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:

Methohexital Sodium Powder for Injection: 2.5 g in 20mL vials; *Brevital® Sodium* (Monarch); (Rx, C-IV)

METHOTREXATE
METHOTREXATE SODIUM

(meth-oh-***trex***-ate) MTX, Amethopterin

ANTINEOPLASTIC, IMMUNOSUPPRESSIVE

Prescriber Highlights

- Antineoplastic/immunosuppressant used primarily for lymphomas & some solid tumors in dogs & cats
- Contraindications: Preexisting bone marrow depression, severe hepatic or renal insufficiency, or hypersensitivity to the drug
- Caution: If patient susceptible or has preexisting clinical signs associated with the adverse reactions associated with this drug (see below)
- Adverse Effects: GI (diarrhea, nausea, & vomiting); Higher dosage: listlessness, GI toxicity (ulcers, mucosal sloughing, stomatitis), hematopoietic toxicity (nadir at 4–6 days), hepatopathy, renal tubular necrosis, alopecia, depigmentation, pulmonary infiltrates & fibrosis; anaphylaxis (rare)
- Avoid human exposure
- Teratogenic; may affect spermatogenesis
- Determine dosages accurately
- Drug interactions

Uses/Indications

Indicated for lymphomas and some solid tumors in dogs and cats (see the Doses section and the recommended treatment protocol references at the end of this section). In human medicine, methotrexate is also being used to treat refractory rheumatoid arthritis and severe psoriasis.

Pharmacology/Actions

An S-phase specific antimetabolite antineoplastic agent, methotrexate competitively inhibits folic acid reductase, preventing the reduction of dihydrofolate to tetrahydrofolate and affecting production of purines and pyrimidines. Rapidly proliferating cells (*e.g.*, neoplasms, bone marrow, GI tract epithelium, fetal cells, etc.) are most sensitive to the drug's effects.

Dihydrofolate reductase has a much greater affinity for methotrexate than either folic acid or dihydrofolic acid and coadministration of folic acid will not reduce methotrexate's effects. Leucovorin calcium, a derivative of tetrahydrofolic acid, can block the effects of methotrexate.

Methotrexate also has immunosuppressive activity, possibly due to its effects on lymphocyte replication. Tumor cells have been noted to develop resistance to methotrexate that may be due to decreased cellular uptake of the drug.

Pharmacokinetics

Methotrexate is well absorbed from the GI tract after oral administration of dosages <30 mg/m2 with a bioavailability of about 60%. In humans, peak levels occur within 4 hours after oral dosing, and between 30 minutes and 2 hours after IM injection.

Methotrexate is widely distributed in the body and is actively transported across cell membranes. Highest concentrations are found in the kidneys, spleen, gallbladder, liver, and skin. When given orally or parenterally, methotrexate does not reach therapeutic levels in the CSF. When given intrathecally, methotrexate attains therapeutic levels in the CSF and also passes into the systemic circulation. Methotrexate is about 50% bound to plasma proteins and crosses the placenta.

Methotrexate is excreted almost entirely by the kidneys via both glomerular filtration and active transport. Serum half-life is less than 10 hours and generally between 2–4 hours.

Contraindications/Precautions/Warnings

Methotrexate is contraindicated in patients with preexisting bone marrow depression, severe hepatic or renal insufficiency, or hypersensitivity to the drug. It should be used with caution in patients who are susceptible to, or have preexisting clinical signs associated with, the adverse reactions associated with this drug.

When administering MTX, either wear gloves or immediately wash hands after handling. Gloves are particularly important if handling split, broken, or crushed tablets. Preparation of intravenous solutions should ideally be performed in a vertical laminar flow hood.

Adverse Effects

In dogs and cats, gastrointestinal side effects are most prevalent with diarrhea, nausea, inappetance (especially cats) and vomiting (especially dogs) seen. Higher dosages may lead to listlessness, GI toxicity (ulcers, mucosal sloughing, stomatitis), hematopoietic toxicity (nadir at 4–6 days), hepatopathy, renal tubular necrosis, alopecia, depigmentation, pulmonary infiltrates, and fibrosis. CNS toxicity (encephalopathy) may be noted if methotrexate is given intrathecally. Rarely, anaphylaxis may be seen.

Reproductive/Nursing Safety

Methotrexate is teratogenic, embryotoxic, and may affect spermatogenesis in male animals. In humans, the FDA categorizes this drug as category ***X*** for use during pregnancy (*Studies in animals or humans demonstrate fetal abnormalities or adverse reaction; reports indicate evidence of fetal risk. The risk of use in pregnant women clearly outweighs any possible benefit.*) In a separate system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as class: ***C*** (*These drugs may have potential risks. Studies in people or laboratory animals have uncovered risks, and these drugs should be used cautiously as a last resort when the benefit of therapy clearly outweighs the risks.*)

Methotrexate is contraindicated in nursing mothers. It is excreted in breast milk in low concentrations with a milk:plasma ratio of 0.08:1. Nursing offspring should be switched to milk replacer if the dam requires methotrexate.

Overdosage/Acute Toxicity

Acute overdosage in dogs is associated with exacerbations of the adverse effects outlined above, particularly myelosuppression and acute renal failure. Acute tubular necrosis is secondary to drug precipitation in the tubules. In dogs, the maximally tolerated dose is reported to be 0.12 mg/kg q24h for 5 days.

Treatment of acute oral overdoses include emptying the gut and preventing absorption using standard protocols if the ingestion is recent. Additionally, oral neomycin has been suggested to help pre-

vent absorption of MTX from the intestine. In order to minimize renal damage, forced alkaline diuresis should be considered. Urine pH should be maintained between 7.5–8 by the addition of 0.5–1 mEq/kg of sodium bicarbonate per 500 mL of IV fluid.

Leucovorin calcium is specific therapy for methotrexate overdoses. It should be given as soon as possible, preferably within the first hour and, definitely, within 48 hours. Doses of leucovorin required are dependent on the MTX serum concentration. Humans having serum concentrations greater than 5×10^{-7} M at 48 hours are likely to develop severe toxicity. Leucovorin in doses ranging from 25–200 mg/m2 every 6 hours doses is given until serum levels fall below 1×10^{-8} M. Dogs treated with leucovorin at 15 mg/m2 every 3 hours IV for 8 doses, then IM q6h for 8 doses were able to tolerate MTX doses as high as 3 g/m2 (O'Keefe and Harris 1990). Another dose of 3 mg/m2 for leucovorin in dogs has also been suggested (Coppoc 1988).

Drug Interactions

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

- **AMIODARONE:** Prolonged PO administration of amiodarone (>2 weeks) may inhibit MTX metabolism
- **ASPARAGINASE:** Asparaginase given concomitantly with MTX may decrease MTX efficacy
- **AZATHIOPRINE:** Potential for increased risk for hepatic toxicity
- **CHLORAMPHENICOL:** May displace MTX from plasma proteins increasing risk for toxicity, but also may reduce MTX absorption and enterohepatic recirculation
- **CISPLATIN:** May have synergistic action with MTX, but alter the renal elimination of MTX
- **CYCLOSPORINE:** May increase MTX levels
- **FOLIC ACID:** May reduce MTX efficacy, but folate deficiency increases MTX toxicity
- **NEOMYCIN (oral):** Oral neomycin may decrease the absorption of oral methotrexate if given concomitantly
- **NSAIDS, SALICYLATES:** In humans, severe hematologic and GI toxicity has resulted in patients receiving both MTX and non-steroidal antiinflammatory agents; use caution in dogs also on MTX
- **PENICILLINS:** May decrease MTX renal elimination
- **PROBENECID:** May inhibit the tubular secretion of MTX and increase its half-life
- **PYRIMETHAMINE:** Pyrimethamine, a similar folic acid antagonist, may increase MTX toxicity and should not be given to patients receiving MTX
- **RETINOIDS:** Potential for increased risk for hepatic toxicity
- **SULFASALAZINE:** Potential for increased risk for hepatic toxicity
- **SULFONAMIDES:** May displace MTX from plasma proteins increasing risk for toxicity
- **TETRACYCLINES:** May displace MTX from plasma proteins increasing risk for toxicity, but also may reduce MTX absorption and enterohepatic recirculation
- **THEOPHYLLINES:** MTX may reduce theophylline elimination
- **TRIMETHOPRIM/SULFA:** Rarely, may increase myelosuppression of MTX
- **VACCINES, LIVE:** Live virus vaccines should be used with caution, if at all during therapy

Laboratory Considerations

- Methotrexate may interfere with the microbiologic assay for **folic acid.**

Doses

Dosages of methotrexate sodium are expressed in terms of methotrexate as are the dosage forms. For more information on using MTX as part of chemotherapy protocols, refer to the protocols found in the appendix or other dosages/protocols found in numerous references, including: *Withrow and MacEwen's Small Animal Clinical Oncology, 4th Ed.* (Withrow and Vail 2007); *Canine and Feline Geriatric Oncology* (Villalobos 2007); *Small Animal Internal Medicine, 3rd Edition* (Nelson and Couto 2003); *Textbook of Veterinary Internal Medicine: Diseases of the Dog and Cat 6th Edition* (Ettinger and Feldman 2005); and *The 5-Minute Veterinary Consult Canine & Feline, 3rd Ed.* (Tilley and Smith 2004).

- **DOGS:**

  For susceptible neoplastic diseases (usually as part of a multidrug protocol):

  a) As part of the LMP protocol for maintenance of canine lymphoma: Chlorambucil 20 mg/m2 PO every 15 days; Methotrexate 2.5–5 mg/m2 PO twice a week; Prednisone 20 mg/m2 PO every other day. When Vincristine is added it is at a dose of 0.5–0.7 mg/m2 and is given every 15 days alternating weeks with the chlorambucil. (Berger 2005)

  b) 2.5 mg/m2 PO 2–3 times weekly; 0.3–0.8 mg/m2 IV every 7 days (O'Keefe and Harris 1990)

  c) "High dose therapy": 5–10 mg/m2 PO, IV, IM or intrathecally followed 2–4 hours later with leucovorin at 3 mg/m2

  "Normal dose therapy": 2.5 mg/m2 once daily. Adjust dosage/frequency according to toxicity (Thompson 1989a)

  d) For lymphoma (as part of protocol): 0.5 mg/kg IV (maximum dose 25 mg) on day 14 (Matus 1989)

  e) In combination with other antineoplastics (per protocol) 5 mg/m2 PO twice weekly or 0.8 mg/kg IV every 21 days; alternatively 2.5 mg/m2 PO daily (USPC 1990)

- **CATS:**

  For susceptible neoplastic diseases (usually as part of a multidrug protocol):

  a) 2.5 mg/m2 PO 2–3 times weekly; 0.3–0.8 mg/m2 IV every 7 days (O'Keefe and Harris 1990)

  b) For lymphoma (as part of protocol—see reference): 0.8 mg/kg IV on day 14 with 5 mg prednisone twice daily PO (Matus 1989)

  c) In combination with other antineoplastics (per protocol) 5 mg/m2 PO twice weekly (USPC 1990)

Monitoring

- Efficacy
- Toxicity:

  a) Monitor for clinical signs of GI irritation and ulceration

  b) Complete blood counts (with platelets) should be performed weekly early in therapy and eventually every 4–6 weeks when stabilized. If WBC is $<4000/mm^3$ or platelet count is $<100{,}000/mm^3$ therapy should be discontinued

  c) Baseline renal function tests. Continue to monitor if abnormal

  d) Baseline hepatic function tests. Monitor liver enzymes on a regular basis during therapy.

Client Information

- Clients must be briefed on the possibilities of severe toxicity developing from this drug, including drug-related mortality.
- Clients should contact the veterinarian if the patient exhibits clinical signs of profound depression, abnormal bleeding (including bloody diarrhea) and/or bruising.

- Wear gloves when administering tablets (particularly if crushed or split); if gloves are not used, wash hands thoroughly after handling tablets.

Chemistry/Synonyms

A folic acid antagonist, methotrexate is available commercially as the sodium salt. It occurs as a yellow powder that is soluble in water. Methotrexate sodium injection has a pH of 7.5–9.

Methotrexate and methotrexate sodium may also be known as: MTX, amethopterin, 4-Amino-4-deoxy-10-methylpteroyl-L-glutamic acid, 4-Amino-10-methylfolic acid, CL-14377, alpha-methopterin, methotrexatum, metotrexato, NSC-740, WR-19039; there are many trade names available.

Storage/Stability/Compatibility

Methotrexate sodium tablets should be stored at room temperature (15–30°C) in well-closed containers and protected from light. The injection and powder for injection should be stored at room temperature (15–30°C) and protected from light.

Methotrexate sodium is reportedly physically **compatible** with the following intravenous solutions and drugs: Amino acids 4.25%/dextrose 25%, D_5W, sodium bicarbonate 0.05 M, cephalothin sodium, cytarabine, 6-mercaptopurine sodium, sodium bicarbonate, and vincristine sulfate. In syringes, methotrexate is physically **compatible** with: bleomycin sulfate, cyclophosphamide, doxorubicin HCl, fluorouracil, furosemide, leucovorin calcium, mitomycin, vinblastine sulfate, and vincristine sulfate.

Methotrexate sodium **compatibility information conflicts** or is dependent on diluent or concentration factors with the following drugs or solutions: heparin sodium and metoclopramide HCl. Compatibility is dependent upon factors such as pH, concentration, temperature and diluent used; consult specialized references or a hospital pharmacist for more specific information.

Methotrexate sodium is reportedly physically **incompatible** when mixed with the following solutions or drugs: bleomycin sulfate (as an IV additive only; **compatible** in syringes and Y-lines), fluorouracil (as an IV additive only; **compatible** in syringes and Y-lines), prednisolone sodium phosphate, droperidol, and ranitidine HCl.

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:

Methotrexate Sodium Tablets (plain & scored): 2.5 mg, 5 mg, 7.5 mg, 10 mg and 15 mg; *Rheumatrex® Dose Pack* (STADA); *Trexal®* (Barr); generic; (Rx)

Methotrexate Sodium Injection: 25 mg/mL (as base) in 2 mL & 10 mL vials; preservative-free in 2 mL, 4 mL, 8 mL, 10 mL, 20 mL, and 40 mL single-use vials; *Methotrexate LPF® Sodium* (Xanodyne); generic; (Rx)

Methotrexate Powder for Injection, lyophilized: preservative free in 1 g in single-use vials; generic; (Rx)

METHOXYFLURANE

(meth-ox-ee-*floo*-rane) Penthrane®

INHALANT ANESTHETIC

Prescriber Highlights

- Infrequently used inhalant general anesthetic agent
- Contraindications: Preexisting renal or hepatic disease
- Caution (benefits vs. risks): Increased CSF or head injury, or myasthenia gravis.
- Adverse Effects: Potential nephrotoxicity
- Drug interactions

Uses/Indications

Methoxyflurane is an inhalant anesthetic, but it is rarely used today primarily due to its potential for causing nephrotoxicity, slow onset of action (a short-acting barbiturate is often used as an induction agent), and prolonged recovery time. However, it does produce some muscle relaxation and analgesia, even at relatively low concentrations and can be administered without a precision vaporizer as it will vaporize to a maximum of about 3%.

Pharmacology/Actions

While the precise mechanism that inhalant anesthetics exert their general anesthetic effects is not precisely known, they may interfere with functioning of nerve cells in the brain by acting at the lipid matrix of the membrane. Some key pharmacologic effects noted with methoxyflurane include: CNS depression, depression of body temperature regulating centers, increased cerebral blood flow, respiratory depression, hypotension, vasodilatation, and myocardial depression (less so than with halothane) and muscular relaxation.

Pharmacokinetics

Methoxyflurane is rapidly absorbed from the alveoli, but it has a comparatively slow onset of activity. It is rapidly distributed into the CNS and crosses the placenta. Approximately 35% of a dose is eliminated via the lungs and approximately 50% is metabolized in the liver; substantial amounts of inorganic fluoride are formed which are excreted by the kidneys.

Minimal Alveolar Concentration (MAC; %) in oxygen reported for methoxyflurane in various species: Dog = 0.23; Cat = 0.23; Horse = 0.22; Human = 0.16. Several factors may alter MAC (acid/base status, temperature, other CNS depressants on board, age, ongoing acute disease, etc.).

Contraindications/Precautions/Warnings

Methoxyflurane should be used cautiously, if at all, in patients with preexisting renal or hepatic disease. It should be used with caution (benefits vs. risks) in patients with increased CSF or head injury, or myasthenia gravis.

Adverse Effects

The most troublesome adverse effect associated with methoxyflurane is its potential for causing nephrotoxicity, particularly with prolonged procedures in patients predisposed to nephrotoxicity. Dogs with normal renal function are probably less susceptible to this effect than are humans, unless concomitantly receiving nephrotoxic agents (NSAIDs, etc.).