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MEDICAL ECONOMICS
THOMSON HEALTHCARE

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THOMSON HEALTHCARE

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Amaryl—Cont.

continued. Porphyria cutanea tarda, photosensitivity reactions, and allergic vasculitis have been reported with sulfonylureas.

Hematologic Reactions

Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic Reactions

Hepatic porphyria reactions and disulfiram-like reactions have been reported with sulfonylureas; however, no cases have yet been reported with AMARYL (glimepiride tablets). Cases of hyponatremia have been reported with glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with certain other sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

Other Reactions

Changes in accommodation and/or blurred vision may occur with the use of AMARYL. This is thought to be due to changes in blood glucose, and may be more pronounced when treatment is initiated. This condition is also seen in untreated diabetic patients, and may actually be reduced by treatment. In placebo-controlled trials of AMARYL, the incidence of blurred vision was placebo, 0.7%, and AMARYL, 0.4%.

OVERDOSAGE

Overdosage of sulfonylureas, including AMARYL, can produce hypoglycemia. Mild hypoglycemic symptoms without loss of consciousness or neurologic findings should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, because hypoglycemia may recur after apparent clinical recovery.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetes mellitus with AMARYL or any other hypoglycemic agent. The patient's fasting blood glucose and HbA1c must be measured periodically to determine the minimum effective dose for the patient; to detect primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, i.e., loss of adequate blood glucose lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels should be performed to monitor the patient's response to therapy.

Short-term administration of AMARYL may be sufficient during periods of transient loss of control in patients usually controlled well on diet and exercise.

Usual Starting Dose

The usual starting dose of AMARYL as initial therapy is 1–2 mg once daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 1 mg once daily, and should be titrated carefully. (See PRECAUTIONS Section for patients at increased risk.)

No exact dosage relationship exists between AMARYL and the other oral hypoglycemic agents. The maximum starting dose of AMARYL should be no more than 2 mg.

Failure to follow an appropriate dosage regimen may precipitate hypoglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy.

Usual Maintenance Dose

The usual maintenance dose is 1 to 4 mg once daily. The maximum recommended dose is 8 mg once daily. After reaching a dose of 2 mg, dosage increases should be made in increments of no more than 2 mg at 1–2 week intervals based upon the patient's blood glucose response. Long-term efficacy should be monitored by measurement of HbA1c levels, for example, every 3 to 6 months.

AMARYL-Metformin Combination Therapy

If patients do not respond adequately to the maximal dose of AMARYL monotherapy, addition of metformin may be considered. Published clinical information exists for the use of other sulfonylureas including glyburide, glipizide, chlorpropamide, and tolbutamide in combination with metformin.

With concomitant AMARYL and metformin therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. However, attempts should be made to identify the minimum effective dose of each drug to achieve this goal. With concomitant AMARYL and metformin therapy, the risk of hypoglycemia associated with AMARYL therapy continues and may be increased. Appropriate precautions should be taken.

AMARYL-Insulin Combination Therapy

Combination therapy with AMARYL and insulin may also be used in secondary failure patients. The fasting glucose level for instituting combination therapy is in the range of > 150 mg/dL in plasma or serum depending on the patient. The recommended AMARYL dose is 8 mg once daily administered with the first main meal. After starting with low-dose insulin, upward adjustments of insulin can be done approximately weekly as guided by frequent measurements of fasting blood glucose. Once stable, combination-therapy patients should monitor their capillary blood glucose on an ongoing basis, preferably daily. Periodic adjustments of insulin may also be necessary during maintenance as guided by glucose and HbA1c levels.

Specific Patient Populations

AMARYL (glimepiride tablets) is not recommended for use in pregnancy, nursing mothers, or children. In elderly, debilitated, or malnourished patients, or in patients with renal or hepatic insufficiency, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions (See CLINICAL PHARMACOLOGY, Special Populations and PRECAUTIONS, General).

Patients Receiving Other Oral Hypoglycemic Agents

As with other sulfonylurea hypoglycemic agents, no transition period is necessary when transferring patients to AMARYL. Patients should be observed carefully (1–2 weeks) for hypoglycemia when being transferred from longer half-life sulfonylureas (e.g., chlorpropamide) to AMARYL due to potential overlapping of drug effect.

HOW SUPPLIED

AMARYL tablets are available in the following strengths and package sizes:

1 mg (pink, flat-faced, oblong with notched sides at double bisect, imprinted with "AMA RYL" on one side and the Hoechst logo on both sides of the bisect on the other side)
Bottles of 100 (NDC 0039-0221-10)

2 mg (green, flat-faced, oblong with notched sides at double bisect, imprinted with "AMA RYL" on one side and the Hoechst logo on both sides of the bisect on the other side)
Bottles of 100 (NDC 0039-0222-10)
Unit Dose Cartons (100) (NDC 0039-0222-11)

4 mg (blue, flat-faced, oblong with notched sides at double bisect, imprinted with "AMA RYL" on one side and the Hoechst logo on both sides of the bisect on the other side)
Bottles of 100 (NDC 0039-0223-10)
Unit Dose Cartons (100) (NDC 0039-0223-11)

Store between 59 and 86° F (15 and 30° C).
Dispense in well-closed containers with safety closures.
Caution: Federal law prohibits dispensing without a prescription.
AMARYL® REG TM HOECHST AG
*US Patent 4,379,785

ANIMAL TOXICOLOGY

Reduced serum glucose values and degranulation of the pancreatic beta cells were observed in beagle dogs exposed to 320 mg glimepiride/kg/day for 12 months (approximately 1,000 times the recommended human dose based on surface area). No evidence of tumor formation was observed in any organ. One female and one male dog developed bilateral subcapsular cataracts. Non-GLP studies indicated that glimepiride was unlikely to exacerbate cataract formation. Evaluation of the co-cataractogenic potential of glimepiride in several diabetic and cataract rat models was negative and there was no adverse effect of glimepiride on bovine ocular lens metabolism in organ culture.

HUMAN OPHTHALMOLOGY DATA

Ophthalmic examinations were carried out in over 500 subjects during long-term studies using the methodology of Taylor and West and Latics et al. No significant differences were seen between AMARYL and glyburide in the number of subjects with clinically important changes in visual acuity, intra-ocular tension, or in any of the five lens-related variables examined.

Ophthalmic examinations were carried out during long-term studies using the method of Chylack et al. No significant or clinically meaningful differences were seen between AMARYL and glipizide with respect to cataract progression by subjective LOCS II grading and objective image analysis systems, visual acuity, intraocular pressure, and general ophthalmic examination.

Prescribing Information as of October 1999

Hoechst-Roussel Pharmaceuticals
Division of Hoechst Marion Roussel, Inc.
Kansas City, MO 64137 USA

Shown in Product Identification Guide, page 306

ANZEMET® Injection

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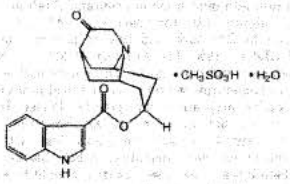
[an-zĕmĕt]
(dolasetron mesylate injection)

Prescribing Information as of February 1999

DESCRIPTION

ANZEMET (dolasetron mesylate) is an antinauseant and antiemetic agent. Chemically, dolasetron mesylate is (2α,6α,8α,9aβ)-octahydro-3-oxo-2,6-methano-2*H*-quinolizin-8-yl-1*H*-indole-3-carboxylate monomethanesulfonate, monohydrate. It is a highly specific and selective serotonin subtype 3 (5-HT_3) receptor antagonist both in vitro and in vivo. Dolasetron mesylate has the following structural formula:



The empirical formula is $C_{19}H_{20}N_2O_3 \bullet CH_3SO_3H \bullet H_2O$, with a molecular weight of 438.50. Approximately 74% of dolasetron mesylate monohydrate is dolasetron base.

Dolasetron mesylate monohydrate is a white to off-white powder that is freely soluble in water and propylene glycol, slightly soluble in ethanol, and slightly soluble in normal saline.

ANZEMET Injection is a clear, colorless, nonpyrogenic, sterile solution for intravenous administration. Each milliliter of ANZEMET Injection contains 20 mg of dolasetron mesylate and 38.2 mg mannitol with an acetate buffer in water for injection. The pH of the resulting solution is 3.2 to 3.8.

CLINICAL PHARMACOLOGY

Dolasetron mesylate and its active metabolite, hydrodolasetron (MDL 74,156), are selective serotonin 5-HT_3 receptor antagonists not shown 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 the released serotonin then activates 5-HT_3 receptors located on vagal efferents to initiate the vomiting reflex.

Acute, usually reversible, ECG changes (PR and QT_c prolongation; QRS widening), caused by dolasetron mesylate, have been observed in healthy volunteers and in controlled clinical trials. The active metabolites of dolasetron may block sodium channels, a property unrelated to its ability to block 5-HT_3 receptors. QT_c prolongation is primarily due to QRS widening. Dolasetron appears to prolong both depolarization and, to a lesser extent, repolarization time. The magnitude and frequency of the ECG changes increased with dose (related to peak plasma concentrations of hydrodolasetron but not the parent compound). These ECG interval prolongations usually returned to baseline within 6 to 8 hours, but in some patients were present at 24 hour follow up. Dolasetron mesylate administration has little or no effect on blood pressure.

In healthy volunteers (N=64), 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 did not alter mood or concentration. Multiple daily doses of dolasetron have had no effect on colonic transit in humans. Dolasetron mesylate has no effect on plasma prolactin concentrations.

Pharmacokinetics in Humans

Intravenous dolasetron mesylate is rapidly eliminated ($t_{1/2}$ <10 min) and completely metabolized to the most clinically relevant species, hydrodolasetron.

The reduction of dolasetron to hydrodolasetron is mediated by a ubiquitous enzyme, carbonyl reductase. Cytochrome P-450 (CYP)IID6 is primarily responsible for the subsequent hydroxylation of hydrodolasetron and both CYPIIIA and flavin monooxygenase are responsible for the N-oxidation of hydrodolasetron.

Hydrodolasetron is excreted in the urine unchanged (53.0% of administered intravenous dose). Other urinary metabolites include hydroxylated glucuronides and N-oxide.

Hydrodolasetron appeared rapidly in plasma, with a maximum concentration occurring approximately 0.6 hour after the end of intravenous treatment, and was eliminated with a mean half-life of 7.3 hours (%CV=24) and an apparent clearance of 9.4 mL/min/kg (%CV=28) in 24 adults. Hydrodolasetron is eliminated by multiple routes, including renal excretion and, after metabolism, mainly 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 feces. 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 protein. In a study with ^{14}C labeled dolasetron, the distribution of radioactivity to blood cells was not extensive. The binding of hydrodolasetron to α_1-acid glycoprotein is approximately 50%. The pharmacokinetics of hydrodolasetron are linear and similar in men and women.

The pharmacokinetics of hydrodolasetron, in special and targeted patient populations following intravenous administration of ANZEMET Injection, are summarized in Table 1. The pharmacokinetics of hydrodolasetron are similar in adult healthy volunteers and in adult cancer patients receiving chemotherapeutic agents. The apparent clearance of hydrodolasetron in pediatric and adolescent patients is 1.4

times to twofold higher than in adults. The apparent clearance of hydrodolasetron is not affected by age in adult cancer patients. Following intravenous administration, the apparent clearance of hydrodolasetron remains unchanged with severe hepatic impairment and decreases 47% with severe renal impairment. No dose adjustment is necessary for elderly patients or for patients with hepatic or renal impairment.

In a pharmacokinetic study in pediatric cancer patients (ages 3 to 11, N=25; ages 12 to 17, N=21) given a single 0.6, 1.2, 1.8, or 2.4 mg/kg dose of ANZEMET Injection intravenously, apparent clearance values were highest and half-lives were lowest in the youngest age group. For the 3 to 11 and the 12 to 17 year age groups, all receiving doses between 0.6 to 2.4 mg/kg, mean apparent clearances are 2 and 1.3 times greater, respectively, than for healthy adults receiving the same range of doses.

Thirty-two pediatric cancer patients ages 3 to 11 years (N=19) and 12 to 17 years (N=13), received 0.6, 1.2, or 1.8 mg ANZEMET Injection diluted with either apple or apple-grape juice and administered orally. In this study, the mean apparent clearances were 3 times greater in the younger pediatric group and 1.8 times greater in the older pediatric group than those observed in healthy adult volunteers. Across this spectrum of pediatric patients, maximum plasma concentrations were 0.6 to 0.7 times those observed in healthy adults receiving similar doses.

In a pharmacokinetic study in 18 pediatric patients (2 to 11 years of age) undergoing surgery with general anesthesia and administered a single 1.2 mg/kg intravenous dose of ANZEMET Injection, mean apparent clearance was greater (40%) and terminal half-life shorter (36%) for hydrodolasetron than in healthy adults receiving the same dose.

For 12 pediatric patients, ages 2 to 12 years receiving 1.2 mg/kg ANZEMET Injection diluted in apple or apple-grape juice and administered orally, the mean apparent clearance was 34% greater and half-life was 21% shorter than in healthy adults receiving the same dose.

[See table 1 at right]

Table 1. Pharmacokinetic Values for Plasma Hydrodolasetron Following Intravenous Administration of ANZEMET Injection*

	Age (years)	Dose	CL_{app} (mL/min/kg)	$t_{1/2}$ (h)	C_{max} (ng/mL)
Young Healthy Volunteers (N=24)	19–40	100 mg	9.4 (28%)	7.3 (24%)	320 (25%)
Elderly Healthy Volunteers (N=15)	65–75	2.4 mg/kg	8.3 (30%)	6.9 (22%)	620 (31%)
Cancer Patients					
Adults (N=273)	19–87	0.6–3.0 mg/kg	10.2 (34%)†	7.5 (43%)†	505 (26%)‡
Adolescents (N=21)	12–17	0.6–3.0 mg/kg	12.5 (37%)	5.5 (31%)	562 (45%)§
Children (N=25)	3–11	0.6–2.4 mg/kg	19.2 (30%)	4.4 (24%)	505 (100%)‖
Pediatric Surgery Patients (N=18)	2–11	1.2 mg/kg	13.1 (47%)	4.8 (23%)	255 (22%)
Patients with Severe Renal Impairment (N=12) (Creatinine clearance ≤10 mL/min)	28–74	200 mg	5.0 (33%)	10.9 (30%)	867 (31%)
Patients with Severe Hepatic Impairment (N=3)	42–52	150 mg	9.6 (19%)	11.7 (22%)	396 (45%)

CL_{app}: apparent clearance $t_{1/2}$: terminal elimination half-life ( ): coefficient of variation in %
*: mean values
†: results from population kinetic study
‡: results from adult cancer study (dose=1.8 mg/kg, N=8)
§: results from adolescents (dose=1.8 mg/kg, N=7)
‖: results from children (dose=1.8 mg/kg, N=5)

CLINICAL STUDIES

Prevention of Cancer Chemotherapy-Induced Nausea and Vomiting

ANZEMET Injection administered intravenously at a dose of 1.8 mg/kg gave similar results in preventing nausea and vomiting as the other selective serotonin 5-HT_3 receptor antagonists studied as active comparators. It was more effective than metoclopramide. Efficacy was based on complete response rates (0 emetic episodes and no rescue medication).

Cisplatin Based Chemotherapy

A randomized, double-blind trial compared single intravenous doses of ANZEMET Injection with metoclopramide in 226 (160 men and 66 women) adult cancer patients receiving ≥80 mg/m² cisplatin. ANZEMET Injection at a dose of 1.8 mg/kg was significantly more effective than metoclopramide in the prevention of chemotherapy-induced nausea and vomiting in this study (Table 2).

[See table 2 at right]

A second randomized, double-blind trial compared single intravenous doses of ANZEMET Injection with intravenous ondansetron in 609 (377 men and 232 women) adult cancer patients receiving ≥70 mg/m² cisplatin. A single intravenous 1.8 mg/kg dose of ANZEMET Injection was shown to be equivalent to a single intravenous 32 mg dose of ondansetron (Table 3).

[See table 3 at right]

Another randomized, double-blind trial compared single IV doses of ANZEMET with a single 3-mg IV dose of granisetron in 474 (315 men and 159 women) patients receiving ≥80 mg/m² cisplatin chemotherapy. A single intravenous 1.8-mg/kg dose of ANZEMET gave similar results as those from granisetron.

Table 2. Prevention of Chemotherapy-Induced Nausea and Emesis from Cisplatin Chemotherapy*

	ANZEMET Injection 1.8 mg/kg†	Metoclopramide‡	*p*-value
Number of Patients	72	69	
Response Over 24 Hours			
Complete Response§	41 (57%)	24 (35%)	0.0009
Nausea Score‖	4	30	0.0400

*: Dose ≥80 mg/m²
†: Administered intravenously
‡: 3 mg/kg intravenous bolus and 0.5 mg/kg/h intravenously over 8 h.
§: No emetic episodes and no rescue medication.
‖: Median 24-h change from baseline nausea score using visual analog scale (VAS): Score range 0="none" to 100="nausea as bad as it could be."

Table 3. Prevention of Chemotherapy-Induced Nausea and Emesis from Cisplatin Chemotherapy*

	ANZEMET Injection 1.8 mg/kg†	Ondansetron 32 mg‡	*p*-value
Number of Patients	198	206	
Response Over 24 Hours			
Complete Response§	88 (44%)	88 (43%)	NS
Nausea Score‖	10	16	NS

*: Dose ≥70 mg/m²
†: Administered intravenously
‡: Includes 12 patients who received 3 doses 0.15 mg/kg of ondansetron intravenously.
§: No emetic episodes and no rescue medication.
‖: Median 24-h change from baseline nausea score using visual analog scale (VAS): Score range 0="none" to 100="nausea as bad as it could be."

Cyclophosphamide Based Chemotherapy

In a study of ANZEMET Injection in 309 patients (96 men and 213 women) receiving moderately emetogenic chemotherapy such as cyclophosphamide based regimens, a single intravenous 1.8 mg/kg dose of ANZEMET Injection was equivalent to metoclopramide administered as a 2 mg/kg intravenous bolus followed by 3 mg/kg intravenously over 8 hours. Complete response rates were 63% and 52%, respectively, p=0.12.

Prevention of Postoperative Nausea and Vomiting

ANZEMET Injection administered intravenously at a dose of 12.5 mg approximately 15 minutes before the cessation of general balanced anesthesia (short-acting barbiturate, nitrous oxide, narcotic and analgesic, and skeletal muscle relaxant) was significantly more effective than placebo in preventing postoperative nausea and vomiting. No increased efficacy was seen with higher doses.

One trial compared single intravenous ANZEMET Injection doses of 12.5, 25, 50, and 100 mg with placebo in 635 women surgical patients undergoing laparoscopic procedures. ANZEMET Injection at a dose of 12.5 mg was statistically superior to placebo for complete response (no vomiting, no rescue medication) (p=.0003). Complete response rates were 50% and 31%, respectively.

Another trial compared single intravenous ANZEMET Injection doses of 12.5, 25, 50, and 100 mg with placebo in 1030 (722 women and 308 men) surgical patients. In women, the 12.5 mg dose was statistically superior to placebo for complete response. The complete response rates were 50% and 40%, respectively. However, in men, there was no statistically significant difference in complete response between any ANZEMET dose and placebo.

Treatment of Postoperative Nausea and/or Vomiting

Two randomized, double-blinded trials compared single intravenous ANZEMET Injection doses of 12.5, 25, 50, and 100 mg with placebo in 124 male and 833 female patients who had undergone surgery with general balanced anesthesia and presented with early postoperative nausea or vomiting requiring antiemetic treatment.

In both studies, the 12.5 mg intravenous dose of ANZEMET was statistically superior to placebo for complete response (no vomiting, no escape medication). No significant increased efficacy was seen with higher doses.

INDICATIONS AND USAGE

ANZEMET Injection is indicated for the following:

(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.

CONTRAINDICATIONS

ANZEMET Injection is contraindicated in patients known to have hypersensitivity to the drug.

WARNINGS

ANZEMET can cause ECG interval changes (PR, QT$_c$, JT prolongation and QRS widening). These 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.

A cardiac conduction abnormality observed on an intraoperative cardiac rhythm monitor (interpreted as complete heart block) was reported in a 61-year-old woman who received 200 mg ANZEMET for the prevention of postoperative nausea and vomiting. This patient was also taking verapamil. A similar event also interpreted as complete heart block was reported in one patient receiving placebo.

A 66-year-old man with Stage IV non-Hodgkins lymphoma died suddenly 6 hours after receiving 1.8 mg/kg (119 mg) intravenous ANZEMET Injection. This patient had other potential risk factors including substantial exposure to doxorubicin and concomitant cyclophosphamide.

PRECAUTIONS

General

Dolasetron should be administered with caution in patients who have or may develop prolongation of cardiac

Continued on next page

Anzemet Injection—Cont.

conduction intervals, particularly QT_c. 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 lead to QT prolongation, and cumulative high dose anthracycline therapy.

Cross hypersensitivity reactions have been reported in patients who received other selective 5-HT_3 receptor antagonists. These reactions have not been seen with dolasetron mesylate.

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. See PRECAUTIONS, General for information about potential interaction with other drugs that prolong the QT_c interval. 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. As with other agents which prolong ECG intervals, caution should be exercised in patients taking drugs which prolong ECG intervals, particularly QT_c.

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 intravenously concomitantly with atenolol. ANZEMET did 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 male mice treated with 150 mg/kg/day and above. In this study, mice (CD-1) were treated orally with dolasetron mesylate 75, 150 or 300 mg/kg/day (225, 450 or 900 mg/m^2/day). For a 50 kg person of average height (1.46 m^2 body surface area), these doses represent 3.4, 6.8 and 13.5 times the recommended clinical dose (66.6 mg/m^2, intravenous) on a body surface area basis. No increase in liver tumors 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 rat (Sprague-Dawley) carcinogenicity study, oral dolasetron mesylate was not tumorigenic at doses up to 150 mg/kg/day (900 mg/m^2/day, 13.5 times the recommended human dose based on body surface area) in male rats and 300 mg/kg/day (1800 mg/m^2/day, 27 times the recommended human dose based on body surface area) in female rats.

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 synthesis (UDS) 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 (600 mg/m^2/day, 9 times the recommended human dose based on body surface area) in female rats and up to 400 mg/kg/day (2400 mg/m^2/day, 36 times the recommended human dose based on body surface area) 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 intravenous doses up to 60 mg/kg/day (5.4 times the recommended human dose based on body surface area) and pregnant rabbits at intravenous doses up to 20 mg/kg/day (3.2 times the recommended human dose based on body surface area). 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 Injection is administered to a nursing woman.

Pediatric Use

Four open-label, noncomparative pharmacokinetic studies have been performed in a total of 108 pediatric patients receiving emetogenic chemotherapy or undergoing surgery with general anesthesia. These patients received ANZEMET Injection either intravenously or orally in juice. Pediatric patients from 2 to 17 years of age participated in these trials, which included intravenous ANZEMET Injection doses of 0.6, 1.2, 1.8, or 2.4 mg/kg, and oral doses of 0.6, 1.2, or 1.8 mg/kg. There is no experience in pediatric patients under 2 years of age. Overall, ANZEMET Injection was well tolerated in these pediatric patients. Efficacy information collected in pediatric patients receiving cancer chemotherapy are consistent with those obtained in adults. No efficacy information was collected in the pediatric postoperative nausea and vomiting studies.

Use in Elderly Patients

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.

Table 4. Adverse Events ≥ 2% from Chemotherapy-Induced Nausea and Vomiting Studies

Event	ANZEMET Injection 1.8 mg/kg (n=695)	Ondansetron/ Granisetron* (n=356)
Headache	169 (24.3%)	73 (20.5%)
Diarrhea	86 (12.4%)	25 (7.0%)
Fever	30 (4.3%)	18 (5.1%)
Fatigue	25 (3.6%)	12 (3.4%)
Hepatic Function Abnormal†	25 (3.6%)	12 (3.4%)
Abdominal Pain	22 (3.2%)	7 (2.0%)
Hypertension	20 (2.9%)	9 (2.5%)
Pain	17 (2.4%)	7 (2.0%)
Dizziness	15 (2.2%)	7 (2.0%)
Chills/Shivering	14 (2.0%)	6 (1.7%)

*: Ondansetron 32 mg intravenous, granisetron 3 mg intravenous.
†: Includes events coded as SGOT- and/or SGPT-increased (see also Liver and Biliary System below)

Table 5. Adverse Events ≥ 2% from Placebo-Controlled Postoperative Nausea and Vomiting Studies

Event	ANZEMET Injection 12.5 mg (n=615)	Placebo (n=739)
Headache	58 (9.4%)	51 (6.9%)
Dizziness	34 (5.5%)	23 (3.1%)
Drowsiness	15 (2.4%)	18 (2.4%)
Pain	15 (2.4%)	21 (2.8%)
Urinary Retention	12 (2.0%)	16 (2.2%)

ANZEMET® Injection
(dolasetron mesylate injection)
20 mg/mL

Strength	Description	NDC Number
12.5 mg	0.625-mL single use ampules (Box of 6)	0088-1208-65
100 mg/5 mL	5-mL single-use vial	0088-1206-32

ADVERSE REACTIONS

Chemotherapy Patients

In controlled clinical trials, 2265 adult patients received ANZEMET Injection. The overall adverse event rates were similar with 1.8 mg/kg ANZEMET Injection and ondansetron or granisetron. Patients were receiving concurrent chemotherapy, predominantly high-dose (≥50 mg/m^2) cisplatin. Following is a combined listing of all adverse events reported in ≥2% of patients in these controlled trials (Table 4).

[See table 4 above]

Postoperative Patients

In controlled clinical trials with 2550 adult patients, headache and dizziness were reported more frequently with 12.5 mg ANZEMET Injection than with placebo. Rates of other adverse events were similar. Following is a listing of all adverse events reported in ≥2% of patients receiving either placebo or 12.5 mg ANZEMET Injection for the prevention or treatment of postoperative nausea and vomiting in controlled clinical trials (Table 5).

[See table 5 above]

In clinical trials, the following infrequently reported adverse events, assessed by investigators as treatment-related or causality unknown, occurred following oral or intravenous administration of ANZEMET to adult patients receiving concomitant cancer chemotherapy or surgery:

Cardiovascular: Hypotension; rarely–edema, peripheral edema. The following events also occurred rarely and with a similar frequency as placebo and/or active comparator: Mobitz I AV block, chest pain, orthostatic hypotension, myocardial ischemia, syncope, severe bradycardia, and palpitations. See PRECAUTIONS section for information on potential effects on ECG.

In addition, the following asymptomatic treatment-emergent ECG changes were seen at rates less than or equal to those for active or placebo controls: bradycardia, tachycardia, T wave change, ST-T wave change, sinus arrhythmia, extrasystole (APCs or VPCs), poor R-wave progression, bundle branch block (left and right), nodal arrhythmia, U wave change, atrial flutter/fibrillation.

Furthermore, severe hypotension, bradycardia and syncope have been reported immediately or closely following IV administration.

Dermatologic: Rash, increased sweating.

Gastrointestinal System: Constipation, dyspepsia, abdominal pain, anorexia; rarely–pancreatitis.

Hearing, Taste and Vision: Taste perversion, abnormal vision; rarely–tinnitus, photophobia.

Hematologic: Rarely–hematuria, epistaxis, prothrombin time prolonged, PTT increased, anemia, purpura/hematoma, thrombocytopenia.

Hypersensitivity: Rarely–anaphylactic reaction, facial edema, urticaria.

Liver and Biliary System: Transient increases in AST (SGOT) and/or ALT (SGPT) values have been reported as adverse events in less than 1% of adult patients receiving ANZEMET in clinical trials. The increases did not appear to be related to dose or duration of therapy and were not associated with symptomatic hepatic disease. Similar increases were seen with patients receiving active comparator. Rarely–hyperbilirubinemia, increased GGT.

Metabolic and Nutritional: Rarely–alkaline phosphatase increased.

Musculoskeletal: Rarely–myalgia, arthralgia.

Nervous System: Flushing, vertigo, paraesthesia, tremor; rarely–ataxia, twitching.

Psychiatric: Agitation, sleep disorder, depersonalization; rarely–confusion, anxiety, abnormal dreaming.

Respiratory System: Rarely–dyspnea, bronchospasm.

Urinary System: Rarely–dysuria, polyuria, acute renal failure.

Vascular (Extracardiac): Local pain or burning on IV administration; rarely–peripheral ischemia, thrombophlebitis/phlebitis.

OVERDOSAGE

A 59-year-old man with metastatic melanoma and no known pre-existing cardiac conditions developed severe hypotension and dizziness 40 minutes after receiving a 15 minute intravenous infusion of 1000 mg (13 mg/kg) of dolasetron mesylate. Treatment for the overdose consisted of infusion of 500 mL of a plasma expander, dopamine, and atropine. The patient had normal sinus rhythm and prolongation of PR, QRS and QT, intervals on an ECG recorded 2 hours after the infusion. The patient's blood pressure was normal 3 hours after the event and the ECG intervals returned to baseline on follow-up. The patient was released from the hospital 6 hours after the event.

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