Drug Interactions

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

- **ANTACIDS/DAIRY PRODUCTS:** Containing cations (Mg^{++}, Al^{+++}, Ca^{++}) may bind to marbofloxacin and prevent its absorption; separate doses of these products by at least 2 hours
- **ANTIBIOTICS, OTHER** (**aminoglycosides, 3rd-generation cephalosporins, penicillins—extended-spectrum**): Synergism may occur, but is not predictable, against some bacteria (particularly *Pseudomonas aeruginosa*) with these compounds. Although marbofloxacin has minimal activity against anaerobes, *in vitro* synergy has been reported when used with **clindamycin** against strains of Peptostreptococcus, Lactobacillus and *Bacteroides fragilis*.
- **CYCLOSPORINE:** Fluoroquinolones may exacerbate the nephrotoxicity and reduce the metabolism of cyclosporine (used systemically)
- **FLUNIXIN:** Has been shown in dogs to increase the AUC and elimination half-life of enrofloxacin and enrofloxacin increases the AUC and elimination half-life of flunixin; it is unknown if marbofloxacin also causes this effect or if other NSAIDs interact with marbofloxacin in dogs
- **GLYBURIDE:** Severe hypoglycemia possible
- **IRON, ZINC** (**oral**): Decreased marbofloxacin absorption; separate doses by at least two hours
- **METHOTREXATE:** Increased MTX levels possible with resultant toxicity
- **NITROFURANTOIN:** May antagonize the antimicrobial activity of the fluoroquinolones and their concomitant use is not recommended
- **PHENYTOIN:** Marbofloxacin may alter phenytoin levels
- **PROBENECID:** Blocks tubular secretion of ciprofloxacin and may also increase the blood level and half-life of marbofloxacin
- **SUCRALFATE:** May inhibit absorption of marbofloxacin; separate doses of these drugs by at least 2 hours
- **THEOPHYLLINE:** Marbofloxacin may increase theophylline blood levels
- **WARFARIN:** Potential for increased warfarin effects

Laboratory Considerations

- In some human patients, the fluoroquinolones have caused increases in liver enzymes, BUN, and creatinine and decreases in hematocrit. The clinical relevance of these mild changes is not known at this time.

Doses

- **DOGS & CATS:**
  a) For susceptible infections (urinary tract, skin and soft tissue): 2.75–5.5 mg/kg PO once daily. Give for 2–3 days beyond cessation of clinical signs (skin/soft tissue infections); and for at least 10 days (urinary tract). If no improvement noted after 5 days, reevaluate diagnosis. Maximum duration of treatment is 30 days. (Package insert; *Zeniquin*®—Pfizer)

Monitoring

- Clinical efficacy
- Adverse effects

Client Information

- Give as the veterinarian prescribes; do not stop treating just because the animal appears well.

Chemistry/Synonyms

A synthetic fluoroquinolone antibiotic, marbofloxacin is soluble in water, but solubility decreases as pH increases.

Marbofloxacin may also be known as Ro 9-1168, *Marbocyl*®, or *Zeniquin*®.

Storage/Stability

Marbofloxacin tablets should be stored below 30°C.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Marbofloxacin Oral Tablets: 25 mg, 50 mg, 100 mg, 200 mg; *Zeniquin*® (Pfizer); (Rx). Approved for use in dogs and cats. Must not be used in food animals.

HUMAN-LABELED PRODUCTS: None

MAROPITANT CITRATE

(mar-***oh***-pit-ent) Cerenia®

NEUROKININ (NK_1) RECEPTOR ANTAGONIST ANTIEMETIC

Prescriber Highlights

- Veterinary approved antiemetic for use in dogs 16 weeks of age & older; also used extra-label in cats
- Acts at the emetic center; therefore effective for emesis mediated via either peripheral or central mechanisms
- Subcutaneous injection is approved for the prevention & treatment of acute vomiting;
- Oral form is approved for the prevention of acute vomiting & the prevention of vomiting due to motion sickness; different oral dosages for each indication
- Oral dose is higher than subcutaneous dose due to decreased bioavailability of the oral tablet

Monograph by Dinah Jordan, PharmD, DICVP

Uses/Indications

Maropitant citrate injectable solution is indicated for the prevention and treatment of acute vomiting in dogs; maropitant citrate tablets are indicated for the prevention of acute vomiting and the prevention of vomiting due to motion sickness in dogs. Both are also used extra-label in cats.

Pharmacology/Actions

Maropitant is a neurokinin-1 (NK_1) receptor antagonist, which acts in the central nervous system by inhibiting Substance P, the key neurotransmitter involved in vomiting. Maropitant suppresses both peripheral & centrally mediated emesis.

Pharmacokinetics

In dogs, maropitant is rapidly absorbed after oral (PO) & subcutaneous (SC) administration. Peak plasma concentrations (Tmax) occur in less than 1 hour following 1 mg/kg subcutaneous administration and less than 2 hours after oral administration of 2 or 8 mg/kg. After oral administration bioavailability is 24% (2 mg/kg) and 37% (8 mg/kg), suggesting first pass metabolism which becomes saturated at the higher dose. Feeding status does not affect bioavailability.

Maropitant follows non-linear pharmacokinetics (PK) at oral therapeutic doses but approximately linear PK at higher doses (20–50 mg/kg). Bioavailability is 91% following subcutaneous administration of 1 mg/kg. An accumulation ratio of 1.5 occurs after once daily use of maropitant for 5 consecutive days at 1 mg/kg SC or 2 mg/kg PO. Accumulation ratio is 2.18 after 2 consecutive days at 8 mg/kg PO daily.

Hepatic metabolism of maropitant involves two cytochrome P450 enzymes: CYP2D15 (low capacity, high affinity) and CYP 3A12 (high capacity, low affinity). The non-linear kinetics at oral doses of 2–16 mg/kg may be due to saturation of the low capacity enzyme and increased involvement of CYP3A12 at higher doses. Twenty-one metabolites have been identified with the major (pharmacologically active) metabolite being CJ-18,518, a product of hydroxylation. Plasma protein binding of maropitant is high (99.5%). Half-life is 8.84 hours (range: 6.07–17.7 hrs) for 1 mg/kg SC; 4.03 hours (range: 2.58–7.09 hrs) for 2 mg/kg. Maropitant is eliminated primarily by the liver. Urinary recovery of maropitant and its major metabolite is minimal (<1%). Large inter-patient pharmacokinetic variations have been observed.

No information on the pharmacokinetics of maropitant in cats was located.

Contraindications/Precautions/Warnings

Use with caution in dogs with hepatic dysfunction.

Use with caution with other medications that are highly protein bound, although clinical significance has not been determined.

Adverse Effects

Maropitant is well tolerated in dogs. Pre-travel vomiting and hypersalivation are the two most common side effects seen after administration of the tablets at the higher dosage required for prevention of motion sickness. Swelling or pain at the injection site has been reported following SC administration of the drug. Diarrhea (4–8%) & anorexia (1.5–5.2%) were the most common side effects noted during U.S. field studies.

Reproductive/Nursing Safety

The safe use of maropitant has not been evaluated in dogs used for breeding, pregnant or lactating bitches. Maropitant should only be used in pregnant or lactating bitches following a benefit/risk assessment by the veterinarian.

Overdosage/Acute Toxicity

Single dose toxicity was studied in mice and rats after oral and intravenous administration. No adverse events were reported after oral administration of up to 30 mg/kg (mice) and 100 mg/kg (rats) and after IV administration of 6.5 mg/kg (mice) and 2.5 mg/kg (rats). The clinical signs of overdosage in mice and rats were similar and independent from the route of administration and included decreased activity, irregular or labored respiration, ataxia and tremors. Salivation, nasal discharge and "raspy" breathing were also noted in rats after oral dosing, while the excretion of reddish urine was observed in some mice and rats following intravenous administration.

In dogs, tolerance has been confirmed in doses of up to 3 times the recommended oral dose of 8 mg/kg, for 3 times longer than the proposed maximum duration of treatment. A GLP compliant study revealed no adverse events in dogs after repeated oral doses delivered by oral gavage (5 mg/kg PO q 24h x 93 days). In the same study at 20 mg/kg/day, effects included emesis in two females on day 1, body weights losses of 8–15% when compared to those at start of study, ECG changes (slight increases in P-R interval, P wave duration and QRS amplitude were noted over the course of treatment), slightly lower serum albumin and slightly higher adrenal weights (females) at 20 mg/kg/day in both sexes.

Oral toxicokinetic studies with the primary metabolite were conducted in mice, rats, rabbits and dogs, indicating that the metabolite was well tolerated.

Drug Interactions

At the time of writing, no specific drug interactions have been identified. During field safety and efficacy studies, a number of medications were used concomitantly with maropitant. Many dogs received multiple medications. The most common concomitant medication was metronidazole. Other commonly used concomitant medications included: dextrose/Ringers solution IV, sodium chloride IV, amoxicillin, ampicillin, cefazolin, cephalexin, enrofloxacin, sulfamethoxazole/trimethoprim, famotidine, sucralfate, cimetidine, dexamethasone, ivermectin, ivermectin/pyrantel, pyrantel, lufenuron/milbemycin, milbemycin, moxidectin, vitamin B, and vaccines. There were no problems observed with any of these drugs in conjunction with maropitant.

Laboratory Considerations

No specific concerns noted.

Doses

- **DOGS:**

(**Note:** The following dosages have also been used extra-label in cats—Jordan)

Prevention of acute vomiting:

1 mg/kg SC given at least one hour prior to anticipated emetogenic event and q24h thereafter for up to 5 consecutive days.

2 mg/kg PO given at least two hours prior to anticipated emetogenic event and q24h thereafter for up to 5 consecutive days.

Treatment of acute vomiting:

1 mg/kg SC q24h for up to 5 consecutive days.

Note: If a longer duration of therapy is needed, a 48 hour washout period is recommended due to accumulation of the drug.

Prevention of vomiting due to motion sickness:

8 mg/kg (minimum dose) PO given at least two hours prior to travel and q24h for up to 2 consecutive days;

Note: If a longer duration of therapy is needed, a 72 hour washout period is recommended.

(Label Information; *Cerenia*®—Pfizer)

Monitoring

- Clinical efficacy measured by decreased episodes of vomiting
- Adverse effects

Client Information

- Tablets should not be tightly wrapped or embedded in food/snacks as this may delay dissolution of tablets
- Avoid prolonged fasting before administration of tablets
- Feeding a small meal or snack one hour before administration of tablets for motion sickness will minimize the occurrence of pre-trip vomiting following administration of tablets

Chemistry/Synonyms

Classified as a substituted quinuclidine, maropitant's molecular weight is 678.81. The chemical name is (2S,3S)-2-benzhydryl-N-(5-tert-butyl-2-methoxybenzyl) quinuclidin-3-amine citrate.

Maropitant may also be known as CJ-11,972.

Storage/Stability

Maropitant injectable solution contains a preservative and is designed for multi-dose use. The vial should be stored at controlled room temperature 20–25°C (68–77°F) with excursions permitted between 15–30°C (59–86°F). The product label states the drug should be used within 28 days of first vial puncture in accordance with FDA requirements. Although the product may be chemically stable beyond this time, multiple punctures may lead to contamination of the product; therefore, extended use beyond the labeled discard date is discouraged.

Maropitant tablets are packaged in foil to protect them from moisture uptake, which was observed in less-protective packaging. A European stability study indicated that tablets removed from the blister pack and halved showed no loss of potency during the 48 hour testing period.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS:

Maropitant Citrate Injectable Solution: 10 mg/mL in 20 mL multi-dose vials; *Cerenia*® (Pfizer); (Rx). Labeled for use in dogs.

Maropitant Citrate Oral Tablets: 16, 24, 60, and 160 mg in blister packs (4 tablets per pack; carton of 10); Tablets are peach-colored and scored with the tablet strength and MPT imprinted on one side and the Pfizer logo imprinted on the other side; *Cerenia*® (Pfizer); (Rx). Labeled for use in dogs.

HUMAN-LABELED PRODUCTS: None

MECHLORETHAMINE HCL

(me-klor-***eth***-a-meen) Mustargen®

ANTINEOPLASTIC

Prescriber Highlights

- Antineoplastic for lymphoreticular neoplasms or pleural & peritoneal effusions (intracavitary)
- Contraindications (relative; risk vs. benefit): Anemia, bone marrow depression, tumor cell infiltration into bone marrow, current infection, sensitivity to mechlorethamine, or patients who have received previous chemotherapy or radiotherapy
- Adverse Effects: Bone marrow depression, GI effects (vomiting, nausea), ototoxicity (high dosages or regional perfusions); Potentially: alopecia, hyperuricemia, hepatotoxicity, peripheral neuropathy, & GI ulcers
- Teratogen
- Avoid extravasation

Uses/Indications

In small animals, mechlorethamine may be useful for the adjunctive treatment of lymphoreticular neoplasms or, with intracavitary administration, for treating pleural and peritoneal effusions. A change in owners of the pharmaceutical product has reportedly resulted in very large price increases for this medication and some veterinary oncologists are substituting dactinomycin for the mechlorethamine in MOPP rescue protocols.

Pharmacology/Actions

Mechlorethamine is an alkylating agent, thereby interfering with DNA replication, RNA transcription, and protein synthesis. It is cell cycle-phase nonspecific.

With intracavitary administration, mechlorethamine causes sclerosing and an inflammatory response on serous membranes, thereby causing adherence of serosal surfaces.

Pharmacokinetics

Because mechlorethamine is so irritating to tissues it must be given IV for systemic use. It is incompletely absorbed after intracavitary administration. After injection, mechlorethamine is rapidly (within minutes) inactivated.

Contraindications/Precautions/Warnings

Mechlorethamine is contraindicated in patients with a known infection or have had a prior anaphylactic reaction to the drug.

Mechlorethamine should be used only when its potential benefits outweigh its risks with the following conditions: anemia, bone marrow depression, tumor cell infiltration into bone marrow, sensitivity to mechlorethamine, or patients who have received previous chemotherapy or radiotherapy.

Adverse Effects

Bone marrow depression (leukopenia, thrombocytopenia) and GI effects (vomiting, nausea) are quite common and can be serious enough to halt therapy. Ototoxicity may occur with either high dosages or regional perfusions. Other potential effects include alopecia, hyperuricemia, hepatotoxicity, peripheral neuropathy, and GI ulcers.

Because severe tissue sloughing may occur, avoid extravasation.

Reproductive/Nursing Safety

Mechlorethamine is a teratogen in lab animals. Use only during pregnancy when the benefits to the mother outweigh the risks to the offspring. Mechlorethamine can suppress gonadal function. In humans, the FDA categorizes this drug 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.*)

While it is not known whether mechlorethamine enters maternal milk, nursing puppies or kittens should receive milk replacer when the dam is receiving mechlorethamine.

Overdosage/Acute Toxicity

Because of the toxic potential of this agent, overdoses must be avoided. Determine dosages carefully.

Drug Interactions

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

- **IMMUNOSUPPRESSANT DRUGS** (*e.g.*, **azathioprine**, **cyclophosphamide**, **corticosteroids**): Use with other immunosuppressant drugs may increase the risk of infection.
- **MYELOSUPPRESSIVE DRUGS** (*e.g.*, **chloramphenicol**, **flucytosine**, **amphotericin B**, or **colchicine**): Use extreme caution when used concurrently with other drugs that are also myelosuppressive, including many of the other antineoplastics and other bone marrow depressant drugs. Bone marrow depression may be additive.
- **VACCINES, LIVE:** Live virus vaccines should be used with caution, if at all, during therapy.