commercially available tablets found them to be stable for at least 90 days when stored at 3 to 5° and at 23 to 25°.

1. Johnson CE, *et al.* Stability of dolasetron in two oral liquid vehicles. *Am J Health-Syst Pharm* 2003; **60:** 2242–4.

Adverse Effects and Precautions

As for Ondansetron, p.1757. Diarrhoea, anorexia, and abdominal pain may also occur. Various ECG changes have been noted with dolasetron. Dolasetron should be used with caution in patients who have, or may develop, prolongation of the QT interval or other alterations in cardiac conduction intervals, and in those with electrolyte imbalances. Other adverse effects include dyspepsia, flatulence, taste disturbances, fever, chills or shivering, sleep disorders, fatigue, and drowsiness. There have been rare reports of intestinal obstruction, pancreatitis, jaundice, seizures, bronchospasm, cardiac arrhythmias, and oedema. Local reactions may occur on intravenous use. No dosage reduction is considered necessary in renal or hepatic impairment, despite possible reductions in clearance.

Effects on the cardiovascular system. For a discussion of the effects of 5-HT_3 antagonists on the cardiovascular system, see under Ondansetron, p.1757.

Phlebitis. Venous irritation has been reported after intravenous use of dolasetron; diluting subsequent doses with sodium chloride 0.9% and infusing it more slowly markedly reduced the frequency of phlebitis.[1]

1. Oshiro MM. Dolasetron-associated venous irritation. *Am J Health-Syst Pharm* 2000; **57:** 1533–4.

Interactions

Plasma concentrations of hydrodolasetron, the active metabolite of dolasetron, are increased by cimetidine and atenolol and decreased by rifampicin. Dolasetron should be used with caution in patients taking drugs that prolong the QT interval, including those likely to cause electrolyte disturbances (see also p.1757).

Pharmacokinetics

Dolasetron given orally or intravenously is rapidly converted to the active metabolite hydrodolasetron by carbonyl reductase, a ubiquitous enzyme. Peak plasma concentrations of hydrodolasetron occur 1 hour after oral, and 0.6 hours after intravenous, doses of dolasetron. The apparent oral bioavailability of dolasetron determined as hydrodolasetron is about 75%. It has a mean elimination half-life of about 7 to 8 hours.

Hydrodolasetron is partially metabolised by the cytochrome P450 isoenzymes CYP2D6 and CYP3A and about 50 to 60% is eliminated unchanged in the urine. Two thirds of a dose of dolasetron is recovered in the urine and one third in the faeces.

Clearance of hydrodolasetron is increased in children, but is not altered in the elderly. Clearance is reduced in severe hepatic impairment (Child-Pugh category B or C) and in severe renal impairment (creatinine clearance less than 10 mL/min) after oral use. After intravenous use, clearance is reduced in severe renal impairment but apparently unchanged in severe hepatic impairment.

◊ References.

1. Lerman J, *et al.* Pharmacokinetics of the active metabolite (MDL 74,156) of dolasetron mesylate after oral or intravenous administration to anesthetized children. *Clin Pharmacol Ther* 1996; **60:** 485–92.
2. Dempsey E, *et al.* Pharmacokinetics of single intravenous and oral doses of dolasetron mesylate in healthy elderly volunteers. *J Clin Pharmacol* 1996; **36:** 903–10.
3. Stubbs K, *et al.* Pharmacokinetics of dolasetron after oral and intravenous administration of dolasetron mesylate in healthy volunteers and patients with hepatic dysfunction. *J Clin Pharmacol* 1997; **37:** 926–36.
4. Dimmitt DC, *et al.* Pharmacokinetics of oral and intravenous dolasetron mesylate in patients with renal impairment. *J Clin Pharmacol* 1998; **38:** 798–806.
5. Dimmitt DC, *et al.* Effect of infusion rate on the pharmacokinetics and tolerance of intravenous dolasetron mesylate. *Ann Pharmacother* 1998; **32:** 39–44.

Uses and Administration

Dolasetron is a 5-HT_3 antagonist with antiemetic actions similar to those of ondansetron (see p.1757). It is used as the mesilate in the prevention of nausea and vomiting (p.1700) associated with chemotherapy, and in the prevention and treatment of postoperative nausea and vomiting.

For *prevention* of acute **nausea and vomiting** associated with **chemotherapy** dolasetron mesilate may be given orally in a dose of 100 mg (in the USA) or 200 mg (in most other countries including the UK) within 1 hour before treatment. Alternatively, it may be given in a dose of 1.8 mg/kg, or 100 mg, by intravenous injection at a rate of up to 100 mg over 30 seconds about 30 minutes before chemotherapy; the same dose may be diluted to 50 mL with a suitable infusion solution and given intravenously over up to 15 minutes. To protect against delayed emesis, a further 200-mg dose may be given orally once daily; in Europe and the UK dolasetron may not normally be given for more than 4 consecutive days per chemotherapy cycle although some countries permit use for up to 7 days.

When given for the *prevention* of **postoperative** nausea and vomiting the recommended dose is usually 50 mg of dolasetron mesilate orally before induction of anaesthesia or 12.5 mg intravenously at the end of anaesthesia. In the USA, it is given as a 100-mg oral dose within 2 hours before surgery, or 12.5 mg intravenously about 15 minutes before the end of anaesthesia. The same intravenous dose may be given for the *treatment* of postoperative nausea and vomiting.

The use of dolasetron mesilate in **children** is licensed in some countries, including the USA. However, others have not licensed such use and in the UK it is contraindicated in children and adolescents under 18 years of age because they may be at increased risk of acute changes in the QT interval, and there have been reports of cardiac conduction disorders, cardiac arrest, and myocardial infarction in children treated with dolasetron. In the USA, children over 2 years of age may be given dolasetron mesilate 1.8 mg/kg orally (within 1 hour before chemotherapy) or intravenously (about 30 minutes before chemotherapy), up to a maximum dose of 100 mg, to prevent acute chemotherapy-induced nausea and vomiting. For prevention of postoperative nausea and vomiting, 1.2 mg/kg by mouth, up to a maximum of 100 mg, may be given within 2 hours before surgery; or 350 micrograms/kg, up to a maximum of 12.5 mg, may be given intravenously 15 minutes before the end of anaesthesia. The same intravenous dose may be given to treat established postoperative nausea and vomiting.

◊ Reviews.

1. Balfour JA, Goa KL. Dolasetron: a review of its pharmacology and therapeutic potential in the management of nausea and vomiting induced by chemotherapy, radiotherapy or surgery. *Drugs* 1997; **54:** 273–98.
2. Anonymous. Dolasetron for prevention of nausea and vomiting due to cancer chemotherapy. *Med Lett Drug Ther* 1998; **40:** 53–4.

Pruritus. Dolasetron and other 5-HT_3 antagonists have been investigated for the management of pruritus (see under Ondansetron, p.1758).

Preparations

USP 31: Dolasetron Mesylate Injection; Dolasetron Mesylate Oral Solution; Dolasetron Mesylate Oral Suspension; Dolasetron Mesylate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Anzemet†; ***Austral.:*** Anzemet; ***Austria:*** Anzemet; ***Braz.:*** Anzemet; ***Canad.:*** Anzemet; ***Cz.:*** Anzemet†; ***Fin.:*** Anzemet†; ***Fr.:*** Anzemet; ***Ger.:*** Anemet; ***Gr.:*** Anzemet; ***Hung.:*** Anemet†; ***Ital.:*** Anzemet; ***Mex.:*** Anzemet; ***Neth.:*** Anzemet; ***S.Afr.:*** Zamanon; ***Switz.:*** Anzemet; ***UK:*** Anzemet; ***USA:*** Anzemet; ***Venez.:*** Anzemet.

Domperidone *(BAN, USAN, rINN)*

Domperidon; Domperidona; Domperidonas; Dompéridone; Domperidoni; Domperidonum; R-33812. 5-Chloro-1-{1-[3-(2-oxobenzimidazolin-1-yl)propyl]-4-piperidyl}benzimidazolin-2-one.

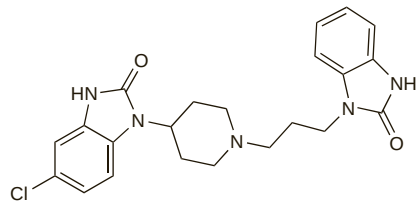
Домперидон

$C_{22}H_{24}ClN_5O_2$ = 425.9.

CAS — 57808-66-9.

ATC — A03FA03.

ATC Vet — QA03FA03.



Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Domperidone). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; soluble in dimethylformamide. Protect from light.

Domperidone Maleate *(BANM, rINNM)*

Dompéridone, maléate de; Domperidoni maleas; Domperidon-imaleaatti; Domperidonmaleat; Domperidon-maleát; Domperidon-maleinát; Domperidono maleatas; Maleato de domperidona.

Домперидона Малеат

$C_{22}H_{24}ClN_5O_2.C_4H_4O_4$ = 542.0.

CAS — 99497-03-7.

ATC — A03FA03.

ATC Vet — QA03FA03.

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Domperidone Maleate). A white or almost white powder; it exhibits polymorphism. Very slightly soluble in water and in alcohol; sparingly soluble in dimethylformamide; slightly soluble in methyl alcohol. Protect from light.

Adverse Effects

Plasma-prolactin concentrations may be increased, which may lead to galactorrhoea or gynaecomastia. There have been reports of reduced libido, and rashes and other allergic reactions. Domperidone does not readily cross the blood-brain barrier and the incidence of central effects such as extrapyramidal reactions or drowsiness may be lower than with metoclopramide (p.1748); however, there have been reports of dystonic reactions.

Domperidone by injection has been associated with convulsions, arrhythmias, and cardiac arrest. Fatalities have restricted use by this route.

Effects on the cardiovascular system. Sudden death has occurred in cancer patients given domperidone *intravenously* in high doses.[1-3] Four cancer patients experienced cardiac arrest after high intravenous doses[4] and 2 of 4 similar patients had ventricular arrhythmias.[5] After such reports the injection has been withdrawn from general use in many countries, including the UK.

Prolongation of the QT interval has been reported in an infant given *oral* domperidone, with normalisation after the drug was stopped.[6]

1. Joss RA, *et al.* Sudden death in cancer patient on high-dose domperidone. *Lancet* 1982; **i:** 1019.
2. Giaccone G, *et al.* Two sudden deaths during prophylactic antiemetic treatment with high doses of domperidone and methylprednisolone. *Lancet* 1984; **ii:** 1336–7.
3. Weaving A, *et al.* Seizures after antiemetic treatment with high dose domperidone: report of four cases. *BMJ* 1984; **288:** 1728.
4. Roussak JB, *et al.* Cardiac arrest after treatment with intravenous domperidone. *BMJ* 1984; **289:** 1579.
5. Osborne RJ, *et al.* Cardiotoxicity of intravenous domperidone. *Lancet* 1985; **ii:** 385.
6. Rocha CMG, Barbosa MM. QT interval prolongation associated with the oral use of domperidone in an infant. *Pediatr Cardiol* 2005; **26:** 720–3.

Effects on the endocrine system. There have been reports of galactorrhoea with gynaecomastia[1] or mastalgia[2,3] generally associated with raised serum-prolactin concentrations. Gynaecomastia without galactorrhoea has also been reported.[4]

1. Van der Steen M, *et al.* Gynaecomastia in a male infant given domperidone. *Lancet* 1982; **ii:** 884–5.
2. Cann PA, *et al.* Galactorrhoea as side effect of domperidone. *BMJ* 1983; **286:** 1395–6.
3. Cann PA, *et al.* Oral domperidone: double blind comparison with placebo in irritable bowel syndrome. *Gut* 1983; **24:** 1135–40.
4. Keating JP, Rees M. Gynaecomastia after long-term administration of domperidone. *Postgrad Med J* 1991; **67:** 401–2.

Extrapyramidal effects. There are reports of extrapyramidal symptoms,[1,2] including acute dystonic reactions[3] and neuroleptic malignant syndrome[4] in individual patients given domperidone.

1. Sol P, *et al.* Extrapyramidal reactions due to domperidone. *Lancet* 1980; **ii:** 802.