

MATERIAL SAFETY DATA SHEET



PREPARATION DATE: December 30, 2002

Replaces previous version dated November 4, 1997.

SECTION 1: Chemical Product and Company Identification

Common Name: (used on the label)
(Trade Name & Synonyms) ANZEMET[®] Injection
dolasetron mesylate, MDL73147EF
Chemical Name: (2 α , 6 α , 8 α , 9 $\alpha\beta$)-octahydro-3-oxo-2,6-methano-
2H-quinolizin-8-yl-1H-indole-3-carboxylate
monomethanesulfonate, monohydrate.
CAS Number: 115956-13-3
Molecular Formula: C₁₉H₂₀N₂O₃•CH₃SO₃H•H₂O
Molecular weight: 438.5

Manufacturer: Aventis Pharmaceuticals, Inc.
Address: Route 202-206
Bridgewater, NJ 08807-0800

Technical Information, M-F, 8 AM – 5 PM EST: (908) 231-4829
24-Hour Transport Emergency, US (Chemtrec): (800) 424-9300
24-Hour Transport Emergency, outside US (Chemtrec) : (703) 527-3887
24-Hour Emergency, Aventis: (908) 231-2666

SECTION 2: Composition/Information on Ingredients

Material: Dolasetron mesylate injection
% Weight: Each milliliter of ANZEMET Injection contains 20
mg of dolasetron mesylate
How supplied: ANZEMET Injection is supplied in single use
ampules and vials as a clear, colorless
solution.
12.5 mg strength: 0.625 mL single use ampules
(Box of 6)
100 mg/5 mL strength: 5 mL single use vial
Nature of Hazard: Pharmaceutical Product.

SECTION 3: Hazards Identification

Anzemet (dolesetron mesylate) is an anti-nauseant antiemetic agent. Dolasetron Mesylate is a highly specific and selective serotonin subtype 3 (5-HT₃) receptor antagonist both in vitro and in vivo.

ANZEMET Injection is indicated for:

- 1) the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin;
- 2) the prevention of postoperative nausea and vomiting. As with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be avoided postoperatively, ANZEMET Injection is recommended even where the incidence of postoperative nausea and/or vomiting is low.
- 3) the treatment of postoperative nausea and/or vomiting.

ANZEMET Tablets are contraindicated in patients known to have hypersensitivity to the drug.

WARNINGS: ANZEMET can cause ECG interval changes (PR, Q_tc, JT, prolongation and QRS widening). The changes are related in magnitude and frequency to blood levels of the active metabolite. These changes are self limiting with declining blood levels. Some patients have interval prolongations for 24 hours or longer. Interval prolongation could lead to cardiovascular consequences, including heart block or cardiac arrhythmias. These have rarely been reported.

PRECAUTIONS: Dolasetron should be administered with caution in patients who have or may develop prolongation of cardiac conduction intervals, particularly Q_tc. These include patients with hypokalemia or hypomagnesemia, patients taking diuretics with potential for inducing electrolyte abnormalities, patients with congenital QT syndrome, patients taking anti-arrhythmic drugs or other drugs which can lead to QT prolongation, and cumulative high dose anthracycline therapy.

Drug Interactions: The potential for clinically significant drug-drug interactions posed by dolasetron and hydrodolasetron appears to be low for drugs commonly used in chemotherapy or surgery, because hydrodolasetron is eliminated by multiple routes. ANZEMET has been safely coadministered with drugs used in chemotherapy and surgery. As with other agents which prolong ECG intervals, caution should be exercised in patients taking drugs which prolong ECG intervals, particularly Q_tc.

The recommended doses of ANZEMET Tablets should not be exceeded.

Preventing Cancer Chemotherapy-Induced Nausea and Vomiting

Adults: The recommended intravenous dosage of ANZEMET Injection from clinical trial results is 1.8 mg/kg given as a single dose approximately 30 minutes before chemotherapy.

Alternatively for most patients, a fixed dose of 100 mg can be administered over 30 seconds.

Pediatric Patients: The recommended intravenous dosage in pediatric patients 2 to 16 years of age is 1.8 mg/kg given as a single dose approximately 30 minutes before chemotherapy, up to a
SECTION 3: Hazards Identification continued. . . .

maximum of 100 mg. Safety and effectiveness in pediatric patients under 2 years of age have not been established. ANZEMET Injection mixed in apple or apple-grape juice may be used for oral dosing of pediatric patients. When ANZEMET Injection is administered orally, the recommended dosage in pediatric patients 2 to 16 years of age is 1.8 mg/kg up to a maximum 100 mg doses given within one hour of chemotherapy. The diluted product may be kept up to two hours at room temperature before use.

Use in the Elderly, Renal Failure Patients, or Hepatically Impaired Patients: No dosage adjustment is recommended.

Prevention or Treatment of Postoperative Nausea and/or Vomiting

Adults: The recommended intravenous dosage of ANZEMET Injection is 12.5 mg given as a single dose approximately 15 minutes before the cessation of anesthesia or as soon as nausea or vomiting presents.

Pediatric Patients: The recommended intravenous dosage in pediatric patients 2 to 16 years of age is 0.35 mg/kg, with a maximum dose of 12.5 mg, given as a single dose approximately 15 minutes before the cessation of anesthesia or as soon as nausea or vomiting presents. Safety and effectiveness in pediatric patients under 2 years of age have not been established.

ANZEMET Injection mixed in apple or apple-grape juice may be used for oral dosing of pediatric patients. When ANZEMET Injection is administered orally, the recommended dosage in pediatric patients 2 to 16 years of age is 1.2 mg/kg up to a maximum 100 mg doses given within two hours before surgery. The diluted product may be kept up to two hours at room temperature before use.

Use in the Elderly, Renal Failure Patients, or Hepatically Impaired Patients: No dosage adjustment is recommended.

SECTION 4: First Aid Measures

Eyes: Flush thoroughly with water for 15 minutes, seek medical attention.

Ingestion: If large amount is ingested, seek medical attention.

Overdosage: In situations where overdose is suspected, supportive care is indicated. There is no known specific antidote. Following a suspected overdose of ANZEMET Injection, a patient found to have second-degree or higher AV conduction block should undergo cardiac telemetry monitoring.

It is not known if dolasetron is removed by hemodialysis or peritoneal dialysis.

SECTION 5: Fire Fighting Measures

Extinguisher Media: Carbon Dioxide, Dry Chemical Powder, Alcohol or Polymer Foam. Water may be effective for cooling.

Special Fire Fighting Procedures: Wear self-contained breathing apparatus and protective clothing to prevent contact with the skin.

SECTION 6: Accidental Release Information

Steps to be taken in case material is released or spilled: Sweep into suitable container and seal.
Waste Disposal Methods: Dispose according to local, state and/or federal regulations.

SECTION 7: Handling and Storage

Store at controlled room temperature 20 - 25° C. Protect from light.

SECTION 8: Exposure Controls/Personal Protection

OSHA Permissible Exposure Limit: Not available.

ACGIH Threshold Limit Value: Not available.

Chemical listed as a carcinogen or potential carcinogen: No.

National Toxicology Program: No.

I.A.R.C. Monographs: No.

OSHA: No.

Dolasetron mesylate: Aventis 8-hour Occupational Exposure Limit 100 ug/m³.

SECTION 9: Physical and Chemical Properties

How Supplied: ANZEMET Injection is supplied in single use ampules and vials as a clear, colorless solution.

2.5 mg strength: 0.625 mL single use ampules
(Box of 6)

100 mg/5 mL strength: 5 mL single use vial

SECTION 10: Stability and Reactivity

After dilution ANZEMET Injection is stable under normal lighting conditions at room temperature for 24 hours or under refrigeration for 48 hours with the following compatible intravenous fluids: 0.9% sodium chloride injection, 5% dextrose injection, 5% dextrose and 0.45 % sodium chloride injection, 5% dextrose and Lactated Ringer's injection, Lactated "Ringer's injection, and 10% mannitol injection. Although ANZEMET Injection is chemically and physically stable when diluted as recommended, sterile precautions should be observed because SECTION 10: Stability and Reactivity continued. . . .

dilutents generally do not contain preservative. After dilution, do not use beyond 24 hours, or 48 hours if refrigerated.

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

SECTION 11: Toxicological Information

Single intravenous doses of dolasetron mesylate at 160 mg/kg in male mice and 140 mg/kg in female mice and rats of both sexes (6.3 to 12.6 times the recommended human dose based on body surface area) were lethal. Symptoms of acute toxicity were tremors, depression and convulsions.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In a 24 month carcinogenicity study, there was a statistically significant increase in the incidence of combined hepatocellular adenomas and carcinomas in male mice treated with 150 mg/kg/day and above.

In a 24 month rat carcinogenicity study, oral dolasetron mesylate was not tumorigenic at doses up to 150 mg/kg/day in male rats and 300 mg/kg/day in female rats.

Dolasetron mesylate was not genotoxic in the Ames test, the rat lymphocyte chromosomal aberration test, the Chinese hamster ovary cell forward mutation test, the rat hepatocyte unscheduled DNA synthesis test or the mouse micronucleus test.

Dolasetron mesylate was found to have no effect on fertility and reproductive performance at oral doses up to 100 mg/kg/day in female rats and up to 400 mg/kg/day in male rats.

Pregnancy: Teratogenic Effects. Pregnancy Category B.

Teratology studies have not revealed evidence of impaired fertility or harm to the fetus due to dolasetron mesylate. These studies have been performed in pregnant rats at oral doses up to 100

mg/kg/day and pregnant rabbits at oral doses up to 100 mg/kg/day. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether dolasetron mesylate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ANZEMET Tablets are administered to a nursing woman.

Pediatric Use

ANZEMET Tablets are expected to be as safe and effective as when ANZEMET Injection is given orally to pediatric patients. ANZEMET Tablets are recommended for children old enough to swallow tablets.

Elderly

Dosage adjustment is not needed in patients over 65. Effectiveness in prevention of nausea and vomiting in elderly patients was no different than in younger age groups.

SECTION 12: Ecological Information

Dolasetron mesylate:

Aerobic biodegradation in water: No significant mineralization; approximately 37.8 % and 2.0% was biotransformed to a non-polar and more polar degradation product, respectively. Biotransformation half-life estimate of approximately 35 days, suggesting a potential removal pathway.

Aerobic biodegradation in soils: Mineralization half-lives of 113-659 days for sandy, silt and loam soils, indicating significant biotransformation.

Aqueous photodegradation in water: Half-lives of 76-112 hours, in pH 5, 7 and 9 light-exposed aqueous buffers. Complete degradation within 6 hours under indirect photodegradation, indicating a possibly important removal mechanism.

Soil/sediment adsorption-desorption: In clay loam, a K_{oc} value of 3855 indicates slight mobility; in sandy and silt loam K_{oc} values of 25536 and 8066 indicate immobility.

Microbial growth inhibition: No inhibition was observed for *Pseudomonas fluorescens*, *Azobacter chroococcum*, *Aspergillus clavatus* and *Penicillium canescens* up to 1000 mg/L. The MICs for *Bacillus megaterium*, *Anabaena flos-aquae*, and *Chaetomium globosum* were 800, 200, and 800 mg/L, respectively.

Acute toxicity in *Daphnia magna*: 48-hour EC_{50} and NOEC of 50 and 25 mg/L, respectively.

Acute toxicity in bluegill fish (*Lepomis macrochirus*): 96-hour LC_{50} and NOEC of 21 and 8.5 mg/L, respectively.

Acute toxicity in earthworms (*Lumbricus terrestris*): $LC_{50} > 982$ mg/kg soil.

SECTION 13: Disposal Considerations

Dispose of according to local, state, and/or federal regulations.

SECTION 14: Transport Information

This material is not regulated as hazardous by U.S.-DOT. A copy of this MSDS should accompany shipments of this material.

SECTION 15: Regulatory Information

No additional information at this time.

SECTION 16: Other Information

The information provided in this Material Safety Data Sheet has been compiled from our experience and the data presented in various technical publications. It is the users responsibility to determine the suitability of this information for the adoption of safety precautions as may be necessary. We reserve the right to revise the Material Safety Data Sheet from time to time as new information becomes available. It is recommended that the user contact the company to make sure the sheet is the latest one issued.