Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None.

HUMAN-LABELED PRODUCTS:

Budesonide Capsules: 3 mg (micronized); *Entocort EC*® (Prometheus); (Rx)

Human budesonide capsules may need to be compounded into dosage strengths suitable for dogs or cats, but the enteric-coated sugar spheres found inside the capsule should not be altered or damaged.

There are also budesonide products (powder and suspension for oral inhalation, and nasal sprays) for the treatment of asthma or allergic rhinitis. Trade names for these products include *Pulmicort*® and *Rhinocort*®.

BUPRENORPHINE HCL

(byoo-pre-***nor***-feen) Buprenex®, Subutex®

OPIATE PARTIAL AGONIST

Prescriber Highlights

- Partial *mu* opiate agonist used primarily as an injectable & buccal analgesic in small animals (but has been used in horses)
- Buccal administration in cats well tolerated & effective
- Rarely, may cause respiratory depression

Uses/Indications

Buprenorphine is most often used as an analgesic for mild to moderate pain in small animals. While it is not as an effective analgesic as pure *mu*-agonists (morphine, hydromorphone, etc.), it generally causes fewer adverse effects. In cats, buccal (oral) administration is often a practical, effective method for helping to control post-operative pain. More experience is occurring using opiates with short-term NSAIDs for post-op pain control.

Buprenorphine has been used in horses, but its short duration of action and expense relative to other opiates limit its usefulness.

Pharmacology/Actions

Buprenorphine has partial agonist activity at the *mu*-receptor. This is in contrast to pentazocine that acts as an antagonist at the *mu*-receptor. Buprenorphine is considered 30 times as potent as morphine and exhibits many of the same actions as the opiate agonists. It produces a dose-related analgesia but at higher dosages analgesic effects may actually decrease. Buprenorphine appears to have a high affinity for *mu*-receptors in the CNS, which may explain its relatively long duration of action. Analgesia may persist for 12 hours, but usually a 6–8 hour duration of analgesic effect is typical.

The cardiovascular effects of buprenorphine may cause a decrease in both blood pressure and cardiac rate. Rarely, human patients may exhibit increases in blood pressure and cardiac rate. Respiratory depression is a possibility, and decreased respiratory rates have been noted in horses treated with buprenorphine. Gastrointestinal effects appear to be minimal with buprenorphine, but further studies are needed to clarify this.

Pharmacokinetics

Buprenorphine is rapidly absorbed following IM injection, with 40–90% absorbed systemically when tested in humans. The drug is also absorbed sublingually (bioavailability≈55%) in people. Oral doses appear to undergo a high first-pass effect with metabolism occurring in the GI mucosa and liver.

The distribution of the drug has not been well studied. Data from work done in rats reflects that buprenorphine concentrates in the liver, but is also found in the brain, GI tract, and placenta. It is highly bound (96%) to plasma proteins (not albumin), crosses the placenta, and it and its metabolites are found in maternal milk at concentrations equal to or greater than those found in plasma.

Buprenorphine is metabolized in the liver by N-dealkylation and glucuronidation. These metabolites are then eliminated by biliary excretion into the feces (≈70%) and urinary excretion (≈27%).

In the horse, onset of action is approximately 15 minutes after IV dosing. The peak effect occurs in 30–45 minutes and the duration of action may last up to 8 hours. Because acepromazine exhibits a similar onset and duration of action, many equine clinicians favor using this drug in combination with buprenorphine.

In cats, buprenorphine has a volume of distribution [Vd(ss)] of approximately 8 L/kg and a clearance of about 20 mL/kg/min. Elimination half-life is about 6–7 hours. When administered via oral mucosa (liquid placed into the side of cat's mouth), absorption was comparable to that seen with IM or IV administration.

Contraindications/Precautions/Warnings

All opiates should be used with caution in patients with hypothyroidism, severe renal insufficiency, adrenocortical insufficiency (Addison's), and in geriatric or severely debilitated patients.

Rarely, patients may develop respiratory depression from buprenorphine; it, therefore, should be used cautiously in patients with compromised cardiopulmonary function. Like other opiates, buprenorphine must be used with extreme caution in patients with head trauma, increased CSF pressure or other CNS dysfunction (*e.g.*, coma).

Patients with severe hepatic dysfunction may eliminate the drug more slowly than normal patients. Buprenorphine may increase bile duct pressure and should be used cautiously in patients with biliary tract disease.

The drug is contraindicated in patients having known hypersensitivity to it.

Adverse Effects

Although rare, respiratory depression appears to be the major adverse effect to monitor for with buprenorphine; other adverse effects (sedation) may be noted. The primary side effect seen in humans is sedation with an incidence of approximately 66%.

Reproductive/Nursing Safety

Although no controlled studies have been performed in domestic animals or humans, the drug has exhibited no evidence of teratogenicity or causing impaired fertility in laboratory animals. In humans, the FDA categorizes this drug as category ***C*** for use during pregnancy (*Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.*)

Overdosage/Acute Toxicity

The intraperitoneal LD_{50} of buprenorphine has been reported to be 243 mg/kg in rats. The ratio of lethal dose to effective dose is at least 1000:1 in rodents. Because of the apparent high index of safety, acute overdoses should be a rare event in veterinary medicine. Treatment with naloxone and doxapram have been suggested in cases of acute overdoses causing respiratory or cardiac effects. Secondary to buprenorphine's high affinity for the *mu* receptor, high doses of naloxone may be required to treat respiratory depression.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving buprenorphine and may be of significance in veterinary patients:

- **ANESTHETICS, LOCAL** (**mepivacaine, bupivacaine**): May be potentiated by concomitant use of buprenorphine
- **ANTICONVULSANTS** (**phenobarbital, phenytoin**): May decrease plasma buprenorphine levels
- **BENZODIAZEPINES**: Case reports of humans developing respiratory/cardiovascular/CNS depression; use with caution
- **CNS DEPRESSANTS** (*e.g.,* **anesthetic agents, antihistamines, phenothiazines, barbiturates, tranquilizers, alcohol,** etc.): May cause increased CNS or respiratory depression when used with buprenorphine
- **ERYTHROMYCIN**: Can increase plasma buprenorphine levels
- **FENTANYL** (and other **pure opiate agonists**): Buprenorphine may potentially antagonize some analgesic effects (**Note:** *This is controversial*), but may also reverse some of the sedative and respiratory depressant effects of pure agonists
- **HALOTHANE**: Potentially can increase buprenorphine effects
- **KETOCONAZOLE, ITRACONAZOLE, FLUCONAZOLE**: Can increase plasma buprenorphine levels
- **MONAMINE OXIDASE** (**MAO**) **INHIBITORS** (*e.g.,* **selegiline, amitraz**): Possible additive effects or increased CNS depression
- **NALOXONE**: May reduce analgesia associated with high dose buprenorphine
- **PANCURONIUM**: If used with buprenorphine may cause increased conjunctival changes
- **RIFAMPIN**: Potentially decrease plasma buprenorphine concentrations

Doses

- **DOGS:**

  For analgesia:
  a) 0.005–0.02 mg/kg IM, IV or SC q6–12h (Hendrix and Hansen 2000)
  b) 0.01–0.015 mg/kg IM, IV (may also be given orally) (Mathews 1999)
  c) 0.005–0.03 mg/kg IV, IM, SC, epidural (Boothe 1999)
  d) 0.006–0.02 mg/kg IV, IM, SQ; duration of effect 6–12 hours and is a relatively effective analgesic, but may be difficult to reverse with naloxone if untoward effects are seen. (Perkowski 2006b)

- **CATS:**

  For analgesia:
  a) 0.005–0.01 mg/kg IM, IV or SC q6–12h (Hendrix and Hansen 2000)
  b) 0.01–0.03 mg/kg PO transmucosally (squirted directly into the mouth) q8h (Lichtenberger 2006e)
  c) 0.01–0.03 mg/kg IM, IV, SC q6–8h; 0.01–0.03 mg/kg PO q6–12h (Hansen 2003a)
  d) 0.01–0.03 mg/kg IM, IV, Buccal. Effects may last up to 6 hours. Buccal use is well accepted by cats. (Robertson and Lascelles 2003)

- **FERRETS:**

  a) 0.01–0.05 mg/kg SC or IM 2–3 times daily (Williams 2000)

- **HORSES:** (**Note:** ARCI UCGFS Class 2 Drug)

  For neuroleptanalgesia:
  a) 0.004 mg/kg IV (given with acepromazine 0.02 mg/kg) (Thurmon and Benson 1987)
  b) 0.006 mg/kg IV (given with xylazine 0.07 mg/kg) (Thurmon and Benson 1987)

- **RABBITS/RODENTS/SMALL MAMMALS:**

  As an analgesic (for control of acute or chronic visceral pain):
  a) Rabbits: 0.02–0.05 mg/kg SC or IM q6–12h; 0.5 mg/kg per rectum q12h
  Rodents: 0.1–3 mg/kg IM or SC q6–12h (Huerkamp 1995)
  b) Rabbits: 0.01–0.05 mg/kg SC, IM or IV q6–12h; 0.5 mg/kg rectally q12h (Ivey and Morrisey 2000)
  c) Guinea pigs: 0.05 mg/kg SC or IV q8–12h
  Mice: 0.05–0.1 mg/kg SC q12h.
  Rats: 0.01– 0.05 mg/kg SC or IV q8–12h or 0.1–0.25 mg/kg PO q8–12h. (Adamcak and Otten 2000)

Monitoring

- Analgesic efficacy
- Respiratory status
- Cardiac status

Client Information

- This agent should be used parenterally in an inpatient setting or with direct professional supervision
- Buccal/SL dosing may be performed at home, but pre-measuring dosages in syringes (if using the injection orally) should be considered

Chemistry/Synonyms

A thebaine derivative, buprenorphine is a synthetic partial opiate agonist. It occurs as a white, crystalline powder with a solubility of 17 mg/mL in water and 42 mg/mL in alcohol. The commercially available injectable product (*Buprenex*®—Norwich Eaton) has a pH of 3.5–5 and is a sterile solution of the drug dissolved in D_5W. Terms of potency are expressed in terms of buprenorphine. The commercial product contains 0.324 mg/mL of buprenorphine HCl, which is equivalent to 0.3 mg/mL of buprenorphine.

Buprenorphine HCl may also be known as: buprenorphini hydrochloridum, CL-112302, NIH-8805, UM-952; *Anorfin*®, *Buprenex*®, *Buprine*®, *Finibron*®, *Magnogen*®, *Nopan*®, *Norphin*®, *Pentorel*®, *Prefin*®, *Suboxone*®, *Subutex*®, *Temgesic*®, or *Temgesic-nX*®.

Storage/Stability/Compatibility

Buprenorphine should be stored at room temperature (15–30° C). Temperatures above 40° C or below freezing should be avoided. Buprenorphine products should be stored away from bright light. Autoclaving may considerably decrease drug potency. The drug is stable between a pH of 3.5–5.

Buprenorphine is reported to be **compatible** with the following IV solutions and drugs: acepromazine, atropine, diphenhydramine, D_5W, D_5W and normal saline, droperidol, glycopyrrolate, hydroxyzine, lactated Ringer's, normal saline, scopolamine, and xylazine. Buprenorphine is reportedly **incompatible** with diazepam and lorazepam.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

The ARCI (Racing Commissioners International) has designated this drug as a class 2 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS:

Buprenorphine HCl for Injection: 0.324 mg/mL (equivalent to 0.3 mg/mL buprenorphine); 1 mL amps & *Carpuject*; *Buprenex*® (Reckitt Benkhiser); Buprenorphine Hydrochloride (Abbott); (Rx, C-III)

Buprenorphine HCl Sublingual Tablets: 2 mg (as base), & 8 mg (as base); *Subutex®* (Reckitt Benkhiser); (Rx, C-III)

Buprenorphine HCl Combinations: Sublingual Tablets: 2 mg buprenorphine base/0.5 mg naloxone; 8 mg buprenorphine base/2 mg naloxone; *Suboxone®* (Reckitt Benkhiser); (C-III)

BUSPIRONE HCL

(byoo-spye-rone) BuSpar®

ANXIOLYTIC

Prescriber Highlights

- Non-benzodiazepine anxiolytic agent used in dogs & cats
- May take a week or more to be effective; not appropriate for acute treatment of situational anxieties
- Use with caution in patients with severe hepatic or renal disease
- Adverse Effects relatively uncommon; cats may exhibit behavior changes

Uses/Indications

Buspirone may be effective in treating certain behavior disorders in dogs and cats, principally those that are fear/phobia related and especially those associated with social interactions. Buspirone may also be useful for urine spraying or treatment of motion sickness in cats.

Pharmacology/Actions

Buspirone is an anxioselective agent. Unlike the benzodiazepines, buspirone does not possess any anticonvulsant or muscle relaxant activity and little sedative or psychomotor impairment activity. Buspirone does not share the same mechanisms as the benzodiazepines (does not have significant affinity for benzodiazepine receptors and does not affect GABA binding). It appears to act as a partial agonist at serotonin (5-HT1A) receptors and as an agonist/antagonist of dopamine (D2) receptors in the CNS. In neurons, buspirone slows the neuronal flow depletion of serotonin stores.

Pharmacokinetics

In humans, buspirone is rapidly and completely absorbed but a high first pass effect limits systemic bioavailability to approximately 5%. Binding to plasma proteins is very high (95%). In rats, highest tissue concentrations are found in the lungs, kidneys, and fat. Lower levels are found in the brain, heart, skeletal muscle, plasma and liver. Both buspirone and its metabolites are distributed into maternal milk. The elimination half-life (in humans) is about 2–4 hours. Buspirone is hepatically metabolized to several metabolites (including one that is active: 1-PP). These metabolites are excreted primarily in the urine.

Contraindications/Precautions/Warnings

Buspirone should be used with caution with either significant renal or hepatic disease. Because buspirone may reduce disinhibition, it should be used with caution in aggressive animals. While buspirone has far less sedating properties than many other anxiolytic drugs, it should be used with caution in working dogs.

Because buspirone often takes a week or more for effect, it should not be used as the sole therapy for situational anxieties.

Adverse Effects

Adverse effects are usually minimal in animals with buspirone and it is generally well tolerated. Bradycardia, GI disturbances and stereotypic behaviors are possible. Cats may demonstrate increased affection. In multi-cat households, cats that have previously been extremely timid in the face of repeated aggression from other cats may, after receiving buspirone begin turning on their attacker.

The most likely adverse effect profile seen with buspirone in humans includes dizziness, headache, nausea/anorexia, and restlessness; other neurologic effects (including sedation) may be noted. Rarely, tachycardias and other cardiovascular clinical signs may be present.

Reproductive/Nursing Safety

While the drug has not been proven safe during pregnancy, doses of up to 30 times the labeled dosage in rabbits and rats demonstrated no teratogenic effects. In humans, the FDA categorizes this drug as category ***B*** for use during pregnancy (*Animal studies have not yet demonstrated risk to the fetus, but there are no adequate studies in pregnant women; or animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.*)

Buspirone and its metabolites have been detected in the milk of lactating rats; avoid use during nursing if possible.

Overdosage/Acute Toxicity

Limited information is available. The oral LD_{50} in dogs is 586 mg/kg. Oral overdoses may produce vomiting, dizziness, drowsiness, miosis and gastric distention. Standard overdose protocols should be followed after ingestion has been determined.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving buspirone and may be of significance in veterinary patients:

- **CNS DEPRESSANTS:** Potentially could cause increased CNS depression
- **DILTIAZEM:** May cause increased buspirone plasma levels and adverse effects
- **ERYTHROMYCIN:** May cause increased buspirone plasma levels and adverse effects
- **GRAPEFRUIT JUICE** (**powder**): May cause increased buspirone plasma levels and adverse effects
- **KETOCONAZOLE, ITRACONAZOLE:** May cause increased buspirone plasma levels and adverse effects
- **MONOAMINE OXIDASE INHIBITORS** (*e.g.*, **selegiline, amitraz**): Use with buspirone is not recommended because dangerous hypertension may occur
- **RIFAMPIN:** May cause decreased buspirone plasma levels
- **TRAZODONE:** Use with buspirone may cause increased ALT
- **VERAPAMIL:** May cause increased buspirone plasma levels

Doses

- **DOGS:**

  For low-grade anxieties and fears:

  a) 1 mg/kg PO q8–24h (mild anxiety); 2.5–10 mg per dog PO q8–24h (mild anxiety); 10–15 mg per dog PO q8–12h (more severe anxiety, thunderstorm phobia) (Overall 2000)

  b) 1–2 mg/kg PO q12h; 5–15 mg per dog PO q8–12h (Siebert 2003c)

  c) 5–10 mg (total dose) PO q8–12h (Reisner and Houpt 2000)