Asparaginase at 400 U/kg SC with the first two lomustine doses and then discontinued; Prednisone started at 2 mg/kg PO once daily and tapered to 1 mg/kg PO every other day. If neutrophil count <500 cells/mcL at one week after lomustine, then doses were decreased by 10 mg/m2 for subsequent doses. All doses were rounded down to the nearest 10 mg dose. (Saba, Thamm et al. 2007)

b) As a rescue agent for relapsed canine lymphomas: 90 mg/m2 PO every 21 days for 3 cycles, then every 4–6 weeks thereafter (Moore, London et al. 1999)

c) As a rescue agent for mast cell tumors when other treatment options have failed: 70–90 mg/m2 PO every 21 days (Chun 2007b)

d) 60–80 mg/m2 PO q4–6 weeks (Brewer 2003)

e) 80 mg/m2 PO every 3 weeks (Lana 2002)

f) For cutaneous lymphosarcoma: Isotretinoin at 3–4 mg/kg PO daily. Prednisone (1 mg/kg/day) may be useful to alleviate pruritus. Lomustine at 50 mg/m2 PO q21–30 days may be effective (White 2005c)

g) For systemic histiocytosis: lomustine at 70 mg/m2 PO every 3 weeks; cyclosporine 5–10 mg/kg once daily (q24h); prednisone 2 mg/kg PO q12–24h. (Hillier 2006d)

h) For canine cutaneous epitheliotropic lymphoma (ELSA): 60 mg/m2 PO every three weeks. Authors concluded that lomustine seemed to be safe and well tolerated. Response duration was short, but high response rate supports incorporating lomustine into protocols to treat ELSA. Additional prospective investigations are warranted. (Risbon, de Lorimeir et al. 2006)

i) For brain tumors: Initially, 60 mg/m2 PO; if toxicity is minimal the dosage is increased slowly to 80 mg/m^2. Treatments given every 5–8 weeks. CBC done every week between treatments. (Fulton 1991)

■ **CATS:**

For the treatment of neoplasms:

a) 60 mg/m2 PO q6 weeks (Brewer 2003)

b) 60 mg/m2 PO q6 weeks or 10 mg (total dose) PO every three weeks. (Kitchell 2005)

Monitoring

- CBC with platelets one week after dosing and prior to next dose; If platelets less than 200,000/mcl; stop therapy until thrombocytopenia is resolved
- Liver function tests; initially before starting treatment and then every 3–4 months

Chemistry/Synonyms

A nitrosourea derivative alkylating agent, lomustine occurs as a yellow powder that is practically insoluble in water and soluble in alcohol.

Lomustine may also be known as: CCNU, lomustinum, NSC-79037, RB-1509, WR-139017, *Belustine®*, *CCNU®*, *Cecenu®*, *CeeNu®*, *CiNU®*, *Citosta®*, *Lomeblastin®*, *Lucostin®*, *Lucostine®*, and *Prava®*.

Storage/Stability

Store capsules in well-closed containers at room temperature. Expiration dates of two years are assigned after manufacture.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Lomustine Capsules: 10 mg, 40 mg & 100 mg with mannitol; Dose Pack (two 100 mg capsules, two 40 mg capsules and two 10 mg capsules); *CeeNu®* (Bristol Labs Oncology); (Rx)

LOPERAMIDE HCL

(loe-*per*-a-mide) Imodium®

OPIATE ANTIDIARRHEAL

Prescriber Highlights

- Synthetic opiate GI motility modifier
- Contraindications: Known hypersensitivity to narcotic analgesics, diarrhea caused by a toxic ingestion until the toxin is eliminated from the GI tract
- Caution: Respiratory disease, hepatic encephalopathy, hypothyroidism, severe renal insufficiency, adrenocortical insufficiency (Addison's), head injuries, or increased intracranial pressure, & acute abdominal conditions (*e.g.*, colic), & in geriatric or severely debilitated patients; use loperamide cautiously in Collie-type breeds
- Adverse Effects: DOGS: Constipation, bloat, & sedation. Potential for: paralytic ileus, toxic megacolon, pancreatitis, & CNS effects. CATS: Use is controversial, may exhibit excitatory behavior.
- Dose carefully in small, small animals

Uses/Indications

Loperamide is used as a GI motility modifier in small animals. Use in cats is controversial and many clinicians do not recommend using in cats.

Pharmacology/Actions

Among their other actions, opiates inhibit GI motility and excessive GI propulsion. They also decrease intestinal secretion induced by cholera toxin, prostaglandin E_2 and diarrheas caused by factors in which calcium is the second messenger (non-cyclic AMP/GMP mediated). Opiates may also enhance mucosal absorption.

Pharmacokinetics

In dogs, loperamide reportedly has a faster onset of action and longer duration of action than diphenoxylate, but clinical studies confirming this appear to be lacking. In humans, loperamide's half-life is about 11 hours. It is unknown if the drug enters milk or crosses the placenta.

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.

Opiate antidiarrheals should be used with caution in patients with head injuries or increased intracranial pressure and acute abdominal conditions (*e.g.*, colic), as it may obscure the diagnosis or clinical course of these conditions. It should be used with extreme caution in patients suffering from respiratory disease or from acute respiratory dysfunction (*e.g.*, pulmonary edema secondary to smoke inhalation). Opiate antidiarrheals should be used with ex-

treme caution in patients with hepatic disease with CNS clinical signs of hepatic encephalopathy. Hepatic coma may result.

Many clinicians recommend not using diphenoxylate or loperamide in dogs weighing less than 10 kg, but this is probably a result of the potency of the tablet or capsule forms of the drugs. Dosage titration using the liquid forms of these agents should allow their safe use in dogs when indicated. Because loperamide is potentially a neurotoxic substrate of P-glycoprotein, it should be used with caution in those herding breeds (*e.g.*, Collies, Shelties, Australian shepherds, etc.) that may have the gene mutation that causes a nonfunctional protein.

Adverse Effects

In dogs, constipation, bloat, and sedation are the most likely adverse reactions encountered when usual doses are used. Potentially, paralytic ileus, toxic megacolon, pancreatitis, and CNS effects could be seen.

Use of antidiarrheal opiates in cats is controversial; this species may react with excitatory behavior.

Reproductive/Nursing Safety

In humans, the FDA categorizes loperamide 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.*)

It is not known whether loperamide is excreted in maternal milk. Safety during nursing has not been established.

Overdosage/Acute Toxicity

In dogs, doses of 1.25 to 5 mg/kg/day produced vomiting, depression, severe salivation, and weight loss. Breeds with a defective MDR-1 gene are more sensitive to CNS depression with loperamide than other breeds.

There were 903 exposures to loperamide reported to the ASPCA Animal Poison Control Center (APCC; www.apcc.aspca.org) during 2000–2006. In these cases 862 were dogs with 395 showing clinical signs and 33 cats with 11 showing clinical signs. The remaining cases were 3 rodents, 4 birds and 1 rabbit, none of which showed clinical signs. Common findings in dogs recorded in decreasing frequency included vomiting, lethargy, diarrhea, depression, hypersalivation, hypothermia, bradycardia and anorexia. Common findings in cats recorded in decreasing frequency included diarrhea, vomiting, anorexia, hypersalivation and vocalization.

Treatment should follow standard decontamination protocols. Naloxone may be used to treat severe effects; higher than usual doses may be required.

Drug Interactions

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

- **AMIODARONE**: By inhibiting P-gp may increase loperamide plasma concentrations
- **CARVEDILOL**: By inhibiting P-gp may increase loperamide plasma concentrations
- **ERYTHROMYCIN**: By inhibiting P-gp may increase loperamide plasma concentrations
- **KETOCONAZOLE, ITRACONAZOLE**: By inhibiting P-gp may increase loperamide plasma concentrations
- **QUINIDINE**: By inhibiting P-gp may increase loperamide plasma concentrations
- **TAMOXIFEN**: By inhibiting P-gp may increase loperamide plasma concentrations
- **VERAPAMIL**: By inhibiting P-gp may increase loperamide plasma concentrations

Laboratory Considerations

- Plasma **amylase** and **lipase** values may be increased for up to 24 hours following administration of opiates.

Doses

- **DOGS:**

  As an antidiarrheal:

  Note: Collies and related breeds may be overly sensitive to loperamide

  a) 0.08 mg/kg, PO three times daily (DeNovo 1988), (Washabau 2004)
  b) 0.1–0.2 mg/kg PO q8–12h (Willard 2003a)
  c) 0.1 mg/kg PO three times a day; probably should not be given longer than 5 days and is potentially contraindicated when diarrhea is suspected to be caused by enteric infections (Hall and Simpson 2000)
  d) 0.1–0.2 mg/kg PO q8h (Jergens 1995)
  e) 0.08 mg/kg PO 3–4 times a day (Cote 2000)
  f) 0.1–0.2 mg/kg PO q6–12h (Leib 2004b)

- **CATS:**

  Note: Use of antidiarrheal opiates in cats is controversial; this species may react with excitatory behavior.

  a) For Diarrhea: Using the suspension 0.04–0.06 mg/kg PO twice daily (Tams 1999)
  b) 0.08–0.16 mg/kg PO q12h (Willard 2003a)

- **RABBITS, RODENTS, SMALL MAMMALS:**

  a) Rabbits: 0.1 mg/kg in 1 mL of water PO q8h for 3 days, then once daily for 2 days (Ivey and Morrisey 2000)
  b) Mice, Rats, Gerbils, Hamsters, Guinea pigs, Chinchillas: 0.1 mg/kg PO q8h for 3 days, then once daily for 2 days; give in 1 mL of water (Adamcak and Otten 2000)

Monitoring

- Clinical efficacy
- Fluid and electrolyte status in severe diarrhea
- CNS effects if using high dosages

Client Information

- If diarrhea persists or if animal appears listless or develops a high fever, contact veterinarian.

Chemistry/Synonyms

A synthetic piperidine-derivative antidiarrheal, loperamide occurs as a white to faintly yellow powder with a pK_a of 8.6 that is soluble in alcohol and slightly soluble in water.

Loperamide may also be known as PJ 185, or R 18553; a common trade name is *Imodium®*.

Storage/Stability/Compatibility

Loperamide capsules or oral solution should be stored at room temperature in well-closed containers. It is recommended that the oral solution not be diluted with other solvents.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Loperamide HCl Oral Liquid: 1 mg/5 mL (0.2 mg/mL), 1 mg/7.5 mL and 1 mg/mL in 60 mL, 90 mL, 118 mL and 120 mL; *Imodium® A-D* (McNeil-CPC); *Pepto® Diarrhea Control* (Procter and Gamble); generic; (OTC)

Loperamide HCl Capsules and Tablets: 2 mg; *Imodium® A-D Caplets* (McNeil-CPC); *Neo-Diaral®* (Roberts); *K-Pek II®* (Rugby); generic; (OTC & Rx)

LORAZEPAM

(lor-*ayz*-eh-pam) Ativan®

BENZODIAZEPINE

Prescriber Highlights

- Benzodiazepine that can be useful as an anxiolytic in dogs & cats & as an alternative to diazepam for treating status epilepticus
- Can be administered intranasally or IV for status epilepticus
- Adverse Effects (most likely): Increased appetite, activity or behavior changes (lethargy/somnolence to hyperexcitability/aggression)

Uses/Indications

Lorazepam may be useful in treating status epilepticus in dogs and the adjunctive treatment of behavior disorders (fears, phobias, anxiety) in dogs and cats. Although, in veterinary medicine, when compared with diazepam, there is much less experience using lorazepam, it has some advantages. Lorazepam is not metabolized by the liver into active metabolites, appears as effective as diazepam, may have longer anticonvulsant duration of action (not proven in dogs), and can be easier to administer (intranasal, IM, sublingual/buccal).

In human medicine, lorazepam is now frequently used in place of diazepam for treating status epilepticus and anxiolytic indications. It is also used for treating cancer chemotherapy-induced nausea and emesis, alcohol withdrawal, and akathisia secondary to antipsychotic medications.

Pharmacology/Actions

Lorazepam and other benzodiazepines depress the subcortical levels (primarily limbic, thalamic, and hypothalamic) of the CNS thus producing anxiolytic, sedative, skeletal muscle relaxant, and anticonvulsant effects. The exact mechanism of action is unknown, but postulated mechanisms include: antagonism of serotonin, increased release of and/or facilitation of gamma-aminobutyric acid (GABA) activity, and diminished release or turnover of acetylcholine in the CNS. Benzodiazepine specific receptors have been located in the mammalian brain, kidney, liver, lung, and heart. Receptors are lacking in the white matter In all species studied.

Pharmacokinetics

In dogs, intravenous administration of 0.2 mg/kg gave peak levels of about 165 ng/mL and remained above 30 ng/mL (considered necessary for anticonvulsant activity in humans) for 60 minutes. After intranasal administration of 0.2 mg/kg to dogs (Mariani, Clemmons et al. 2003), peak levels of about 106 ng/mL were achieved; in 3/6 dogs studied, levels stayed above 30 ng/mL for 60 minutes. Levels reached 30 ng/mL between 3–9 minutes after intranasal administration. While elimination half-life has been reported as approximately 1 hour in dogs, concentrations in the brain may persist longer than in the serum as lorazepam has a high affinity for benzodiazepine receptors in the CNS. Rectal administration of lorazepam in dogs does not appear to yield serum concentrations high enough for efficacious treatment of status epilepticus due to a high first-pass effect. Lorazepam is converted into glucuronide forms in the liver in most species. These metabolites are not active. Primary elimination route is via the urine in dogs. In cats, elimination is approximately 50% in the urine (primarily as the glucuronide) and 50% in the feces.

In humans, absolute bioavailability is about 90% after oral administration and, unlike diazepam, it is relatively rapidly and completely absorbed after IM dosing. Sublingual administration has similar bioavailability as oral dosing, but serum levels peak sooner. Elimination half-life appears to be much longer in humans (12 hours) than in dogs (≈1 hour).

Contraindications/Precautions/Warnings

Lorazepam is contraindicated in patients known to be hypersensitive to benzodiazepines, or with severe respiratory insufficiency unless being mechanically ventilated.

When using for negative behaviors, withdraw the drug gradually or a rebound effect may occur. Physical dependency has been induced in dogs. If long-term regular usage has occurred, withdraw the drug gradually.

Injectable lorazepam must not be given intra-arterially; arteriospasm may occur resulting in necrosis.

Adverse Effects

In small animals, benzodiazepines can cause increased appetite, aggression, increased activity/excitement, and vocalization. With initiation of therapy, dosage increases, or at higher dosages, ataxia, somnolence and lethargy can occur.

Reproductive/Nursing Safety

For humans, lorazepam is designated by the FDA as category ***D*** for use during pregnancy *(There is evidence of human fetal risk, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.)* However, studies in animals generally suggest that the drug is relatively safe for use during pregnancy at usual dosages. Except in one study in mice that were given approximately 400X the human dose producing offspring with an increased rate of cleft palate formation, animal studies have not shown significant increased rates of teratogenicity. If high doses are used just prior to delivery, "floppy infant" syndrome has been seen in humans.

Small amounts of lorazepam are distributed into milk, but it should be safe to use during nursing.

Overdosage/Acute Toxicity

Overdoses of lorazepam are generally limited to CNS depression (confusion, lethargy, somnolence, decreased reflexes, etc.). Very large overdoses can cause ataxia, hypotension, coma, and death (very rare).

Treatment of acute orally-ingested toxicity consists of standard protocols for removing and/or binding the drug in the gut and supportive systemic measures. In patients with normal renal function, forced diuresis with intravenous fluids/electrolytes and mannitol may enhance excretion of lorazepam. The use of analeptic agents (CNS stimulants such as caffeine) is generally not recommended. Flumazenil may be considered for adjunctive treatment of serious