

PRODUCT INFORMATION

ANZEMET TABLETS & INJECTIONS

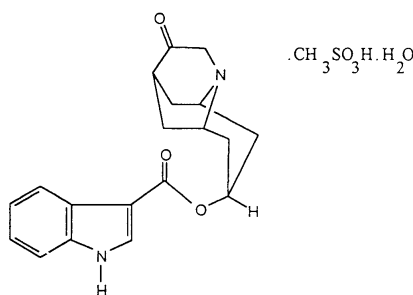
NAME OF THE MEDICINE

Non-proprietary Name

Dolasetron mesylate

Chemical Structure

Anzemet is dolasetron mesylate or (2 α , 6 α , 8 α , 9 β)-octahydro-3-oxo-2,6-methano-2H-quinolizin-8 yl-1H-indole-3 carboxylate monomethanesulfonate, monohydrate. The empirical formula is C₁₉H₂₀N₂O₃•CH₃SO₃H•H₂O (MW = 438.5). The structural formula appears below:



CAS Number

CAS number: 115956-13-3

DESCRIPTION

Dolasetron mesylate is a white to off-white powder. Freely soluble in water and in propylene glycol; slightly soluble in alcohol and in sodium chloride 0.9%.

Each Anzemet tablet contains dolasetron mesylate (50mg), lactose, pregelatinised maize starch, croscarmellose sodium, magnesium stearate, carnauba wax, white beeswax, opadry pink YS-1-14555-A and opacode black S-1-8093.

Each Anzemet injection contains dolasetron mesylate(12.5mg), mannitol, sodium acetate trihydrate, glacial acetic acid and water for injections.

PHARMACOLOGY

Dolasetron mesylate and its major metabolite are selective 5-HT₃ antagonists for the prevention and treatment of nausea and vomiting. They are devoid of activity at most other known serotonin receptors, and have no affinity for dopamine or adrenergic receptors. The 5-HT₃ receptors are located on pre-and postganglionic neurones and on neurones of the sensory and enteric nervous systems in the periphery and, centrally, in the chemoreceptor trigger zone of the area postrema. It is thought that chemotherapeutic agents and radiotherapy produce nausea and vomiting by releasing serotonin from the enterochromaffin cells of the small intestine and that the released serotonin can then activate 5-HT₃ receptors located on vagal afferents to initiate the vomiting reflex. The effect of dolasetron mesylate in the management of cancer therapy induced nausea and vomiting is due to antagonism of 5-HT₃ receptors on peripherally and/or centrally located neurones.

The mechanisms of action in post-operative nausea and vomiting are not known but there may be pathways common to chemotherapy induced nausea and vomiting.

Dolasetron mesylate and its active reduced metabolite have been shown to have electrophysiological properties associated with a reduction of the upstroke velocity (V_{\max}) of the cardiac action potential due to blockade of the fast sodium channels. Consistent with these preclinical findings, small, reversible, dose dependent widening of PR and QRS on ECG have been observed during clinical trials, which returned to baseline within 6-8 hours.

Pharmacokinetics

Absorption

Dolasetron mesylate is rapidly (half-life <10 minutes) and completely metabolised to the active, reduced metabolite following intravenous and oral dosing, with maximum plasma concentrations of active metabolite occurring less than one hour after dosing with dolasetron mesylate.

The formation of the active metabolite is stereoselective in man and in animals. The R(+) enantiomer accounts for the majority of the metabolite present in plasma (>75%) and urine (>86%) following both intravenous and oral administration of dolasetron mesylate, and has an approximately 3-fold greater 5-HT₃ antagonistic activity than the S(-) enantiomer.

The pharmacokinetics of the active metabolite are linear over the therapeutic dose range. After daily repeat dosing, exposure at steady state is predicted by single dose kinetics.

The absolute bioavailability of dolasetron mesylate tablets is approximately 75%. The tablet is bioequivalent to an oral solution. Food does not affect the apparent bioavailability of dolasetron mesylate tablets.

Distribution

The active metabolite is widely distributed in the body with a mean apparent volume of distribution of 5.0 to 7.9 L/kg. Its plasma protein binding is approximately 69-77% and is not affected by disease state or chemotherapy agents.

Excretion

The active metabolite is eliminated by renal excretion (30%) and metabolism, mainly glucuronidation and hydroxylation. In man, the elimination half-life of the active metabolite is 7-9 hours.

Special groups

The pharmacokinetics of the active metabolite in elderly subjects and in cancer patients are similar to that seen in healthy male or female volunteers. Apparent clearance is reduced in subjects with severe renal or hepatic impairment. Since the drug is eliminated by multiple routes and well tolerated, no dose adjustment is necessary in renally or hepatically impaired patients.

CLINICAL TRIALS

Anzemet injection and tablets are effective for the management of nausea and vomiting associated with emetogenic cancer therapy and surgery as shown by efficacy data from 10 randomised, double-blind studies in 4,820 patients and from five randomised, double-blind studies in 2,186 patients respectively. In all of these studies, efficacy was based on complete response rates (i.e. no emetic episodes and no rescue medication over 24 hours).

Prevention of Post-operative Nausea and Vomiting

IV Anzemet Studies

Data from three large randomised, double-blind trials in 1,946 surgical patients receiving Anzemet injection or placebo at the cessation of general balanced anaesthesia (short-acting barbiturate, nitrous oxide, a narcotic analgesic and skeletal muscle relaxant) show that

Anzemet is superior to placebo with maximal antiemetic efficacy in control of nausea at a dose of 12.5mg; no increased efficacy was seen with higher doses. 60.9% of patients receiving the 12.5mg dose were ASA status 1 and 63.6% of patients receiving placebo were ASA status 1.

The first randomised, double-blind trial compared single IV doses of Anzemet to placebo in 635 female patients undergoing laparoscopic procedures. In this study, the 12.5mg IV dose of Anzemet was superior to placebo for complete response and control of nausea.

The second randomised, double-blind trial compared single IV doses of Anzemet with placebo in 1,030 surgical patients. In this study, the 12.5mg dose of Anzemet was superior to placebo for complete response and control of nausea.

The third randomised, double-blind trial compared single IV doses of Anzemet with placebo in 281 female surgical patients. In this study, the 12.5mg dose produced a complete response rate of 54% compared with 43% for placebo and also superior control of nausea compared to placebo.

Oral Anzemet Studies

Data from two large randomised, double-blind trials in 1,162 surgical patients receiving 25 to 200mg oral Anzemet or placebo prior to induction of general balanced anaesthesia (short acting barbiturate; fentanyl nitrous oxide with supplemental isoflurane) show that Anzemet is significantly superior to placebo with maximal efficacy and control of nausea at a dose of 50mg; no increased efficacy was seen with higher doses. Doses of 50mg and higher were statistically superior to placebo. 75% of patients receiving the 50mg dose were ASA status 1 and 74.5% of patients receiving placebo were ASA status 1.

The first randomised, double-blind trial compared single oral Anzemet doses of 25 to 200mg to placebo in 789 patients undergoing gynaecological surgery. The 50mg dose produced a complete response rate superior to that seen with placebo.

The second randomised, double-blind trial compared single oral Anzemet doses of 25 to 200mg to placebo in 373 patients undergoing gynaecological surgery. In this study, the 50mg dose produced a complete response rate higher than placebo.

Treatment of Post-operative Nausea and/or Vomiting

Data from two randomised, double-blind trials in 957 surgical patients receiving IV Anzemet or placebo show that Anzemet is superior to placebo in the treatment of post-operative nausea and/or vomiting with maximal efficacy in control of nausea at a dose of 12.5mg. No increased efficacy was seen with higher doses. Trials compared single IV doses of Anzemet with placebo in patients who had undergone surgery with general balanced anaesthesia and presented with early post-operative nausea or vomiting requiring antiemetic treatment.

66.8% of patients receiving the 12.5mg dose were ASA status 1 and 69.3% of patients receiving placebo were ASA status 1.

The first randomised, double-blind trial compared single IV doses of Anzemet with placebo in 620 surgical patients. In this study, the 12.5mg IV dose of Anzemet was superior to placebo for complete response.

The second randomised, double-blind trial compared single IV doses of Anzemet to placebo in 337 surgical patients. In this study, the 12.5mg dose produced a complete response rate superior to placebo and also provided superior control of nausea compared to placebo.

Elderly Patients

In clinical trials, 1,072 volunteers and patients 65 years and older received intravenous and/or orally administered Anzemet. Effectiveness and safety were similar in younger and older patients.

INDICATIONS

IV Injection

Anzemet is indicated for use in adults for the prevention and treatment of post operative nausea and vomiting.

Oral Tablet

Anzemet is indicated for use in adults for the prevention of post operative nausea and vomiting.

CONTRAINDICATIONS

Dolasetron mesylate is contraindicated in:

- Paediatric patients aged 18 years and under
- Adult patients using dolasetron administered intravenously for the prevention of nausea and vomiting associated with initial and repeat courses of cancer chemotherapy
- Patients with a known hypersensitivity to the drug or any of the ingredients.

PRECAUTIONS

Cross hypersensitivity reactions have been reported in patients who received other selective 5HT₃ receptor antagonists.

Rapid IV administration (faster than 12.5 mg per 30 seconds) should be avoided (see **ADVERSE EFFECTS**).

Dolasetron mesylate has been shown to cause ECG changes, including prolongation of 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.

In settings where cardiac conduction interval prolongation may be present, a careful evaluation of benefit versus risk should be done before the start of therapy. This is particularly in patients with markedly prolonged QTc interval (e.g. in association with congenital QT prolongation), patients with AV block II-III or bundle branch block, patients receiving concomitant drugs that are known to prolong the QTc interval, and patients with electrolyte disturbances (e.g., hypokalemia or hypomagnesemia or patients receiving diuretics with potential for inducing electrolyte disturbance).

Interval prolongation could lead to cardiovascular consequences, including heart block or cardiac arrhythmias.

Special Risk Groups

Patients with Renal Impairment

Results from Phase I clinical trials and from searches of the adverse event database indicate that the Anzemet safety profile in patients with renal impairment is similar to that of the overall patient population.

Patients with Hepatic Impairment

Results from Phase I clinical trials and from searches of the adverse event database indicate that the Anzemet safety profile in patients with hepatic impairment is similar to that of the overall patient population.

Elderly Patients

Results from Phase I clinical trials and from searches of the adverse event database indicate that the Anzemet safety profile in elderly patients is similar to that of the overall patient population.

Children

The use of dolasetron mesylate is contraindicated in paediatric patients (see **CONTRAINDICATIONS**) as:

- Acute electrocardiographic changes have occurred very commonly.
- There is data to suggest that acute changes in QTc interval are greater in children than in adults.
- Individual cases of sustained supraventricular and ventricular arrhythmias, cardiac arrest and myocardial infarction have been reported in children and adolescents.

Patients with a History of Cardiovascular Disease and Patients Receiving Concomitant Cardiovascular Medication

Analysis of the adverse event database for these patients indicates that they are at no greater risk than the overall population, in particular with regard to both magnitude and incidence of ECG interval changes. However experience is limited and such patients should be treated with caution.

Carcinogenicity/Mutagenicity

Dolasetron mesylate was shown to be non-genotoxic in a standard battery of tests. No carcinogenic effects were seen in male or female rats in a two year dietary study at doses up to 150 and 300mg/kg/day respectively. Systemic exposure to the active metabolite at these dose levels was 4 to 8 times higher than that achieved at the maximum clinical dose. Hepatocellular adenomas and carcinomas were seen in male mice given dolasetron mesylate in the diet at dose levels of 150 and 300mg/kg/day, and an increased incidence of uterine polyploid adenomas was observed in female mice at the same dose levels. Preneoplastic changes were seen in the livers of male mice dosed at 75mg/kg/day; systemic exposure to the active metabolite at the latter dose levels was lower than that in humans. No effects on fertility were seen in male rats at oral dose levels up to 400mg/kg/day, but fertility of female rats was slightly impaired following oral administration at 100mg/kg/day.

Use in Pregnancy

Category B1

Dolasetron mesylate was not teratogenic when administered to rats and rabbits at intravenous dose levels up to 60 and 20mg/kg/day respectively, or at oral dose levels up to 100mg/kg/day in both species. No perinatal effects were seen in rats dosed orally at 100mg/kg/day.

There is no experience in pregnant humans. As with other medications, dolasetron mesylate should not be used during pregnancy unless the expected benefit to the patient is thought to outweigh any possible risk to the foetus.

Use in Lactation

It is not known whether dolasetron mesylate or its metabolites are excreted in the milk of humans or animals. In rats, oral administration of 100mg/kg/day had no effects on the survival, growth and development of the pups, although the reproductive capacity of the F₁ generation has not been adequately assessed. It is recommended that mothers receiving dolasetron mesylate should not breast feed their babies.

Interactions with other Medicines

Studies with an inducer and an inhibitor of cytochrome P₄₅₀ show that these drugs do not affect the disposition of dolasetron mesylate to any significant degree. Dolasetron mesylate does not induce cytochrome P₄₅₀. No clinically significant pharmacodynamic or pharmacokinetic interactions have been observed.

A review of the adverse experiences in the safety database has not demonstrated any clinically meaningful interaction between dolasetron and drugs commonly used in cancer patients receiving chemotherapy or patients undergoing surgical procedures and general anaesthesia or patients taking cardiovascular therapies.

Effect on Laboratory Tests

Falls in haemoglobin, haematocrit and RBC were found in approximately 5-10% of patients receiving either dolasetron or ondansetron in chemotherapy studies, and probably reflect the underlying disease and/or chemotherapy rather than dolasetron.

There was a higher incidence of decreases in haemoglobin and RBC in the post-operative nausea and vomiting studies compared to chemotherapy studies, but the incidence was similar in both the placebo and dolasetron groups. There were increases in WBC in 5-10% of the patients in both groups. These findings probably reflect the effect of the surgical procedure and/or haemodilution secondary to intravenous fluids.

There was a low incidence of abnormal liver function tests in both chemotherapy (0.5% oral, 3-4% iv) and post-operative nausea and vomiting ($\leq 1\%$) studies. In the latter studies, the incidence was similar in both the dolasetron and placebo group. These changes appeared to be transient.

ADVERSE EFFECTS

Anzemet was generally well tolerated in 6,694 patients receiving concomitant cancer chemotherapy or undergoing surgery in clinical trials.

The most frequently reported ($\geq 2\%$) adverse events in 1879 patients receiving oral Anzemet were headache (13.4%), bradycardia (mostly sinus) (6.2%), hypotension (3.6%), dizziness (2.9%), diarrhoea (2.3%), pruritis (2.2%) and tachycardia (mostly sinus) (2.1%). These events occurred with similar frequency in patients receiving comparator 5-HT₃ receptor antagonists or placebo.

The most frequently reported ($\geq 2\%$) adverse events in 4815 patients receiving IV Anzemet were headache (16.2%), diarrhoea (6.6%), bradycardia (mostly sinus) (6.5%), dizziness (3.7%), pain (3.0%), drowsiness (2.3%), fever (2.2%) and tachycardia (mostly sinus) (2.1%).

Similar occurrence rates were reported in patients receiving comparator 5-HT₃ antagonists or placebo.

In a study where IV and oral Anzemet were administered to 343 cancer patients for up to seven consecutive days (with or without dexamethasone), treatment-related adverse events were headache (41.1%), constipation (28.6%), dizziness (12.5%), sleep disorder (12.8%), dyspepsia (12.8%), fatigue (12.2%), diarrhoea (11.1%), drowsiness (10.5%) and abdominal pain (10.2%); these events occurred with similar frequency with the comparator 5-HT₃ receptor antagonist.

Over all Anzemet clinical trials in cancer and surgical patients, the incidence of adverse reactions in single dose studies can be classified as **very common (incidence $\geq 10\%$):** headache; **common (incidence $\geq 1\%$ and $< 10\%$):** bradycardia (mostly sinus), diarrhoea, dizziness, hypotension, increased serum transaminases, tachycardia; **uncommon (incidence $\geq 0.1\%$ and $< 1\%$):** abdominal pain, chest pain, constipation, dyspepsia, fatigue, hypertension, orthostatic hypotension; **rare (incidence $\geq 0.01\%$ and $< 0.1\%$):** intestinal obstruction, pancreatitis, jaundice, seizure, bronchospasm, myocardial ischaemia, syncope, severe bradycardia and oedema. With the exception of headache, dizziness and increased serum transaminases, the relationship of these events to Anzemet has not been established.

Liver transaminase increases occurred in >2% of patients during I.V. chemotherapy and radiotherapy, but in lesser incidence during post operative therapy, or I.V. surgery.

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

Patients receiving single-dose Anzemet therapy who had a history of cardiovascular disease, who received concomitant cardiovascular medication, or who received cardiotoxic chemotherapy, had similar adverse event rates to comparable patients treated with other 5-HT₃ receptor antagonists.

While the number of patients receiving longer term Anzemet therapy and having co-existing cardiovascular risk factors including near maximal cumulative anthracycline doses, concomitant pro-arrhythmic agents or pre-existing cardiac arrhythmias was small, these patients were safely treated.

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

Local pain or burning on IV administration has also been observed.

There are very rare reports of wide complex tachycardia or ventricular tachycardia and ventricular fibrillation/cardiac arrest following intravenous administration (see **PRECAUTIONS**).

There have been rare reports of anaphylactic/anaphylactoid reactions including skin reactions such as rash, pruritis and urticaria, respiratory reactions such as bronchospasm and very rare reports of facial oedema/angioedema and shock.

DOSAGE AND ADMINISTRATION

Anzemet is administered as a single daily dose.

Anzemet injection can be injected intravenously over 30 seconds or diluted to 50mL in normal saline, 5% glucose or other compatible intravenous fluids (see below) and infused over a period of up to 15 minutes.

Rapid administration (faster than 12.5mg per 30 seconds) should be avoided (see **ADVERSE EFFECTS**).

Post-Operative Nausea and Vomiting

For prevention of post-operative nausea and vomiting, Anzemet may be administered by mouth at the induction of anaesthesia or, alternatively, a single injection may be given at the cessation of anaesthesia. For treatment, a single daily intravenous dose should be administered when nausea or emesis presents.

The recommended dose for prevention of post-operative nausea and vomiting is 12.5mg by injection or 50mg by mouth. For treatment of post-operative nausea and vomiting, the recommended dose is 12.5mg by injection.

Dosage Adjustment

Studies in special risk groups (elderly, renally or hepatically impaired patients) indicate that it is not necessary to adjust the dose of dolasetron mesylate in these patients.

Analysis of the adverse event database for cytotoxic agents, histamine H₂ antagonists, selective serotonin re-uptake inhibitors (anti-depressants), post-surgical narcotics, neuromuscular blocking agents and reversal medications used following anaesthesia shows that there is no clinically significant interaction between dolasetron and medications commonly used in the cancer patients receiving chemotherapy or patients undergoing surgical procedures under general anaesthesia.

There is therefore no need for dose adjustments when Anzemet is coadministered with any of the drugs used for cancer chemotherapy or post-operative surgery.

Review of the database also indicates that co-medication with cardiovascular therapy (ACE inhibitors, diuretics, digoxin, class 1b anti-arrhythmics, beta-blockers, calcium channel blockers) does not alter the safety profile of dolasetron. There is therefore no need for dose adjustment in this situation.

Compatibility with other Drugs and Fluids

Dolasetron mesylate injection should only be admixed with those infusion fluids which are recommended, namely 5% glucose, 0.9% sodium chloride, 10% mannitol, compound sodium lactate, 0.18% sodium chloride / 4% glucose.

Dolasetron mesylate injection has been shown to be stable for at least 48 hours at 30°C when diluted at 0.05mg/mL or 2mg/mL with 5% glucose, 0.9% sodium chloride, 0.18% sodium chloride/4% glucose intravenous infusion, and with 10% mannitol and compound sodium lactate intravenous infusions. However, in line with good pharmaceutical practice, diluted intravenous fluids should be used immediately after preparation, although they may be stored for up to 24 hours at 2-8°C.

Dolasetron mesylate injection has been shown to be incompatible with acyclovir sodium, aminophylline, amphotericin B, ampicillin sodium, carmustine, cefazolin sodium, chloramphenicol sodium succinate, clindamycin phosphate, dexamethasone, potassium phosphate, thiopentone sodium, 5-fluorouracil, heparin sodium, methylprednisolone succinate, sodium bicarbonate and trimethoprim with sulfamethoxazole. It is therefore recommended that Anzemet injection should not be mixed with any other drugs or administered through the same IV tubing and Y-site unless the Y-site and tubing have been thoroughly and completely flushed with compatible IV solution between administering the two drug solutions.

Dolasetron mesylate injection is compatible with polypropylene syringes.

OVERDOSAGE

There is no specific antidote for dolasetron mesylate and patients with suspected overdose should be managed with symptomatic and supportive therapy. If clinically indicated, the patient should have cardiac monitoring.

There have been reports of overdose. Severe hypotension, dizziness, and prolongation of the PR, QRS and QTc intervals were reported after overdose of intravenous infusion. (See **ADVERSE EFFECTS** for information on asymptomatic ECG interval prolongations).

Acute toxicity studies in rodents showed signs of central nervous system toxicity, including tremors and depression; convulsions occurred at intravenous doses greater than 112mg/kg and at oral doses greater than 300mg/kg. Emesis was observed in dogs at intravenous doses greater than 4.5mg/kg and at oral doses greater than 5mg/kg. No effects were observed in monkeys at intravenous or oral doses up to 30 and 200mg/kg, respectively.

PRESENTATION AND STORAGE CONDITIONS

Anzemet Injection

12.5 mg Vials

Type 1 glass vials with a butyl rubber closure and plastic (polypropylene) flip-off top with aluminium overseal packed in a carton. Each Anzemet injection vial contains 0.625mL giving 12.5mg of dolasetron mesylate. There are 6 vials per carton.

The vials should be stored below 25°C and protected from light.

Anzemet Tablet

Tablets are packaged in a PVC/PVDC/aluminium foil blister strip contained in a carton. Anzemet 50mg tablets are round, light-pink biconvex tablet, printed A on one face and 50 on reverse, approximately 7.2 mm in diameter. There are 5 tablets per blister strip.

The tablets should be stored below 30°C.

NAME AND ADDRESS OF SPONSOR

sanofi-aventis australia pty ltd
12-24 Talavera Road
Macquarie Park
NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF APPROVAL

Date of TGA Approval: 24 July 2009

Date of most recent amendment: 25 May 2011