5.52	10.6
	F	Day 1	0.5	2.28	5.1
		Day 14		4.40	8.2
20 mg/kg	M	Day 1	1	6.57	15.3
		Day 28		19.20	42.8
	F	Day 1	0.5	4.70	15.3
		Day 14		13.64	31.3
60 mg/kg	M	Day 1	0.5	10.36	64.6
		Day 28		82.41	161.5
	F	Day 1		9.62	74.8
		Day 14		75.23	1037
Hydromorphone					
7 mg/kg	M	Day 1	0.5	4.07	5.35
		Day 28		8.64	5.17
	F	Day 1	0.5	3.65	25.3
		Day 14		5.65	NC
20 mg/kg	M	Day 1	1	13.37	9.24
		Day 28		32.83	4.97
	F	Day 1		7.94	7.89
		Day 14		14.85	6.19
60 mg/kg	M	Day 1	0.5	16.08	NC
		Day 28		79.91	9.2
	F	Day 1	0.5	20.71	NC
		Day 14		54.28	5.2

Dosing Solution Analysis

The dose formulations were within 92-95% of labeled claim (target concentration) and were determined to be stable for up to 58 days when stored under refrigeration. No detectable hydrocodone bitartrate was found in the vehicle control formulations.

Necropsy

- Treated dams that were mated with naïve males showed a reduced number of corpora lutea (20 and 60 mg/kg) and corollary reduced total implants. The Sponsor considered the reduced corpora lutea to be related to hydrocodone-related body weight reduction. Examinations on pre-implantation loss and post-implantation loss in these dams revealed no treatment related effects.
- Naïve dams that were mated with treated males showed no remarkable findings.

Table 71. Summary of Fertility Parameters in the Segment I Study

Dose, mg/kg/day	0	7	20	60
Treated dams x naïve male				
Mating index	100%	100%	100%	100%
Fertility index	96%	100%	100%	100%
Corpora lutea/dam	15.9	15.1	14.5*	13.8*
Implantation sites/dam	15.2	14.7	14.2	13.6*
Preimplantation loss	4.2%	2.8%	1.6%	2.1%
Postimplantation loss	7.0%	9.7%	3.7%	5.5%
Treated male x naïve dams				
Mating index	100%	95%	92%	92%
Fertility index	96%	100%	100%	96%
Corpora lutea/dam	15.9	15.9	16.2	15.4
Implantation sites/dam	15.2	14.8	15.2	15.2
Preimplantation loss	4.2%	7.3%	6.2%	1.1%
Postimplantation loss	7.0%	4.3%	5.7%	2.9%

Reproductive Organ Weights

Following a 4-week treatment with 60 mg/kg hydrocodone, mean absolute epididymis weight was reduced by 8% compared to vehicle control mean. Organ to body weight ratios were also altered.

**Reproductive Toxicity Study (Segment I) of Orally Administered
Hydrocodone Bitartrate (CEP-33237) in Rats**

Table 11. Mean Male Organ Weights
(g)

Parameter	Treatment Group			
	Vehicle Control 0 mg/kg	Low Dose 7 mg/kg	Mid Dose 20 mg/kg	High Dose 60 mg/kg
Testes (total)	Mean	3.54	3.54	3.54
	SD	0.26	0.27	0.28
	N	25	25	25
Epididymides (total)	Mean	1.28	1.27	1.24
	SD	0.14	0.12	0.11
	N	25	25	25

* Significantly different from the vehicle control group, $p \leq 0.05$

**Reproductive Toxicity Study (Segment I) of Orally Administered
Hydrocodone Bitartrate (CEP-33237) in Rats**

Table 12. Mean Male Organ-to-Body Weight Ratios

Parameter	Treatment Group			
	Vehicle Control 0 mg/kg	Low Dose 7 mg/kg	Mid Dose 20 mg/kg	High Dose 60 mg/kg
Terminal Body Weight (g)	Mean	513	471*	454*
	SD	34	35	31
	N	25	25	25
Testes (total)	Mean	0.691	0.755*	0.780*
	SD	0.057	0.080	0.059
	N	25	25	25
Epididymides (total)	Mean	0.250	0.270*	0.274*
	SD	0.028	0.031	0.030
	N	25	25	25

* Significantly different from the vehicle control group, $p \leq 0.05$

Absolute uterus weights were reduced in HD females, however, this was apparently due to body weight decrements as relative weights were not clearly changed.

**Reproductive Toxicity Study (Segment I) of Orally Administered
Hydrocodone Bitartrate (CEP-33237) in Rats**

Table 13. Mean Female Organ Weights
(g)

<u>Parameter</u>		Treatment Group			
		Vehicle Control <u>0 mg/kg</u>	Low Dose <u>7 mg/kg</u>	Mid Dose <u>20 mg/kg</u>	High Dose <u>60 mg/kg</u>
Ovaries	Mean	0.142	0.139	0.137	0.122*
	SD	0.024	0.024	0.023	0.019
	N	24	25	25	25
Uterus	Mean	9.19	9.43	9.91	9.19
	SD	1.24	1.36	1.69	1.39
	N	24	25	25	25

* Significantly different from the vehicle control group, $p \leq 0.05$

**Reproductive Toxicity Study (Segment I) of Orally Administered
Hydrocodone Bitartrate (CEP-33237) in Rats**

Table 14. Mean Female Organ-to-Body Weight Ratios

		Treatment Group			
		Vehicle Control	Low <u>7 mg/kg</u>	Mid <u>20 mg/kg</u>	High <u>60 mg/kg</u>
Terminal Body Weight (g)	Mean	319	321	317	297*
	SD	18	24	21	18
	N	24	25	25	25
Ovaries	Mean	0.045	0.043	0.043	0.041
	SD	0.008	0.007	0.007	0.007
	N	24	25	25	25
Uterus	Mean	2.89	2.95	3.13	3.10
	SD	0.40	0.44	0.54	0.42
	N	24	25	25	25

* Significantly different from the vehicle control group, $p \leq 0.05$

- Male necropsy evaluation: treatment with hydrocodone in male rats resulted in no remarkable findings in epididymal sperm density or sperm morphology examinations (See table below). Right cauda weights were reduced by 10 and 15% compared to controls in the MD and HD group, respectively.

Table 72. Summary of Sperm Characteristics in the Segment I Study

Dose, mg/kg/day	0	7	20	60
Right cauda weight (g)	0.271	0.257	0.243*	0.229*
Sperm count (10^8 /g cauda)	7.48	7.79	7.46	7.75
Sperm motility (%)	86.3	89.6	88.3	86.7
Sperm morphology (% abnormal)	6	NE	NE	5

* Significantly different from vehicle control group, $p \leq 0.05$.

9.2 Embryonic Fetal Development

The following study was reviewed by Dr. Huiqing Hao.

Study title: Definitive Oral Developmental Toxicity Study (Seg II) of Hydrocodone Bitartrate in rats

Study no.: DS-2011-009

Study report location: 4.2.3.5.2

Conducting laboratory and location:

(b) (4)



Date of study initiation: 02/21/2011

GLP compliance: Yes, a signed GLP compliance statement was included in the report

QA statement: Yes

Drug, lot #, and % purity: Hydrocodone bitartrate, Lot 1010000552, purity 100.2%

Key Study Findings

Pregnant rats were administered hydrocodone bitartrate from Gestation Day 6 to 17 at 10, 33, and 100 mg/kg with the following key findings:

- Maternal toxicity was evident at all doses (i.e., reduced food consumption, body weight, and body weight gain).
- Embryo-fetal toxicity was observed at 33 and 100 mg/kg reflected in the increased number of early resorptions, increased post-implantation loss, and increased non-viable litters.
- No teratogenic findings were observed. Increases in the incidence of the variant wavy/bulbous ribs were observed at 10 and 33 mg/kg and was attributed to the maternal toxicity.
- The low dose of 10 mg/kg ($AUC_{0-t} = 17.7 \text{ ng.h/mL}$) was considered to be a NOAEL for embryo-fetal toxicity.

Methods

Doses: 0, 10, 33, 100 mg/kg
Frequency of dosing: Once daily
Dose volume: 10 mL/kg
Route of administration: Oral gavage
Formulation/Vehicle: Deionized water
Species/Strain: Sprague Dawley rat
Number/Sex/Group: 24/dose
Satellite groups: 6/dose for TK study
Study design: Gravid rats were given the test article orally on Days 6-17 of gestation and sacrificed on Day 21.
Deviation from study protocol: No deviations impacting the outcome of the study occurred

Observations and Results

Mortality

None

Clinical Signs

Vaginal discharge (red) was noted in three 100 mg/kg treated dams around Gestation Days 8-12; this was likely evidence of fetal loss. Additionally alopecia was more frequently observed in the 10 and 33 mg/kg groups.

Body Weight

Dose-related decrease of body weight gain was observed. The average body weight gains during treatment (Gestation Days 6-18) was 85%, 56%, 36% of control for the 10, 33 and 100 mg/kg groups, respectively.

Food Consumption

Reduced food consumption was noted in all treatment groups. Overall food consumption during treatment (Gestation Days 7-18) was 87%, 72%, 70% of control for the 10, 33, and 100 mg/kg groups, respectively.

Toxicokinetics

Following oral administration of hydrocodone, C_{max} of hydrocodone and its metabolite, hydromorphone were reached at 0.5-1 hours post dose. Systemic exposures to hydrocodone and hydromorphone were generally dose proportional. There was no significant systemic accumulation of hydrocodone or hydromorphone after repeated administration over the treatment period of 12 days. The tables below present details.

Table 73. TK Parameters in the Segment II Study (Rat)

		T _{max} , h	C _{max} , ng/mL	AUC _{0-t} , ng.h/mL	T _{1/2} , h
	Dose, mg/kg	Hydrocodone			
Day 6	10	0.5	8.33	15.1	NC
	33	1.0	24.56	83.6	8.47
	100	0.5	78.27	276.0	6.01
Day 17	10	0.5	10.72	17.7	NC
	33	0.5	57.16	82.8	NC
	100	0.5	287.82	315.6	NC
		Hydromorphone			
Day 6	10	1.0	8.71	27.0	NC
	33	0.5	22.31	171.5	7.52
	100	0.5	85.96	481.0	9.51
Day 17	10	0.5	7.54	16.5	2.38
	33	0.5	30.62	88.2	3.81
	100	0.5	168.44	397.8	4.94

Day: gestation day; NC: not calculable

Dosing Solution Analysis

The dose formulations were within 94-95% of labeled claim (target concentration) and were determined to be stable for up to 36 days when stored under refrigeration. No detectable hydrocodone bitartrate was found in the vehicle control formulations.

Necropsy

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

The number of corpora lutea, total number of implantation sites, and pre-implantation loss were not affected by treatment. A trend toward increases in pre-implantation loss was observed at the MD and HD but there was considerable variability and the increases were not significant.

Post-implantation loss and nonviable litters were increased at the MD and HD. The non-viable litters were the primary cause of the increase in early fetal loss and were considered to be related to maternal toxicity.

Offspring (Malformations, Variations, etc.)

Fetal weights (male, female, and combined) and the litter size were unaffected.

The only treatment-related finding was increased incidence of wavy/bulbous ribs (see the table below). The Sponsor stated that the wavy ribs were likely due in part to maternal toxicity and, the rib changes noted in the 10 mg/kg can be construed as an indicator of potential toxicity to the fetus at higher doses as evident by the early fetal

loss in these groups. The low incidence of wavy ribs in the 100 mg/kg group might be due to reduced number of viable litters.

Table 74. Litter Viability in the Rat Segment II Study

Parameter	Treatment Group			
	Vehicle Control 0 mg/kg	Low Dose 10 mg/kg	Mid Dose 33 mg/kg	High Dose 100 mg/kg
Initial Group Size (sperm-positive)	24	24	24	24
Actual Group Size (gravid)	24	24	24	24
Viable Litters ^a (at least 1 live implant)	24	24	22	13
Non-pregnant	0	0	0	0
Non-viable Litters ^b (no live implants)	0	0	2	11
% Non-viable	0	0	8	46
Group Size (full-term gravid)	24	24	24	24
% Pre-implantation Loss ^c	Mean ^d	3.5	3.6	8.2
	SD	5.0	7.3	15.5
	N	24	24	24
% Post-implantation Loss ^e	Mean	4.1	4.2	14.7
	SD	6.4	6.2	30.1
	N	24	24	24

^a Viable litters refers to the number of dams with at least 1 live implant on gestation day 21.

^b Nonviable litters refers to the number of dams that had no live implants, but were pregnant on gestation day 21

^c % Pre-implantation Loss = [(Total Corpora Lutea – Total Implants) ÷ Total Corpora Lutea]

*100. When the number of implants is greater than the number of corpora lutea, a zero was used to indicate 0% pre-implantation loss.

^d The mean reported utilizes the litter as the unit of observation ± standard deviation (SD); the N used is the number gravid unless the parameter requires an intact fetus for evaluation (e.g., malformed), in which case the N utilized is viable litters.

^e % Post-implantation Loss = [(Total Implants - Live) ÷ Total Implants] *100

* Significantly different from control, p ≤ 0.05

Table 75. Summary of Findings in the Offspring in the Segment II Study (Rat)

Dose, mg/kg	0	10	33	100
Total Dam	24	24	24	24
Viable litters	24	24	22	13
Average fetal weight, g	5.78	5.76	5.66	5.49
Average litter size	11.6	11.8	10.4	11.4
N, fetal/litter for skeletal examinations	138/24	140/24	113/21	75/13
Wavy or Bulbous ribs, affected fetal/litter	4/3	21/10	22/11	1/1

Study title: Definitive Oral Toxicity Study (Seg II) of Hydrocodone Bitartrate in Rabbits

Study no.: DS-2011-010
Study report location: 4.2.3.5.2
Conducting laboratory and location: [REDACTED] (b) (4)

Date of study initiation: 03/17/2011
GLP compliance: Yes, a signed GLP compliance statement was included in the report
QA statement: Yes
Drug, lot #, and % purity: Hydrocodone bitartrate, Lot 1010000552, purity 100.2%

Key Study Findings

Female rabbits were treated from Gestation Day 6 to 18 with hydrocodone bitartrate at 5.3, 16, and 48 mg/kg.

- Maternal toxicity including reduced food consumption and lower body weight gain in does treated with 5.3 mg/kg/day or higher.
- There were no treatment related findings in the fetal body weights, external, visceral, and skeletal examinations.
- Therefore, the no-observed-adverse-effect level (NOAEL) of hydrocodone bitartrate for maternal toxicity was 5.3 mg/kg/day ($AUC_{0-t} = 26.1 \text{ ng.h/mL}$), and the NOAEL for developmental toxicity was 48 mg/kg/day ($AUC_{0-t} = 764.1 \text{ ng.h/mL}$).

Methods

Doses: 0, 5.3, 16 and 48 mg/kg
Frequency of dosing: Daily
Dose volume: 5 mL/kg
Route of administration: Oral gavage
Formulation/Vehicle: Deionized water
Species/Strain: New Zealand White rabbit
Number/Sex/Group: 24 females
Satellite groups: 3/dose were used for TK study
Study design: Pregnant rabbits were given test article on Gestation Days 6-18, inclusive, and euthanized on Gestation Day 29

Deviation from study protocol: No significant deviations occurred impacting on the study results.

Observations and Results

Mortality

No treatment-related deaths occurred during the study. One rabbit in the 16 mg/kg group was found dead shortly after dosing due to gavage-related accident.

Clinical Signs

Scant feces was noted at a much higher incidence in the 48 mg/kg treated does and was likely associated with reduced food consumption and opioid-induced decrease in GI motility.

Body Weight

Body weight gain was lower in treated groups, most prominently at MD and HD. Although these animals started to gain weight during the post dosing period, the discrepancy persisted until the end of the study, the resultant terminal body weights of 48 mg/kg group were approximately 7% lower than control.

Table 76. Summary of Body Weights (g) in the Segment II Study (Rabbit)

Dose, mg/kg	0	5.3	16	48
GD6	3252	3233	3211	3190
GD21	3505	3423	3309*	3037*
ΔGD21-GD6	253	190	98	-153
GD29	3639	3605	3519	3394*
ΔGD29-GD6	387	372	308	204

*Significantly different from controls, $p \leq 0.05$

Food Consumption

Food consumption was significantly reduced in all treatment groups throughout the treatment period. The overall reduction during the 13 days of treatment was 10%, 26%, and 65% for the LD, MD and HD, respectively. During the post dosing period, however, these groups were noted to be eating more than control from Gestation Day 24 until termination on Gestation Day 29.

Toxicokinetics

Systemic exposure to hydrocodone was more than dose proportional. The $T_{1/2}$ values were consistent for all groups, ranging from 1.4 to 2.5 hours and there was no accumulation of hydrocodone over the 13 days of treatment.

Systemic exposure to hydrocodone metabolite, hydromorphone was generally dose proportional. Hydromorphone $T_{1/2}$ was in a range of 2.1-5.3 hours which is slightly longer than 1.4-2.5 hours of hydrocodone. There was no significant hydromorphone accumulation over the 13 days of treatment. Systemic exposure to hydromorphone was generally less than that observed for hydrocodone. This finding is likely due to slow absorption of hydrocodone from gastrointestinal tract, rather than faster clearance of hydromorphone based on $T_{1/2}$ comparison. The table below presents the detailed TK data.

Table 77. Summary of TK Parameters in the Segment II Study (Rabbit)

Dose, mg/kg		5.3	16	48
Hydrocodone				
C _{max} , ng/mL	GD 6	8.0	225.8	152.6
	GD 18	10.0	62.9	280.0
AUC _{0-t} , ng.h/mL	GD 6	28.1	290.5	557.4
	GD 18	26.1	117.1	764.1
T _{1/2} , hours	GD 6	2.5	1.6	2.3
	GD 18	1.4	1.5	1.9
Hydromorphone				
C _{max} , ng/mL	GD 6	1.5	20.1	8.2
	GD 18	2.2	10.0	14.8
AUC _{0-t} , ng.h/mL	GD 6	5.6	30.6	51.4
	GD 18	8.5	26.1	98.6
T _{1/2} , hours	GD 6	2.6	2.1	5.3
	GD 18	2.1	3.2	3.8

Dosing Solution Analysis

The dosing solution concentrations were within 92-93% of label claim and were stable for up to 63 days when stored under refrigeration.

Necropsy

Uterine weight was slightly lower in the 16 and 48 mg/kg group (control, 489 g; MD, 482 g; HD, 472 g).

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

There were no remarkable macroscopic findings in F0 animals.

The number of corpora lutea, total number of implantation sites, numbers of live and dead fetuses, and the pre- and post-implantation loss were unaffected by treatment with hydrocodone bitartrate. Total resorption was higher than concurrent control (3-4% of implantations versus 0.4% in the control), but was within the historical control (11.7%) (Feussner, et al., 1992).

Offspring (Malformations, Variations, etc.)

Fetal weights (male, female and combined) and sex ratio were not affected by hydrocodone treatment.

There were no treatment related findings in external, visceral, cephalic, and skeletal examinations.

One fetus from a doe in the 48 mg/kg group had external malformations (acephaly, kyphosis, meningocele, stub tail, arthrogryposis [forelimbs] and club foot), visceral malformations (heart vessel defect of common truncus, malformed kidneys and absent adrenals), and skeletal formations (fused/absent/misshapen centrae and/or vertebrae, absent ribs, no head/skull). Additionally, one fetus from a doe at 16 mg/kg group had herniated diaphragms. The incidence of these findings was 0.46% in this study which is within historic range of (<0.7%) (MARRTA/MTA, March 1996). These findings were considered to be spontaneous rather than treatment related.

9.3 Prenatal and Postnatal Development

The following study was reviewed by Dr. Huiqing Hao.

Study title: An Oral Pre and Post-natal Study of Hydrocodone Bitartrate in the Rat

Study no.:	DS-2010-042
Study report location:	4.2.3.5.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	12/13/2010
GLP compliance:	Yes, a signed GLP compliance statement was included in the report
QA statement:	Yes
Drug, lot #, and % purity:	Hydrocodone bitartrate, Lot 1010000552, purity 100.2%

Key Study Findings

In this study, pregnant rats were exposed to hydrocodone bitartrate (7, 20, and 60 mg/kg) from Gestation Day 6 to Post-partum Day 21, inclusively.

- Decreases in body weights of 19% and 36% were seen in dams at 20 and 60 mg/kg and these doses were considered to be maternally toxic.
- Increased post-implantation loss in F0 dams at the HD and reduced survival index (Postnatal Days 0-4) in the F1 pups was observed at the MD and HD.
- Lower body weights from birth through the lactation phase were observed in the F1 generation at the HD.
- There were no treatment-related differences in sensory function, reflex response, acoustical startle response, motor activity, learning and memory, mating performance or fertility in the F1 generation.

- Body weights and developmental landmarks of the F2 generation were also similar across groups.
- The no-observed-adverse effect level (NOAEL) for reproductive and developmental toxicity in this study was 7 mg/kg (AUC_{0-t} of 14 ng.h/mL).

Methods

Doses: 0, 7, 20, 60 mg/kg
Frequency of dosing: Daily
Dose volume: 10 mL/kg
Route of administration: Oral gavage
Formulation/Vehicle: Deionized water
Species/Strain: Sprague Dawley CD rat
Number/Sex/Group: 24/dose
Satellite groups: 6/dose for TK study
Study design: Gravid rats (F0) were given the test article orally for 38 days (Gestation Day 6 through lactation and until Post-partum Day 21). F0 dams were allowed a natural parturition; F1 litters were culled, but were not intentionally exposed to the test article. During the lactation phase of the study, growth and development of the F0 offspring (F1 generation) was evaluated; after which at least one male and one female from each F1 litter within a treatment group were randomly selected for paring at a future mating trial. At sexual maturity (10-12 weeks of age), the F1 rats were mated for a period of at least 2 weeks (siblings were not intermated). F1 pups not selected for mating and all F0 dams were sacrificed at F1 weaning, and a gross necropsy was performed. All F1 dams were allowed a natural parturition and their F2 litters were culled. F1 dams and their F2 litters were euthanized at weaning.
Deviation from study protocol: No deviations impacting the outcome of the study occurred.

Observations and Results (Optional Table)

F₀ Dams

Survival: Two F0 dams (one at 7 mg/kg and one at 20 mg/kg) died during the lactation phase. The one at 7 mg/kg died on Lactation Day 10 from renal complications with kidney findings of white/tan foci and dilatation; the one at 20 mg/kg died on Lactation Day 1 with signs of tremor and cold to touch, which the Sponsor considered to be complication following parturition.

Clinical signs: No remarkable findings

Body weight: F0 dam body weight gains were lower in treatment groups, more prominently at the 20 and 60 mg/kg during gestation phase. The resulting lower body weight was noted throughout the study (Gestation Day 12 to Lactation Day 21), although body weight gains in treatment groups were similar or slightly higher than control during lactation phase.

Dam body weight (g)

Dose, mg/kg	0	7	20	60
GD 6	238	241	236	241
GD 20	350	343	327*	313*
		-2%	-7%	-10%
ΔGD 20-GD 6	112	102	91	72
LD 0	276	271	257*	250*
		-2%	-7%	-9%
LD 21	302	300	287*	280*
		-5%	-7%	
ΔLD 21-LD 0	26	26	31	30

GD, gestation day; LD, lactation day

* Significantly different from control, p ≤0.05

Food consumption: Food consumption was reduced in treatment groups throughout the study with a clear dose relationship during gestation phase (25% reduction for the high dose).

Dam food consumption (g)

Dose, mg/kg	0	7	20	60
GD 6-GD 20	325	301	273	243
LD 0-LD 21	1180	1228	1132	903

Uterine content: Treatment related findings were primarily observed at the 60 mg/kg including lower pregnancy rate (gravid number/sperm positive number: 21/24 versus 24/24), lower gestation index (control, 100%; HD 95% of pregnant rats with live litters due to 100% litter resorption in animal No.86), higher post-implantation loss (control, 3.3%; LD, 4.3%; MD, 5.8%; HD, 15.2% including animal No. 86; 11.4% excluding animal No. 86).

Necropsy observation: No remarkable findings

Toxicokinetics: F0 dams:
 Gestation phase: Orally administrated hydrocodone was rapidly absorbed (hydrocodone T_{max} was 0.5 hour) and metabolized (hydromorphone T_{max} was 0.5 hour). Systemic exposures (C_{max} and AUC) of hydrocodone on Gestation Days 6 (first day of dosing) and 20 were generally dose proportional. There was no significant dose accumulation (AUC on Gestation Day 20 was approximately 1.7 fold higher than that of Gestation Day 6 at the 60 mg/kg). Systemic exposures to the hydrocodone metabolite, hydromorphone were similar to that of hydrocodone, dose proportional and no accumulation over the 15 days of treatment (see the two tables below).

Dose, mg/kg		7	20	60
Hydrocodone				
C_{max} , ng/mL	GD6	5.79	16.78	26.74
	GD20	9.75	33.27	148.01
AUC_{0-t} , ng.h/mL	GD6	10.8	53.4	124.2
	GD20	14.0	52.8	210.1
$T_{1/2}$, h	GD6	2.07	9.14	6.88
	GD20	1.60	1.00	1.51
Hydromorphone				
C_{max} , ng/mL	GD6	4.71	15.30	31.71
	GD20	9.36	30.95	108.98
AUC_{0-t} , ng.h/mL	GD6	17.3	87.3	271.4
	GD20	17.4	102.8	258.9
$T_{1/2}$, h	GD6	NC	9.03	14.61
	GD20	NC	4.03	6.64

F0 at post-partum: At Post-partum Days 4, 14 and 21, blood samples from F0 dams were collected at 2 hours post-dose. The plasma concentration of hydrocodone was detected in a dose related manner (see the table below). Note, these plasma concentrations are not C_{max} as they were collected at 2 hours post-dose rather than at T_{max} (0.5 hour based on data collected at gestation phase).

Plasma hydrocodone concentration in F0 dams post parturition

Dose, mg/kg	PND 4	PND 14	PND 21
7	2.19	2.37	1.90
20	4.60	3.47	5.04
60	10.49	13.34	8.30

F1 pups: Plasma hydrocodone concentrations in the pooled samples collected from culled pups at 2 hours post-dose on PND4, PND14 and PND21. On PND4, the pup plasma hydrocodone was below limit of quantitation (BLQ) of 0.2 ng/mL for the LD, 0.42 ng/mL for the MD and 2.93 ng/mL for the HD. On PND14 and PND21, plasma concentrations were mostly BLQ. The lower exposures in the pups on the later sampling days might be due to reduced milk consumption since the pups began eating solid food around PND10 and were mostly feeding on solid food by PND21.

Dosing Solution Analysis The dose formulation were within 92-96% of label claim and were determined to be stable for up to 59 days when stored under refrigeration.

F₁ Generation

Survival: Viability indices (No. of live pups on Day 4 post-partum/No of live pups on Day 0 post- partum) were reduced in treatment groups (control, 98.7%; LD, 97.5%; MD, 92.3%; HD, 73.1%). Note, the Sponsor reported values (control, 99%; LD, 100%; MD, 93%; HD 81%) excluding “spontaneous deaths” which however was not defined.

The lactation indices (No. of live pups on Day 21 post-partum/No. of live pups on Day 4 post-partum, post-cull) were not affected by treatment (control, 100; LD, 95%; MD 99%; HD, 94%).

There was no treatment related mortality in adult F1 animals.

Clinical signs: Clinical signs were only observed in association with reduced viability.

Body weight: Litter weights of the 60 mg/kg treated group were significantly lower than control during the lactation period (21% lower on Lactation Day 21)

**Table 8 (cont'd). Summary of Average Litter Body Weights – F₁ Generation
(Pre-weaning)**

Males		Treatment Group			
		Vehicle Control 0 mg/kg	Low Dose 7 mg/kg	Mid Dose 20 mg/kg	High Dose 60 mg/kg
Day 0	Mean	6.63	6.97	6.71	6.43
	SD	0.49	0.60	0.51	0.63
	N ^a	24	24	24	20
Day 4	Mean	10.61	10.96	10.02	8.63*
	SD	1.18	1.17	0.82	0.82
	N	24	24	21	16
Day 7	Mean	16.94	17.40	15.95	12.98*
	SD	2.01	1.67	1.46	1.14
	N	24	24	21	16
Day 14	Mean	33.65	35.40	32.50	25.18*
	SD	3.79	2.70	3.30	3.33
	N	24	23	21	16
Day 21	Mean	55.49	59.18	55.10	43.52*
	SD	6.27	4.56	5.78	8.40
	N	24	22	21	16

^a N=Number of Dams

*Significantly different from control, p≤0.05

Food consumption: F1 generation food consumption (after Postnatal Day 28-33) was significantly reduced in males from the 60 mg/kg group (8-13.5% lower). However, no similar findings were observed in any other groups.

Physical development: The development of eye opening was not affected. Also, average time of vaginal opening and preputial separation were similar across groups (control, 34.9 days; LD, 32.9 days; MD, 33.1 days; HD, 34.3 days). Pinna unfolding time was not reported.

Neurological assessment: Righting test, sensory function (pupil response, tactile placing) and reflex (aerial righting reflex and hind-limb extension), acoustical startle response (computerized evaluation), motor activity and nose poke (learning and memory, aka, find the peanut task) were not affected by treatment.

Reproduction: The mating index, fertility index, and latency to mate were unaffected by treatment. The implantation sites, litter size (total born for combined sexes), post-implantation loss were similar for the F1 control and treated groups.

Other: Macroscopic examination revealed no remarkable findings in F1 adults.

F₂ Generation

Survival: Increased number of dead pups was seen in the 7 mg/kg group over PND 0-4; as such, survival was significantly lower in this group. The reduction in survival was not seen at higher doses. Therefore, this finding was not considered to be treatment related. Survival over Lactation Days 4-21 was similar across all groups.

Body weight: Litter weight and pup weight were unaffected by treatment.

External evaluation: Not examined

Male/Female ratio: The male:female ratio was similar across groups (control, 1:1; LD, 1:1; MD, 1.2:1; HD, 0.9:1)

10 Special Toxicology Studies

11 Integrated Summary and Safety Evaluation

Teva has submitted NDA 27975 for VANTRELA ER, an extended-release HC product which contains excipients that are intended to confer abuse-deterrent properties. This NDA has been submitted as a 505(b)(1) application which cross-references NDA 20716 (Vicoprofen). Teva has right of reference to NDA 20716.

The Applicant has assessed the genetic toxicology, reproductive and developmental toxicology of HC bitartrate. Additionally, qualification of multiple impurities and justification of novel excipients was provided. Carcinogenicity studies were submitted through a right of reference obtained by Teva.

All excipients can be found either in previously approved products or have acceptable daily intakes at higher levels and do not require further justification for the levels when the product is consumed at the MTDD of HC. With the exception of glyceryl behenate, all excipients were found in the IIG in drugs approved for chronic use that when used at their maximum daily dose exceeded levels in this formulation when used at the MTDD of HC. Although glyceryl behenate is listed in the IIG, levels when this formulation is used at the MTDD of HC exceed levels of drugs approved for chronic use at their MDD. Glyceryl behenate is the glycerol ester of behenic acid and is found in dietary sources including canola oil and peanut oil. At the MTDD of HC, 2.4 g of glyceryl behenate would be consumed. Since estimates of the consumption of all mono- and diglycerides in the diet approximately between 1 to 10 g per person per day, the amount of glyceryl behenate in this product is considered acceptable.

The Applicant is referencing DMF [REDACTED] (b) (4) for the HC drug substance. The drug substance impurities [REDACTED] (b) (4) and [REDACTED] (b) (4) exceeded qualification

thresholds in ICH Q3A(R2).

[REDACTED] and [REDACTED] all tested negative in the Ames assay and in the in vitro chromosome assay. A weight-of-evidence argument for lack of genotoxic potential was made for [REDACTED].^{(b) (4)} Multiple Ames assays and in vitro chromosome aberration assays were conducted with lots of differing purities. The lot with the higher purity tested negative in the Ames and was considered nonmutagenic. Both lots tested positive in the in vitro chromosome aberration assay. However, [REDACTED]^{(b) (4)} tested negative in an in vivo micronucleus assay and an in vivo comet assay in liver. The weight of evidence suggests that this impurity is not genotoxic. Additionally, all of the impurities were predicted to be non-mutagenic by both the Derek and Sarah platforms. A 13-week toxicology study in rats with [REDACTED]^{(b) (4)} and a 13-week toxicology study in rats with a cocktail of [REDACTED]^{(b) (4)} and [REDACTED]^{(b) (4)} showed NOELs at the highest doses tested and yielded acceptable exposure margins to qualify all impurities at the proposed specifications. All proposed drug substance impurity specifications have been adequately qualified.^{(b) (4)}

[REDACTED] is also a drug product degradant and the proposed specification exceeded ICH Q3B(R2) qualification thresholds. The aforementioned studies also provide acceptable qualification for the proposed drug product specification for [REDACTED]^{(b) (4)}.

The standard ICH battery of genetic toxicology studies was conducted with HC. Hydrocodone tested negative in the in vitro bacterial reverse mutation assay and the in vivo mouse micronucleus assay. In contrast, HC tested positive for clastogenic activity in the in vitro chromosome aberration assay. Hydrocodone is considered to have clastogenic potential. A fourth test would typically be required to fully characterize the clastogenic potential of HC. However, regardless of the outcome of a fourth genetic toxicology study, a carcinogenicity assessment would provide the definitive answer as to the impact of potential genotoxicity of HC. Carcinogenicity assessments in mice and rats with HC were submitted to this NDA by Teva through a right of reference. Hydrocodone bitartrate was found to be negative for carcinogenic potential in both rat and mouse. Therefore, a fourth genetic toxicology test is not needed.

A 13-week repeat-dose toxicity study in rats was conducted with HC. This study was designed as a dose-range finding study in support of dose selection for the carcinogenicity bioassay, therefore, the doses tested were not very high. Although pharmacologic effects of HC were observed (body weight decreases and decreased food consumption) no toxicity was noted and no target organs were identified.

A 13-week repeat-dose toxicity study in mice was conducted with HC. This study was also designed as a dose-range finding study in support of dose selection for a carcinogenicity bioassay in mice. As in the rat study, pharmacologic effects of HC were observed (body weight decreases and decreased food consumption) but no toxicity was noted and no target organs were identified.

The highest available strength for this product will be 90 mg HC and the product is labeled to be used BID. Therefore, the human dose of 180 mg/day will be used as the exposure comparison with the animal exposures in the developmental and reproductive toxicity studies and carcinogenicity studies in the product labeling.

A full battery of developmental and reproductive toxicology studies has been conducted with HC. The fertility and early embryofetal development study in rats with oral doses of 7, 20, and 60 mg/kg HC showed decreased food consumption and reduced body weight gain, especially at the early days of treatment. A longer latency to mate in males was observed but it was attributed to the sedative effects of HC. No other fertility endpoints in males were affected. Male reproductive system (sperm motility, spermatozoa count, sperm morphology, and testicular histopathology), were not affected. Reduced absolute epididymal weight was observed which correlated with reductions in body weight. Epididymal and testicular weights relative to body weight were reduced in males. Overall, although the effects may be attributed to body weight loss, we cannot dismiss a potential impact of hydrocodone on male reproductive organs. This is not unexpected with an opioid which is known to reduce luteinizing hormone. In females, reduced number of corpora lutea and associated reduced implants but were within historical control values and no pre- and post-implantation loss was noted. Overall, no effects on overall reproductive outcome were noted and the high dose of 60 mg/kg ($AUC_{0-t} = 133$ ng.h/mL) was considered to be the NOAEL in this study. However, the decrease in testicular and epididymal weights and increased latency to mate in males, and reduced corpora lutea and implantations in females suggest a reproductive function NOAEL of 7 mg/kg in both males and females.

Embryo-fetal developmental studies were conducted in rats (10, 33 and 100 mg/kg) and rabbits (5.3, 16 and 48 mg/kg) with oral administration of hydrocodone bitartrate. Maternal toxicities in these two species were similar, including reduced food consumption and lower body weight gain at all doses. Embryo-fetal toxicities were noted in rats including increase of post-implantation loss and increased non-viable litters. There were no similar findings reported in the rabbit study. No teratogenic findings were observed in either rats or rabbits. The NOAEL for embryo-fetal toxicity in rats was 10 mg/kg ($AUC_{0-t} = 17.7$ ng.h/mL) based on findings of increase of post-implantation loss, and increased non-viable litters observed at higher doses. In the rabbit study no adverse effects were observed on the reproductive and developmental parameters in either the dam or offspring. The NOAEL for embryo-fetal toxicity was the high dose of 48 mg/kg ($AUC_{0-t} = 764.1$ ng.h/mL).

In a pre- and post-natal development study, rats treated with oral doses of 7, 20, and 60 mg/kg of hydrocodone bitartrate orally. Decreases in body weights of 19% and 36% were seen in dams at MD and HD and were considered maternally toxic. Increased post-implantation loss in F0 dams at the HD and reduced survival index in the F1 pups was observed at the MD and HD. Lower body weights from birth through the lactation phase were observed in the F1 generation at the HD. There were no treatment-related differences in sensory function, reflex response, acoustical startle response, motor activity, learning and memory, mating performance or fertility in the F1

generation. Body weights and developmental landmarks of the F2 generation were also similar across groups. The no-observed-adverse effect level (NOAEL) for reproductive and developmental toxicity in this study was 7 mg/kg ($AUC_{0-t} = 14 \text{ ng.h/mL}$).

12 Appendix/Attachments

Reference List

Feussner EL, Lightkep GE, Hennesy RA, Hoberman AM and Christian MS (1992) A decade of rabbit fertility data: study of historical control animals. *Teratology* **46**:349-365.

Haseman JK, Young E, Eustis SL and Hailey JR (1997) Body weight-tumor incidence correlations in long-term rodent carcinogenicity studies. *Toxicol Pathol* **25**:256-263.

Hampton AL, Hish GA, Aslam MN, Rothman ED, Bergin IL, Patterson KA, Naik M, Paruchuri T, Varani J and Rush HG (2012) Progression of ulcerative dermatitis lesions in C57BL/6Crl mice and the development of a scoring system for dermatitis lesions. *J Am Assoc Lab Anim Sci* **51**:586-593.

Haseman JK, Hailey JR and Morris RW (1998) Spontaneous neoplasm incidences in Fischer 344 rats and B6C3F1 mice in two-year carcinogenicity studies: a National Toxicology Program update. *Toxicol Pathol* **26**:428-441.

Haseman JK, Young E, Eustis SL and Hailey JR (1997) Body weight-tumor incidence correlations in long-term rodent carcinogenicity studies. *Toxicol Pathol* **25**:256-263.

McConnell EE, Solleveld HA, Swenberg JA and Boorman GA (1986) Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *J Natl Cancer Inst* **76**:283-289.

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/s/

ELIZABETH BOLAN
01/11/2017

RICHARD D MELLON
01/11/2017

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA 207975

NDA/BLA Number: 207975 Applicant: Teva

Stamp Date: November 30,
2014

Drug Name: CEP33237 **NDA/BLA Type:** 505(b)(2)
Extended-Release
Hydrocodone Bitartrate

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc.)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA 207975**

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		A literature-based justification for the levels of excipients has been provided by the Applicant. The adequacy of these data will be determined upon review.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?			Defer to CSS
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None at this time.

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

ELIZABETH BOLAN
02/06/2015

RICHARD D MELLON
02/06/2015