PRODUCT MONOGRAPH

^{Pr}ANZEMET®

(Dolasetron Mesylate)

20 mg/mL Intravenous Injection

50 and 100 mg Tablets

Antiemetic

(5-HT_3 receptor antagonist)

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ACTION AND CLINICAL PHARMACOLOGY

Dolasetron and its active metabolite, hydrodolasetron (MDL 74156), are selective 5-HT_3 receptor antagonists shown not to have activity at other known serotonin receptors and with low affinity for dopamine receptors. The serotonin 5-HT_3 receptors are located on the nerve terminals of the vagus in the periphery and centrally in the chemoreceptor trigger zone of the area postrema. It is thought that chemotherapeutic agents produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine, and that serotonin then activates the 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex.

Acute, reversible, ECG changes (PR and QTc; QRS widening), caused by dolasetron, have been observed in controlled clinical trials. Dolasetron appears to prolong both depolarization and, to a lesser extent, repolarization time. Although QTc prolongation is primarily due to QRS widening, JT prolongation has also been observed. The magnitude and frequency of the ECG changes increased with dose (related to the peak plasma concentration of hydrodolasetron but not the parent compound). These ECG changes usually returned to baseline within 6 to 8 hours, but in some patients have lasted 24 h or longer. Dolasetron mesylate administration has little or no effect on blood pressure.

In healthy volunteers (N=4), dolasetron mesylate in single intravenous doses up to 5 mg/kg produced no effect on pupil size or meaningful changes in EEG tracings. Results from neuropsychiatric tests revealed that dolasetron mesylate does not alter mood or concentration. Multiple daily doses of dolasetron have no effect on colonic transit in humans. Dolasetron has no effect on plasma prolactin concentrations.

Pharmacokinetics in Humans (Intravenous Administration)

Intravenous dolasetron is rapidly eliminated ($t_{½}$<10 min) and completely metabolized to the most clinically relevant species, hydrodolasetron. Hydrodolasetron appears rapidly in plasma, with a maximum concentration occurring approximately 0.6 hours after the end of intravenous treatment, and is eliminated with a mean half-life of 7.3 hours (CV=24%, n=30) in adult cancer patients. Hydrodolasetron is eliminated by multiple routes, including renal excretion, after metabolism mainly by glucuronidation and hydroxylation. Hydrodolasetron exhibits linear pharmacokinetics over the intravenous dose range of 50 to 200 mg and they are independent of infusion rate. Doses lower than 50 mg have not been studied. Two-thirds of the administered dose is recovered in the urine and one-third in the faeces. Hydrodolasetron is widely distributed in the body with a mean apparent volume of distribution of 5.8 L/kg (CV=25%; n=24) in adults.

Sixty-nine to 77% of hydrodolasetron is bound to plasma proteins. In a study with ^{14}C- labelled dolasetron, the distribution of radioactivity to blood cells was not extensive. The binding of hydrodolasetron to α1-acid glycoprotein is approximately 51%. The pharmacokinetics are similar in men and women. The pharmacokinetics of hydrodolasetron, in special and targeted patient populations following IV administration of dolasetron, are summarized in Table 1. The pharmacokinetics of hydrodolasetron are similar in adult healthy volunteers and adult cancer patients receiving chemotherapeutic agents. The apparent clearance of hydrodolasetron is not affected by age in adult cancer patients. Following IV administration, the apparent clearance of hydrodolasetron remains unchanged with severe hepatic impairment and decreases 47% with severe renal impairment.

Table 1. Pharmacokinetic Values for Hydrodolasetron Following Intravenous Administration of Dolasetron Mesylate (1.8 mg/kg)

	Age (years)	Cl_{app} (ml/min/kg)	$t_{½}$ (hr)	AUC_{∞} (ng/mlxhr)	C_{max} (ng/ml)
Young healthy volunteers (n=24)	19-40	9.4 (28%)	7.3 (24%)	2567[B]	457[B]
Elderly healthy volunteers (n=15)	65-75	8.3 (30%)	6.9 (22%)	3021[B]	465[B]
Cancer patients (n=273)	19-87	10.2 (34%)	7.5 (43%)	3640 (32%)	505 (26%)

Cl_{app}: apparent clearance
C_{max}: maximal serum concentration
$t_{½}$: terminal elimination half-life
B: Results dose-normalized to the recommended dose assuming linear kinetics
Values in brackets () represent the coefficient of variation in %

Pharmacokinetics in Humans (Oral Administration)

Oral dolasetron is well absorbed, although parent drug is rarely detected in plasma due to rapid and complete metabolism to the most clinically relevant species, hydrodolasetron. Hydrodolasetron appears rapidly in plasma, with a maximum concentration occurring approximately 1 hour after dosing, and is eliminated with a mean half-life of 8.1 hours (CV=18%; n=30). The apparent absolute bioavailability of oral dolasetron, determined by the major active metabolite hydrodolasetron, is about 75%. Food does not affect the apparent bioavailability of dolasetron taken by mouth. Hydrodolasetron is eliminated by multiple routes, including renal excretion, after metabolism, mainly glucuronidation and hydroxylation. Two-thirds of the administered dose is recovered in the urine and one-third in the faeces. Hydrodolasetron is widely distributed in the body with a mean apparent volume of distribution of 5.8 L/kg (CV=25%; n=24). Sixty-nine to 77% of hydrodolasetron is bound to plasma proteins. The binding of hydrodolasetron to α1-acid glycoprotein is approximately 51%. In a study with ^{14}C-labelled dolasetron, the distribution of radioactivity to blood cells was not extensive. The pharmacokinetics of hydrodolasetron are linear and similar in men and women.

The pharmacokinetics of hydrodolasetron following oral administration, in special and targeted patient populations, are summarized in Table 2. The pharmacokinetics of hydrodolasetron are similar between adult healthy volunteers and cancer patients receiving chemotherapeutic agents. The apparent clearance of hydrodolasetron following oral administration of dolasetron is not affected by age in adult cancer patients. The apparent clearance of hydrodolasetron decreases 42% with severe hepatic impairment and 44% with severe renal impairment.

Table 2. Pharmacokinetic Values for Hydrodolasetron Following Oral Administration of Dolasetron Mesylate (100 mg)

	Age (years)	Cl_{app} (ml/min/kg)	$t_{½}$ (hr)	$AUC_{\infty}B$	C_{max} (ng/ml)
Young healthy volunteers (n=24)	19-45	10.5 (32%)	8.2 (21%)	1605[B]	299[B]

Elderly healthy volunteers (n=14)	65-75	9.5 (36%)	7.2 (32%)	2106[B]	402[B]
Cancer patients (n=17)	30-84	11.5 (47%)	7.9 (33%)	-[Ή]	-[Ή]

Cl_{app}: Apparent oral clearance
C_{max}: Maximal serum concentration
$t_{½}$: Terminal elimination half-life
Ή: Sampling times did not allow for determination
B: Results dose-normalized to the recommended dose assuming linear kinetics
Values in brackets () represent the coefficient of variation in %

Clinical Trials

Intravenous Administration

One thousand nine hundred and seventeen patients receiving emetogenic chemotherapy (including high dose cisplatin $\geq$70mg/m^2) were studied in five randomized, double blind trials in which 597 patients were treated with the recommended dose of 1.8 mg/kg ANZEMET Injection (Table 3). Efficacy was based on complete response rates (no emetic episodes and no rescue medication). ANZEMET Injection (dolasetron mesylate) administered intravenously at a dose of 1.8 mg/kg gave similar results in preventing nausea and vomiting as the other selective 5-HT_3 receptor antagonists studied as active comparators. ANZEMET Injection was more effective than metoclopramide.

Table 3. Prevention of Chemotherapy-Induced Nausea and Emesis in Cisplatin♦ Chemotherapy with ANZEMET Injection (1.8 mg/kg)

Response over 24 hours	Patients responding (%) (n=597)
Complete Response†	313 (52.4%)
Nausea Score⊗	10.5
Total Response❖	223 (37.4%)

♦: Cisplatin was used at moderately and highly emetogenic doses; cyclophosphamide, doxorubicin, fluorouracil, epirubicin, and vincristine were used at moderately emetogenic doses and were the most commonly used chemotherapeutic agents in these trials
†: No emetic episodes and no rescue medication
⊗: Median 24-hr change from baseline nausea score using visual analog scale (VAS); score range 0 = "none" to 100 = "nausea as bad as it could be"
❖: Complete response plus no nausea (VAS<5mm)

Oral Administration

One thousand and twenty six patients receiving emetogenic chemotherapy were studied in three randomized, double blind trials in which 227 patients were treated with 100 mg oral ANZEMET (dolasetron mesylate). Efficacy was based on complete response rates (no emetic episodes and no rescue medication). ANZEMET administered at an oral dose of 100 mg gave similar results in preventing nausea and vomiting as the other selective 5-HT_3 receptor antagonists studied as active comparators.

Table 4. Prevention of Chemotherapy-Induced Nausea and Vomiting in Moderately Emetogenic Chemotherapy with ANZEMET Tablets (100mg)§

Response over 24 hours	Patients responding (%) (n=227)
Complete Response¶	147 (64.8%)
Nausea Score‡	2.5
Total Response□	111 (48.9%)

§: Cisplatin, carboplatin, doxorubicin, and cyclophosphamide were used at moderately emetogenic doses
¶: No emetic episodes and no rescue medication
‡: Median 24-hr change from baseline nausea score using visual analog scale (VAS); score range 0 = "none" to 100 = "nausea as bad as it could be"
□: Complete response and no nausea (VAS<5mm)

INDICATIONS AND CLINICAL USE

Adults:

ANZEMET (dolasetron mesylate) is indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin.

Pediatrics (<18 years of age):
See **CONTRAINDICATIONS.**

CONTRAINDICATIONS

ANZEMET (dolasetron mesylate) is contraindicated

- in patients with known hypersensitivity to the drug or any components of its formulations (see COMPOSITION).
- Any therapeutic use in children and adolescents under 18 years of age.
- The prevention and treatment of post-operative nausea and vomiting in adults.

These contraindications apply to both intravenous (IV) and oral formulations.

WARNINGS

ECG changes and cardiovascular events
ANZEMET (dolasetron mesylate) can cause ECG interval changes (PR and QTc prolongations and QRS widening) in healthy volunteers and patients. In patients receiving chemotherapy or undergoing surgery, JT prolongations have also been observed following ANZEMET, active comparator or placebo. JT prolongations have not been observed in healthy volunteers receiving ANZEMET. ECG interval changes are related in magnitude and frequency to blood levels of the active metabolite, hydrodolasetron. These changes are self-limiting with declining blood levels. Some patients have interval prolongations for 24 hours or longer. Interval prolongations could lead to cardiovascular consequences, including heart block or cardiac arrhythmias. These have been rarely reported in patients receiving ANZEMET.

Complete heart block was observed interoperatively in a 61-year old woman who received 200 mg ANZEMET (dolasetron mesylate) oral tablet for the prevention of post-operative nausea and vomiting. This patient was also taking verapamil. A 66-year old man receiving chemotherapy was found dead six hours after receiving 1.8 mg/kg (119 mg) intravenous ANZEMET Injection and concomitant anthracycline therapy. Vital signs taken at 1.0 and 4.5 hours after ANZEMET Injection indicated an adequate blood pressure and increasing heart rate. This patient had other potential risk factors including substantial exposure to doxorubicin and concomitant cyclophosphamide.

The use of dolasetron mesylate is contraindicated in children and adolescents under 18 years of age and in adults for the prevention and treatment of post-operative nausea and vomiting (see **CONTRAINDICATIONS**) as:

- acute electrocardiographic changes have occurred very commonly in pediatrics aged 2 to 18 years;
- individual cases of sustained supraventricular and ventricular arrhythmias, myocardial infarction and one case of fatal cardiac arrest have been reported in association with ANZEMET in pediatrics. A causal relationship with ANZEMET was suspected based on temporal association in all cases. Most of the cases of cardiovascular events occurred in adolescents. In all cases ANZEMET was indicated for postoperative nausea and vomiting. They concerned mainly the I.V. route, and in one case oral administration.

Dolasetron (5-HT_3 receptor antagonist) should be administered with caution in patients who have or may develop prolongation of cardiac conduction intervals, particularly QTc, due to potential for additive effects. These include, also patients with AV block II-III, bundle branch block, patients receiving concomitant class I and III antiarrythmics and 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 lead to QT prolongation, and cumulative high dose anthracycline therapy. Interval prolongation could lead to cardiovascular consequences, including heart block or cardiac arrhythmias.

Because ANZEMET affects cardiac conductivity, the recommended doses should not be exceeded.

Allergic Reactions
Cross hypersensitivity reactions have been reported in patients who have received other selective 5 HT_3 receptor antagonists. It has not been seen with dolasetron mesylate.

PRECAUTIONS

Cardiovascular
Dolasetron (5-HT_3 receptor antagonist) should be administered with caution in patients who have or may develop prolongation of cardiac conduction intervals, particularly QTc, due to potential for additive effects (see WARNINGS, ECG changes and cardiovascular events).

Pediatrics (<18 years of age):
See **CONTRAINDICATIONS.**

Renal Impairment
Dosage adjustment is not necessary in mild to moderate renal impairment. However, dolasetron is not recommended in patients with severe renal impairment because of the possibilitiy of prolonged QTc intervals and other cardiac conduction abnormalities from elevated hydrodolasetron levels.

Hepatic Impairment
Dosage adjustment is not necessary in mild to moderate hepatic impairment. The oral formulation of dolasetron is not recommended in patients with severe hepatic impairment because of the possibilitiy of prolonged QTc intervals and other cardiac conduction abnormalities from elevated hydrodolasetron levels.

Pregnancy
There are no adequate and well-controlled studies in pregnant women. This drug is not recommended for use during pregnancy.

Animal reproduction studies have shown no evidence of teratogenicity when dolasetron mesylate was administered throughout organogenesis.

Lactation
It is not known whether dolasetron is excreted in human milk. ANZEMET should not be administered to a nursing woman.

Geriatrics
Dosage adjustment is not needed in patients over 65.

Carcinogenicity
In a 24-month carcinogenicity study in CD-1 mice, there was a statistically significant (p=0.001) increase in the incidence of combined hepatocellular adenomas and carcinomas in male mice treated orally with 150 mg/kg/day dolasetron and above. No increase in liver tumours was observed at a dose of 75 mg/kg/day in male mice and at doses up to 300 mg/kg/day in female mice.

In a 24 month carcinogenicity study in Sprague-Dawley rats, oral dolasetron mesylate was not tumorigenic at doses up to 150 mg/kg/day in males and 300 mg/kg/day in females.

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 (see WARNINGS for information about potential interaction with other drugs that prolong QTc intervals). Blood levels of hydrodolasetron increased 24% when dolasetron was coadministered with cimetidine (nonselective inhibitor of cytochrome P-450) for 7 days, and decreased 28% with coadministration of rifampin (potent inducer of cytochrome P-450) for 7 days. ANZEMET Injection has been safely coadministered with drugs used in chemotherapy and surgery. In patients taking furosemide, nifedipine, diltiazem, ACE inhibitors, verapamil, glyburide, propranolol, and various chemotherapy agents, no effect was shown on the clearance of hydrodolasetron. Clearance of hydrodolasetron decreased by about 27% when dolasetron mesylate was administered concomitantly with atenolol. Dolasetron mesylate does not influence anesthesia recovery time in patients. Dolasetron mesylate did not inhibit the antitumor activity of four chemotherapeutic agents (cisplatin, 5-fluorouracil, doxorubicin, cyclophosphamide) in four murine models.

ADVERSE REACTIONS

The safety of ANZEMET (dolasetron mesylate) has been evaluated in over 7,000 patients in North American and European clinical trials. ANZEMET was well tolerated, with headache being the most frequently reported adverse event. The incidence of adverse events from pivotal controlled clinical trials is presented below.

ANZEMET Injection
In controlled and uncontrolled clinical trials, 2265 adult patients received ANZEMET Injection of which 731 patients were treated at the recommended therapeutic dose (1.8 mg/kg). The most frequently reported adverse events ($\geq$2%) in patients receiving ANZEMET Injection are presented in Table 5. Patients were receiving chemotherapy (primarily cisplatin) and intravenous fluids. Adverse events were recorded for at least 24 hours following ANZEMET Injection administration.

Table 5. ANZEMET Intravenous Adverse Events ≥2% in Chemotherapy-Induced Nausea and Vomiting

Event	ANZEMET Injection 1.8 mg/kg (n=731)
Headache	188 (25.7%)
Diarrhea	93 (12.7%)
Fever	36 (4.9%)
Hepatic Function Abnormal§	28 (3.8%)
Fatigue	25 (3.4%)
Abdominal Pain	23 (3.1%)
Tachycardia	21 (2.9%)
Chills/Shivering	20 (2.7%)
Hypertension	20 (2.7%)
Extrasystoles	19 (2.6%)
Pain	18 (2.5%)
Dizziness	15 (2.1%)

§: Includes events coded as SGOT- or SGPT-increased

Oral Administration

In controlled clinical trials, 943 patients received oral ANZEMET of which 227 patients were treated at the recommended therapeutic dose (100 mg). These patients were receiving concurrent chemotherapy, predominantly cyclophosphamide and doxorubicin regimens. Table 6 lists adverse events occurring in ≥2% of patients in comparative clinical trials:

Table 6. Oral ANZEMET Adverse Events Occurring ≥2% in Chemotherapy-Induced Nausea and Vomiting Patients

	ANZEMET 100 mg (n=227)
Headache	52 (22.9%)
Diarrhea	12 (5.3%)
Fatigue	13 (5.7%)
Bradycardia	9 (4.0%)
Pain	7 (3.1%)
Dizziness	7 (3.1%)
Tachycardia	6 (2.6%)
T Wave Change	6 (2.6%)
ST-T Wave Change	6 (2.6%)
Chills/Shivering	5 (2.2%)
Dyspepsia	5 (2.2%)

LESS FREQUENTLY OCCURRING ADVERSE EVENTS:

ANZEMET Injection:

In controlled and uncontrolled clinical trials the following Adverse Events occurred at a frequency of 0.3% to 2.0% in patients treated with ANZEMET Injection at the recommended dose (1.8 mg/kg):

Application Site: Injection site pain.

Autonomic Nervous System: Dry mouth, flushing.

Body as a Whole: Malaise.

General Cardiovascular: Chest pain, edema, edema peripheral, fluid overload, hypotension.

Central and Peripheral Nervous System: Drowsiness, paresthesia, tremor, vertigo.

Gastro-Intestinal System: Abdominal distension, anorexia, appetite increased, constipation, dyspepsia, flatulence, hiccup, nausea, stomatitis.

Hearing, Taste, and Vision: Taste perversion.

Heart Rate and Rhythm: atrial arrhythmia, sinus arrythmia, atrial flutter/fibrillation, first degree AV block, bradycardia, cardiac arrest, ECG abnormal specific, QT/QTc prolonged, ST-T Wave change, T wave change.

Hematologic: Bone marrow aplasia, epistaxis.

Musculo-Skeletal System: Myalgia.

Psychiatric: Agitation, anxiety, confusion, sleep disorder.

Resistance Mechanism: Sepsis.

Respiratory System: Abnormal breath sounds, bronchospasm, cough, dyspnea, pneumonia, pulmonary congestion, throat irritation, upper respiratory congestion.

Skin and Appendages: Facial edema, increased sweating.

Urinary System: Urinary retention.

Oral Administration:

In controlled clinical trials the following Adverse Events occurred at a frequency of 0.9% to 2.0% in patients treated with oral ANZEMET at the recommended dose (100 mg):

Autonomic Nervous System: Dry mouth, flushing.

Body as a Whole: Fever.

Cardiovascular (general): Dependent edema, hypotension.

Central and Peripheral Nervous System: Drowsiness.

Gastro-Intestinal System: Abdominal pain, anorexia, increased appetite, constipation, eructation, flatulence, nausea.

Hearing, Taste, and Vision: Taste perversion.

Heart Rate and Rhythm: Atrial arrythmia, sinus arrhythmia, extrasystoles.

Liver and Biliary System: SGOT increased.

Metabolic and Nutritional: Dehydration.

Resistance Mechanism: Influenza-like symptoms.

Respiratory System: Dyspnea, nasal irritation, sneezing, throat irritation.

POSTMARKET SURVEILLANCE:

ANZEMET Injection:

Cases of local pain and burning on IV administration have been observed.

In very rare cases, severe hypotension, bradycardia and possibly loss of consciousness may occur immediately or closely following IV bolus administration of dolasetron mesylate. These events have occurred in patients receiving dolasetron mesylate for the prevention of cancer chemotherapy-induced nausea and vomiting.

Dolasetron mesylate has been shown to cause ECG prolongations, including QTc, PR and QRS intervals. These changes are related in magnitude and frequency to blood levels of the active metabolite; the changes are self limiting with declining blood levels. Some patients have interval prolongation for 24 hours or longer. Interval prolongation could lead to cardiovascular consequences including heart block or cardiac arrhythmias. There are very rare reports of wide complex tachycardia or ventricular tachycardia and of ventricular fibrillation/cardiac arrest following intravenous administration.

Individual cases of sustained supraventricular and ventricular arrhythmias, myocardial infarction and one case of fatal cardiac arrest have been reported in association with ANZEMET in pediatrics. A causal relationship with ANZEMET was suspected based on temporal association in all cases. Most of the cases of cardiovascular events occurred in adolescents. In all cases ANZEMET was indicated for postoperative nausea and vomiting. They concerned mainly the I.V. route, and in one case oral administration.

There are rare reports of anaphylactic/anaphylactoid reactions including skin reactions such as rash, puritus, and urticaria, respiratory reactions such as bronchospasm, very rare reports of facial edema/angioedema and shock.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been reports of overdose. Severe hypotension, dizziness and prolongation of the PR, QRS and QTc intervals were reported after overdose intravenous infusion.

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

Following a suspected overdose of ANZEMET, a patient found to have second-degree or higher AV conduction block should undergo cardiac telemetry monitoring.

There is no known specific antidote for dolasetron mesylate, and patients with suspected overdose should be managed with supportive therapy. Individual doses as large as 5 mg/kg intravenously or 400 mg orally have been safely given to healthy volunteers or cancer patients.

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 were lethal. Symptoms of acute toxicity were tremors, depression and convulsions.

DOSAGE AND ADMINISTRATION

The following recommended doses of ANZEMET (dolasetron mesylate) should not be exceeded due to the effects on cardiac conductivity (see WARNINGS, PRECAUTIONS):

Adults:
ANZEMET is contraindicated for the prevention and treatment of post-operative nausea and vomiting in adults

(see **CONTRAINDICATIONS**).

IV Administration
Adults: The recommended intravenous dosage of ANZEMET Injection is 1.8 mg/kg given as a single dose approximately 30 minutes before chemotherapy. Most patients can be adequately treated with 100 mg. For light patients (<56 kg) or heavy patients (>90 kg), 1.8 mg/kg should be used.

The injection solution can be infused as rapidly as 100 mg over 30 seconds, or it can be diluted in a compatible IV solution such as normal saline or 5% dextrose to 50 mL and infused over 15 minutes. More rapid IV administration should be avoided (see ADVERSE REACTIONS). Dolasetron mesylate should not be mixed with other drugs. Flush the infusion line before and after administration of dolasetron mesylate.

Oral Administration
Adults: The recommended oral dosage of ANZEMET is one 100 mg tablet given within one hour prior to chemotherapy.

Pediatrics
ANZEMET is contraindicated for any therapeutic use in children and adolescents under 18 years of age (see **CONTRAINDICATIONS**).

Geriatrics
It is not necessary to adjust the dose of dolasetron mesylate in elderly patients.

Hepatic Impairment
No dosage adjustment is necessary in mild to moderate hepatic impairment. However, oral dolasetron is not recommended in patients with severe hepatic impairment because of the possibility of prolonged QTc intervals and other cardiac conduction abnormalities from elevated hydrodolasetron levels.

Renal Impairment
No dosage adjustment is necessary in mild to moderate renal impairment. However, dolasetron is not recommended in patients with severe renal impairment because of the possibility of prolonged QTc intervals and other cardiac conduction abnormalities from elevated hydrodolasetron levels.

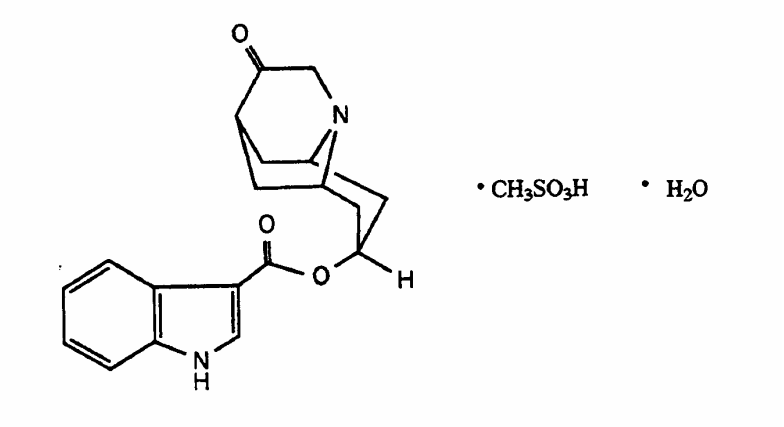
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Dolasetron mesylate

Chemical Name: (2α,6α,8α,9α -octahydro-3-oxo-2,6,-methano-2H-quinolizin-8-yl-1H-indole-3 -carboxylate monomethanesulfonate, monohydrate

Chemical Structure:



Emperical Formula:

$C_{19}H_{20}N_2O_3 \bullet CH_3SO_3H \bullet H_2O$

Molecular Weight: 438.50

Description:

Dolasetron mesylate is a white to off-white powder. At room temperature, it is very soluble in water, freely soluble in methanol, slightly soluble in chloroform, and insoluble in hexane.

pH: 3.543 and 4.287 at 5% w/v and 0.5% w/v, respectively

pKa: 6.398 at 25°C

Composition

Injection

ANZEMET (dolasetron mesylate) Injection is a clear, colourless, sterile, non-pyrogenic solution for intravenous injection. Each mL contains 20 mg dolasetron mesylate monohydrate as well as the non-medicinal ingredients mannitol, glacial acetic acid, sodium acetate trihydrate, and water for injection. ANZEMET Injection has a pH range of 3.2 to 3.8.

Tablets

ANZEMET Tablets are available in strengths containing 50 and 100 mg dolasetron mesylate monohydrate per tablet. Each tablet also contains the following non-medicinal ingredients: carnauba wax, croscarmellose sodium, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, polysorbate 80, pregelatinized starch, titanium dioxide and white wax. The 50 and 100 mg tablet also contain red iron oxide.

STABILITY AND STORAGE RECOMMENDATIONS
ANZEMET (dolasetron mesylate) Injection should be stored at controlled temperature (15 - 30°C) and protected from light.

ANZEMET Tablets should be stored at controlled temperature (15 - 30°C).

Parenteral Products
Administration of Intravenous Infusion Solutions

Compatibility with Intravenous Solutions:
ANZEMET (dolasetron mesylate) Injection should only be admixed with the following recommended infusion fluids:
- 0.9% w/v Sodium Chloride Injection
- 5% w/v Glucose Injection
- 10% w/v Mannitol Injection
- 0.45% w/v Sodium Chloride and 5% w/v Glucose Injection
- Lactated Ringer's Injection
- 5% w/v Glucose Injection and Lactated Ringer's Injection

Dolasetron mesylate is compatible with polypropylene syringes, IV bags, and associated tubing.

Compatibility with Other Drugs:
Dolasetron mesylate should not be mixed with other drugs. Flush the infusion line before and after administration of dolasetron mesylate.

ANZEMET injection at a 4 mg/mL concentration has been determined to be physically incompatible with the following drugs when administrated through the same intravenous line: carmustine, 5-fluorouracil, acyclovir sodium, ampicillin sodium, cefazolin sodium, chloramphenicol sodium succinate, clindamycin phosphate, dexamethasone sodium phosphate, methylpredinisolone sodium succinate, trimethoprim with sulfamethoxazole, aminophylline, amphotericin B, heparin sodium, potassium phosphate and sodium bicarbonate. ANZEMET injection at a concentration of 20 mg/mL is physically incompatible with thiopental sodium.

Note: As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.

Dilution: To prepare ANZEMET Injection for intravenous infusion, aseptically transfer the appropriate amount of ANZEMET Injection to the desired volume of infusion fluid.

Diluent Volume	Quantity of ANZEMET Injection	Final Concentration	Administration*	
			Dose	Infusion Rate
50 mL	50 mg (2.5 mL)	0.95 mg/mL	50 mg/15 min	53 mL/15 min
50 mL	100 mg (5 mL)	1.82 mg/mL	100 mg/15 min	55 mL/15 min

* ANZEMET Injection can also be injected over 30 seconds.

Stability and Storage of Diluted Solutions
Dilutions of intravenous fluids should be used immediately after preparation or stored for no more than 24 hours at 2-8°C.

AVAILABILITY OF DOSAGE FORMS

ANZEMET Injection
ANZEMET (dolasetron mesylate) Injection 20 mg/mL is supplied in clear glass vials and ampoules of 5 mL (100 mg dolasetron mesylate).

ANZEMET Tablets
ANZEMET **50 mg** pale pink, round, film-coated tablets are printed "**50**" in the center of the tablet and "**A**" on the other side.

ANZEMET **100 mg** pink, oval, film-coated tablets are printed with "**ANZEMET**" on one side and "**100**" on the other.

Tablets are available in bottles of 15 tablets.

INFORMATION FOR THE CONSUMER

Please read this information leaflet carefully before you start to take your medicine, even if you have taken this drug before. Keep this leaflet handy in order to consult it while taking your medication. This leaflet is only a short summary of the information available. For further information or advice, ask your doctor or pharmacist.

What Is ANZEMET?

- **ANZEMET** (dolasetron mesylate) is a prescription medicine that belongs to a family of drugs called antiemetics.
- **ANZEMET** is available in tablet form and as an intravenous injection. The intravenous injection is administered only by a doctor or nurse in a hospital or clinic setting.

How Does ANZEMET Work?

- **ANZEMET** is taken to prevent nausea (feeling of stomach sickness) and vomiting, which may occur in patients undergoing cancer chemotherapy. It is thought that chemotherapy treatments cause release of a naturally occurring substance in the body (serotonin), which can cause you to feel sick or vomit. **ANZEMET** blocks the effect of serotonin, and may prevent you from feeling nauseous or vomiting.

When ANZEMET should <u>not</u> be used?

- Do not use **ANZEMET** if you are allergic to it or to any components of its formulation (see list of components in the section "What Does **ANZEMET** Contain?").
- Do not use **ANZEMET** if you are under 18 years of age.
- Do not use **ANZEMET** if you are a surgery patient.

What Do I Need To Do Before Taking ANZEMET?
Tell Your Doctor:

- If you are allergic to any of the ingredients in **ANZEMET** tablets (see list of ingredients at the end of this leaflet).
- If you have a history of heart problems.
- If you have a history of kidney or liver problems.
- If you are taking <u>any</u> medications, and especially if you are taking medications to control heartbeat or certain diuretics.

How Do I Take ANZEMET Properly?

- The label on the container of your medicine should tell you how to take your medicine. It is important that you follow these instructions exactly. If you have any questions regarding these instructions, ask your doctor or pharmacist.
- DO NOT TAKE MORE TABLETS OR TAKE YOUR TABLETS MORE OFTEN THAN PRESCRIBED.
- Swallow your tablets whole with a little water. **ANZEMET** tablets may be taken with or without food.
- If you vomit within one hour of taking your medicine, you should take the same amount of medicine again. If vomiting continues, consult your doctor.
- If you miss a dose and do not feel sick, take the next dose when it is scheduled. If you miss a dose and feel sick or vomit, take a tablet as soon as possible.

Can ANZEMET Be Used During Pregnancy Or Breast-feeding?

- This medicine should not be taken if you are pregnant, if you are likely to become pregnant or if you are breast-feeding a baby.

What If I Have Problems While Taking ANZEMET?

- If you experience wheezing and tightness of the chest, chest pain, heart throbbing, swelling of eyelids, face or lips, or develop a skin rash, skin lumps or hives, contact your doctor immediately. Do not take any more medicine unless your doctor tells you to do so.
- Most people have no problems after taking **ANZEMET** tablets. However, a few people may have side effects such as headaches, diarrhea or dizziness. If you experience these effects, there is no need to stop taking this medicine, but you should tell your doctor about them at your next visit.
- Tell your doctor if your nausea or vomiting does not improve while taking **ANZEMET** tablets.

What If I Take Too Much ANZEMET?

- If you accidentally take more tablets than prescribed, contact your doctor or hospital emergency department immediately.

Where Should I Store ANZEMET?

- Leave your tablets in their original packaging and store at room temperature (15° to 30°C)
- KEEP **ANZEMET** OUT OF THE REACH OF CHILDREN.
- If your doctor decides to stop treatment with this medicine, do not keep any left over medicine unless your doctor tells you to do so.

Who Do I Ask If I Have Any Questions About ANZEMET?

- Consult your doctor or pharmacist.

What Does ANZEMET Contain?

- **ANZEMET** Tablets contain either 50 mg or 100 mg of dolasetron mesylate. Each tablet also contains the following non-medicinal ingredients: carnauba wax, croscarmellose sodium, hydroxypropyl methylcellulose, **lactose**, magnesium stearate, polyethylene glycol, polysorbate 80, pregelatinized starch, red iron oxide, titanium dioxide, and white wax.

Who Supplies ANZEMET?

- **ANZEMET** is supplied by:
  sanofi-aventis Canada Inc.
  2150 St. Elzear Blvd. W., Laval, Quebec H7L 4A8

REMINDER:

- **ANZEMET HAS BEEN PRESCRIBED ONLY FOR YOU. DO NOT GIVE IT TO ANYBODY ELSE.**

PHARMACOLOGY

Animal Pharmacology

In Vitro

In conventional radioligand binding assays *in vitro*, dolasetron and its metabolites exhibited high affinity for 5-HT_3 receptors. Dolasetron and its reduced metabolite dose-dependently inhibited 5-HT_3 receptor-mediated inward ionic currents on voltage-clamped NG108-15 mouse neuroblastoma x rat glioma hybrid cells. In this assay, the reduced metabolite was more potent than dolasetron, with IC_{50} values of 0.1 and 3.8 nM, respectively. In the isolated, perfused rabbit heart, dolasetron and its reduced metabolite were equipotent in blocking the positive chronotropic effect of serotonin.

Results of *in vitro* studies indicate that dolasetron and the reduced metabolite have electrophysiological properties. Micromolar concentrations of dolasetron in dog Purkinje fibres produced concentration-dependent reductions in action potential duration, contractile force, and the maximum upstroke velocity of the action potential (V_{max}) that were inversely dependent on stimulation frequency. The reduction in V_{max} was also observed in guinea pig papillary muscle fibres during superfusion with dolasetron and the reduced metabolite.

In conscious dogs, cumulative total intravenous doses of 3 mg/kg and 10 mg/kg dolasetron reversibly increased the PR interval by 9 and 17 msec (10% and 19%), respectively. The 10 mg/kg dose did not significantly increase the QT_c interval, however, a cumulative dose of 30 mg/kg induced a 47 msec (16%) increase. These effects are probably not related to an action at 5-HT_3 receptors but rather result from an interaction with cardiac muscle voltage-dependent sodium channels. The actions of dolasetron and its reduced metabolite were tested on the cloned α-subunit of the human cardiac muscle sodium channel; significant channel blocking activity was only observed at concentrations exceeding 10 μM.

In Vivo

The ability of dolasetron and its metabolites to antagonize 5-HT_3 receptors *in vivo* was assessed by examining their ability to inhibit the Bezold-Jarisch Reflex (BJR), a transient reflex fall in blood pressure and heart rate produced by small intravenous doses of serotonin. Dolasetron and its metabolites all inhibited the BJR in the anaesthetized rat in a dose-dependent manner. A dose of 0.14 mg/kg IV of dolasetron or its reduced metabolite completely abolished the BJR in anaesthetized rats for the 85 minute duration of the experiment. An oral dose of 1 mg/kg dolasetron caused a rapid (< 10 minutes) and essentially complete inhibition of the BJR during the first hour of dosing, with significant inhibition (50%) still present at the end of the 4-hour observation period.

The antiemetic activity of dolasetron was established in the ferret and the dog. Single oral doses of $\geq$ 0.5 mg/kg dolasetron or two intravenous doses of $\geq$ 0.5 mg/kg dolasetron (30 minutes prior to and 45 minutes following 10 mg/kg IV cisplatin) were sufficient to significantly reduce the number of cisplatin-induced vomits over the 4-hour observation period. Similarly, two 0.5 mg/kg IV doses of the reduced metabolite of dolasetron also exerted a significant antiemetic effect. In conscious beagle dogs, 0.1 to 0.3 mg/kg IV dolasetron, administered as a single dose 30 minutes prior to intravenous cisplatin, significantly prolonged the time to first emetic episode and significantly reduced the number of emetic episodes over the 6-hour observation period.

In conscious dogs, intravenous administration of dolasetron 4 mg/kg/day for 5 days was virtually without significant effect on blood pressure and heart rate. In anaesthetized dogs, 0.5 to 4.0 mg/kg intravenous dolasetron had no significant effects on cardiovascular reflexes; however, a cumulative intravenous dose of 18.5 mg/kg reduced left ventricular dp/dt_{max} (maximum rate of pressure change in left ventricle during systole) and administration of a further 12.5 mg/kg significantly decreased left ventricular pressure, systemic blood pressure and heart rate.

Even at high doses of dolasetron, no overt effects were noted in the mouse or rat during *in vivo* tests on behaviour, body temperature, antinociceptive, anti-inflammatory and local anaesthetic activity, writhing response, tail flick latencies, convulsant potential, muscle relaxant effects and anxiolytic effects.

TOXICOLOGY

Acute Toxicity

Species	LD_{50} Values with 95% Confidence Limits (mg/kg)	
	Oral	Intravenous
Mouse	545 (469-611)	165 (155-175)
Rat	446 (373-521)	150 (142-158)

Following administration of single oral doses of 300 - 2200 mg/kg and single IV doses of 100 - 224 mg/kg to mice and rats, the clinical signs observed were primarily those associated with the central nervous system. Following oral administration, depression was seen in essentially all mice and rats, and convulsions observed at ≥ 525 mg/kg in mice and at ≥ 700 mg/kg in rats. Following IV administration, tremors and/or depression were seen at all doses in mice and at doses ≥ 112 mg/kg in rats, with convulsions occurring at ≥ 140 mg/kg in mice and at ≥ 126 mg/kg in rats. In both species, onset of most clinical signs occurred within minutes of oral and IV dosing, and persisted for approximately five hours or until the death of the animal. Gross postmortem examinations revealed no target organ toxicity in either oral or IV studies, with death apparently occurring as a result of central nervous system effects.

No adverse clinical signs were observed in beagle dogs at oral doses up to 5 mg/kg and IV doses up to 4.5 mg/kg. At higher doses (≥ 10 mg/kg PO and ≥ 6 mg/kg IV), the most common adverse event noted was emesis. At 30 mg/kg IV, lacrimation, salivation, tremors, chewing motion, and panting were also observed. Dolasetron mesylate was well tolerated in Cynomolgus monkeys at oral doses up to 200 mg/kg and IV doses up to 30 mg/kg.

Subacute Toxicity

Dolasetron was administered orally to rats at dosage levels of 200, 300, 400 or 500 mg/kg/day for one month, with the drug administered after an overnight fast in the last two weeks of the study. Clinical effects, consisting of depression, ataxia and tremors, were seen at ≥ 300 mg/kg/day only when rats were dosed after an overnight fast. Increases in mean liver weights were observed in females dosed at 200 and ≥ 400 mg/kg/day. Deaths occurred in males at doses ≥ 400 mg/kg/day and in females at doses ≥ 300 mg/kg/day. Target organ toxicity appeared to be the kidney and/or ureter at doses of 500 mg/kg/day (male) and 400 mg/kg/day (female). Oral doses up to 100 mg/kg/day administered by gavage to rats for 3 months produced no treatment-related clinical signs. No treatment-related abnormalities were noted during gross and histopathological examination at any of the dosages, although increases occurred in body weight, food consumption, and relative liver weights in the 100 mg/kg female rats.

Doses of 0, 15, 30, and 60 mg/kg/day were administered to rats intravenously by tail vein injection for 1 month. In the 60 mg/kg/day group, 3/18 male rats had convulsions during the first week and some rats showed reduced activity during the first week. Otherwise, the major finding was dose-related injection site lesions (≥ 30 mg/kg/day) characterized by inflammation, haemorrhage and necrosis, which resulted in an increased splenic extramedullary hematopoiesis and increased relative spleen weight (60 mg/kg/day males only).

In beagle dogs administered oral doses of up to 100 mg/kg/day for 1 or 2 weeks, a dose-related increase in emesis was observed at doses ≥ 10 mg/kg/day. Tremors and excessive salivation were seen at doses ≥ 20 mg/kg/day. Doses ≥ 50 mg/kg/day caused depression. A male dog dosed at 100 mg/kg/day for one week experienced 10% weight loss, while a female dosed at 100 mg/kg/day died on day four following convulsions. No treatment-related changes were seen upon necropsy. Intravenous doses of 1 or 3 mg/kg/day for one month were well tolerated. At intravenous doses of 6 mg/kg/day, emesis was frequently observed, but no treatment-related effects were noted upon clinical or postmortem examination. ECGs taken from all dogs pretest, 2 hours after the 5th and 28th dose, and 24 hours after the 28th dose were normal, with no changes

from pretest.

Dolasetron mesylate was well tolerated in monkeys when administered orally by gavage at doses up to 100 mg/kg/day for 1 week or at doses up to 50 mg/kg/day for three months, and when administered intravenously at doses up to 10 mg/kg/day for three months. Clinical signs, body and organ weights, and gross and histopathological examination revealed no treatment-related adverse effects.

Chronic Toxicity

Fasted Sprague-Dawley rats were given daily oral doses of 0, 30, 75 or 400 mg/kg/day dolasetron for 12 months. Except for sporadic convulsions at all doses in males and at ≥ 75 mg/kg/day in females, doses of 30 and 75 mg/kg/day were generally well tolerated. Significant treatment-related findings were death at 400 mg/kg/day, starting on day 20 (28% mortality with over twice as many deaths in males than in females), and a few incidents of tremors and decreased activity, more often in males, which were sometimes followed by death. The main cause of death was target organ toxicity consisting of urinary tract lesions and kidney toxicity. Both findings occurred at 400 mg/kg/day and were characterized by: red or brown urine clinically with haematuria on urinalysis (males only); renal proximal convoluted tubule degeneration characterized by cytoplasmic vacuolation, increased cytoplasmic granularity, nuclear pyknosis or desquamation (males and females); reversible lower urinary tract epithelium irritation (males only), characterized by ulceration/necrosis, haemorrhage, suppurative inflammation or reactive hyperplasia of urothelium in the renal pelvis, ureter, or urinary bladder; and transitory, reversible increased BUN concentrations at 6 months (males).

Dolasetron was administered orally to dogs at doses of 0, 3, 10, 15 or 20 mg/kg/day for 12 months. The only treatment-related effects were emesis at ≥ 10 mg/kg/day and excessive salivation at ≥ 15 mg/kg/day. ECGs taken 2 and 18 hours post-dose (or 15 hours post-dose for 3 mg/kg dogs) after 6 and 12 months' treatment and after 1 month recovery were all within normal limits. Histopathological examination of the ureter at the renal pelvis showed a mixed inflammatory cell lesion in control and treated dogs. The lesion differed histologically from that observed in the rat, was not associated with altered clinical chemistry or urinalysis parameters, and was not considered treatment-related.

The significance to man of dolasetron induced urinary tract lesions in the rat is minimal, as they occurred only in fasted rats at oral doses ≥ 400 mg/kg/day, which is approximately 140 times the maximum clinical dose. These urinary tract lesions have not been observed in the rat after intravenous administration of 120 mg/kg/day for 5 days or 60 mg/kg/day for 1 month, nor have they been observed following oral or intravenous administration in the rabbit, dog or monkey.

Mutagenicity and Carcinogenesis

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

In a 24-month carcinogenicity study, there was a statistically significant ($p<0.001$) increase in the incidence of combined hepatocellular adenomas and carcinomas in males treated with 150 mg/kg/day and above. In this study, CD-1 mice were treated orally with dolasetron mesylate 75, 150 or 300 mg/kg/day. No increase in liver tumors were observed at a dose of 75 mg/kg/day in male mice and at doses up to 300 mg/kg/day in female mice.

In a 24-month Sprague-Dawley rat carcinogenicity study, oral dolasetron mesylate was not tumorigenic at doses up to 150 mg/kg/day and 300 mg/kg/day in females.

Reproduction and Teratology

Reproduction and teratology studies were conducted in the rat and in the rabbit. Female rats were administered dolasetron mesylate doses up to 100 mg/kg PO or 60 mg/kg IV on days 7 through 18 of gestation; female rabbits received doses up to 100 mg/kg PO or 20 mg/kg IV on days 7 through 19 of gestation. Dolasetron mesylate had no effect on reproductive parameters (implantation rate, resorption rate, pre- or post-implantation loss, corpora lutea or viable fetuses) at any dosage level following intravenous administration in rats and rabbits and following oral administration in rats. In the oral dosing study conducted

in rabbits, all treatment groups showed a 3- to 4-fold increase in the percentage of early resorptions and a significant increase in post-implantation loss. However, these effects were considered to be secondary to reduced maternal food consumption and decreased maternal weight. No evidence of teratogenicity was observed at any of the dosage levels following intravenous or oral administration. Fetal examination revealed no soft tissue, visceral, or skeletal abnormalities that appeared to be drug-related.

Oral doses of 0, 20, 60 and 100 mg/kg/day dolasetron mesylate were administered to female rats 14 days prior to breeding and throughout breeding, gestation and lactation. No effect on fertility, as assessed by time to mating, copulation and fertility indices, was observed at any dosage level. Evaluation of F_1 pups exposed *in utero* and during lactation indicated no treatment-related effects on survival, growth or subsequent reproductive performance. F_2 pups developed normally.

Dolasetron mesylate did not affect the fertility of male rats when administered orally at doses up to 400 mg/kg/day for 3 months. No congenital defects were noted in fetuses of females mated to dolasetron-treated males.

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