lin 1 g and clarithromycin 500 mg, both twice daily. These regimens are given for 1 week. **Dual therapy** regimens such as omeprazole 20 mg twice daily or 40 mg daily with either amoxicillin 750 mg to 1 g twice daily or clarithromycin 500 mg three times daily, are less effective and must be given for 2 weeks. Omeprazole alone may be continued for a further 4 to 8 weeks.

Doses of 20 mg daily orally are used in the treatment of **NSAID-associated ulceration**; a dose of 20 mg daily may also be used for prophylaxis in patients with a history of gastroduodenal lesions who require continued NSAID treatment.

The initial recommended dosage for patients with the **Zollinger-Ellison syndrome** is 60 mg orally once daily, adjusted as required. The majority of patients are effectively controlled by doses in the range 20 to 120 mg daily, but doses up to 120 mg three times daily have been used. Daily doses above 80 mg should be given as divided doses (usually 2).

Omeprazole is also used for the prophylaxis of **acid aspiration** during general anaesthesia, in a dose of 40 mg the evening before surgery and a further 40 mg two to six hours before the procedure.

The dose of omeprazole may need to be reduced in patients with hepatic impairment (see below).

PARENTERAL DOSAGE.

In patients who are unsuited to receive oral therapy omeprazole sodium may be given on a short-term basis by intravenous infusion, in a usual dose equivalent to 40 mg of the base over a period of 20 to 30 minutes in 100 mL of sodium chloride 0.9% or glucose 5%. It may also be given by slow intravenous injection. Higher intravenous doses have been given to patients with Zollinger-Ellison syndrome.

◊ General reviews.

1. Richardson P, *et al.* Proton pump inhibitors: pharmacology and rationale for use in gastrointestinal disorders. *Drugs* 1998; **56:** 307–35.
2. Langtry HD, Wilde MI. Omeprazole: a review of its use in Helicobacter pylori infection, gastro-oesophageal reflux disease and peptic ulcers induced by nonsteroidal anti-inflammatory drugs. *Drugs* 1998; **56:** 447–86.
3. Berardi RR, Welage LS. Proton-pump inhibitors in acid-related diseases. *Am J Health-Syst Pharm* 1998; **55:** 2289–98.
4. Brown GJE, Yeomans ND. Prevention of the gastrointestinal adverse effects of nonsteroidal anti-inflammatory drugs: the role of proton pump inhibitors. *Drug Safety* 1999; **21:** 503–12.
5. Erstad BL. Proton-pump inhibitors for acute peptic ulcer bleeding. *Ann Pharmacother* 2001; **35:** 730–40.
6. Robinson M, Horn J. Clinical pharmacology of proton pump inhibitors: what the practising physician needs to know. *Drugs* 2003; **63:** 2739–54.
7. Dekel R, *et al.* The role of proton pump inhibitors in gastro-oesophageal reflux disease. *Drugs* 2004; **64:** 277–95.
8. Anonymous. Proton pump inhibitors for GERD in children. *Med Lett Drugs Ther* 2007; **49:** 17–18.

Administration. Omeprazole is given orally as tablets or capsules containing enteric-coated pellets or granules, which should be swallowed whole and not crushed or chewed. In children or patients with swallowing difficulties, UK licensed product information (*Losec; AstraZeneca*) states that the tablet be dispersed in water and then mixed with fruit juice (with a pH less than 5) or yogurt before swallowing without chewing. Similarly the contents of the capsules can be mixed with water, fruit juice (with a pH less than 5) or yogurt and swallowed without chewing. A mixture of omeprazole and sodium bicarbonate as a powder for oral suspension is available in some countries.

Administration in children. Licensed UK *oral* doses of omeprazole for the treatment of gastro-oesophageal reflux disease in children 1 year of age and over are determined by body-weight as follows:

- 10 to 20 kg: 10 mg once daily
- over 20 kg: 20 mg once daily

These doses may be doubled if necessary. Treatment may be given for 4 to 12 weeks.

For gastro-oesophageal reflux disease, acid-related dyspepsia, treatment of duodenal and benign gastric ulcers including NSAID-associated ulceration, prophylaxis of acid aspiration, and Zollinger-Ellison syndrome, the *BNFC* recommends an oral dose of 700 micrograms/kg once daily in neonates and children 1 month to 2 years of age. If needed, doses may be increased in neonates after 7 to 14 days, to 1.4 mg/kg once daily; some neonates may require up to 2.8 mg/kg once daily. Children's doses may be increased up to 3 mg/kg (to a maximum of 20 mg) once daily.

For *parenteral* dosage in children the *BNFC* recommends an intravenous dose of 500 micrograms/kg (to a maximum of 20 mg) once daily in children aged 1 month to 12 years; this may be increased to 2 mg/kg (to a maximum of 40 mg) once daily if needed.

For the eradication of *Helicobacter pylori* in children, the *BNFC* recommends an oral dose of omeprazole 1 to 2 mg/kg (to a maximum dose of 40 mg) once daily. This is given with antibacterial therapy under specialist supervision.

For administration of the tablets or capsules to children, see Administration, above.

Administration in hepatic impairment. Bioavailability and half-life of omeprazole can increase in patients with hepatic impairment. UK licensed product information recommends that a maximum daily oral dose of 20 mg be used in these patients; a daily intravenous dose of 10 to 20 mg is considered sufficient.

Asthma. Gastro-oesophageal reflux has been suggested as a potential exacerbating factor for asthma (p.1108), and acid suppressive therapy with omeprazole has been reported to reduce asthma symptoms in some[1] but not other[2] studies. A meta-analysis of acid suppressive therapy concluded it was not effective in improving asthma symptoms in most patients with gastro-oesophageal reflux,[3] and the link between reflux and asthma symptoms has been disputed.[4]

1. Harding SM, *et al.* Asthma and gastroesophageal reflux: acid suppressive therapy improves asthma outcome. *Am J Med* 1996; **100:** 395–405.
2. Ford GA, *et al.* Omeprazole in the treatment of asthmatics with nocturnal symptoms and gastro-oesophageal reflux: a placebo-controlled cross-over study. *Postgrad Med J* 1994; **70:** 350–4.
3. Gibson PG, *et al.* Gastro-oesophageal reflux treatment for asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 11/12/07).
4. Field SK. A critical review of the studies of the effects of simulated or real gastroesophageal reflux on pulmonary function in asthmatic adults. *Chest* 1999; **115:** 848–56.

Dyspepsia. Although earlier UK guidelines on the use of proton pump inhibitors in dyspepsia (p.1695) suggested that they should not be used routinely in non-ulcer dyspepsia,[1] subsequent guidelines on its general management in both the UK[2] and the US[3] consider that a 1-month empirical trial in patients aged under 55 without symptoms suggestive of more serious disease is a valid first-line treatment.

1. NICE. Guidance on the use of proton pump inhibitors in the treatment of dyspepsia (issued July 2000). Available at: http://www.nice.org.uk/nicemedia/pdf/proton.pdf (accessed 11/02/08)
2. NICE. Dyspepsia: management of dyspepsia in adults in primary care (Clinical Guideline 17: issued August 2004, updated June 2005). Available at: http://www.nice.org.uk/nicemedia/pdf/CG017NICEguideline.pdf (accessed 11/02/08)
3. American Gastroenterological Association. American Gastroenterological Association medical position statement: evaluation of dyspepsia. *Gastroenterology* 2005; **129:** 1753–5. Also available at: http://download.journals.elsevierhealth.com/pdfs/journals/0016-5085/PIIS0016508505018172.pdf (accessed 11/02/08)

Inflammatory bowel disease. There are a few reports[1-3] of responses to omeprazole in patients with inflammatory bowel disease (p.1697). Combination of omeprazole with mesalazine has also been tried.[2]

1. Heinzow U, Schlegelberger T. Omeprazole in ulcerative colitis. *Lancet* 1994; **343:** 477.
2. Dickinson JB. Is omeprazole helpful in inflammatory bowel disease? *J Clin Gastroenterol* 1994; **18:** 317–19.
3. Guslandi M, Tittobello A. Symptomatic response to omeprazole in inflammatory bowel disease. *J Clin Gastroenterol* 1996; **22:** 159–60.

Scleroderma. Gastro-oesophageal reflux is one of the gastrointestinal manifestations of systemic sclerosis, and proton pump inhibitors such as omeprazole play a major role in the management of such gastrointestinal disease.[1] For a discussion of the broader management of the condition see p.1817.

1. Williamson DJ. Update on scleroderma. *Med J Aust* 1995; **162:** 599–601.

Preparations

BP 2008: Gastro-resistant Omeprazole Capsules; Gastro-resistant Omeprazole Tablets;
USP 31: Omeprazole Delayed-Release Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Acimed; Aziatop; Brux; Danlox; Fabrazol; Fendiprazol; Gastec; Gastroprazol; Gastrotem; Klomeprax; Losec; Mucoxol; Omeprasec; Pepticus†; Pravil; Procelac; Prysma; Regulacid; Timezol; Ulcozol; Zoltenk; ***Austral.:*** Acimax; Losec; Maxor†; Meprazol; Omepral; Probitor; ***Austria:*** Helicostad; Losec; Lostad; Medoprazol; Omec; Omegastron; Omepralan; Probitor†; Semiglen†; ***Belg.:*** Docomepra; Logastric; Losec; Omepratop; Sedacid; ***Braz.:*** Belprazol†; Bioprazol†; Elprazol†; Estomepe; Eupept; Fegran†; Gasec; Gaspiren; Gastrib†; Gastrium; Gastrozol; Klispel; Lomepral†; Loprazol; Losaprol†; Losar†; Losec; Lozap†; Lozeprel; Lozix†; Meprazan; Mesopran†; Neoprazol; Novoprazol†; Omegastrol; Omenax; Omep†; Omepramed; Omeprazin; Omeprotec†; Oprazon; Peprazol; Pepsicaps; Prazolex; Prazonil; Prazotom†; Ulcecaps†; Ulcefor; Ulcozol†; Uniprazol; Victrix; Zolpramex†; ***Canad.:*** Losec; ***Chile:*** Lomex; Losec; Micromex; Omeprax; Pepticum†; Prazolo†; Ulc-Out; Ulcelac; Ulcrux†; Zatrol; Zomepral; ***Cz.:*** Apo-Ome; Gasec; Helicid; Lomac; Losec; Loseprazol; Omepirex; Omeprol; Omolin; Onprelen; Oprazole†; Ortanol; Pepticum†; Problok†; Tulzol; Ultop; ***Denm.:*** Losec; ***Fin.:*** Losec; ***Fr.:*** Mopral; Zoltum; ***Ger.:*** Antra; Gastracid; Ome TAD; Ome-nerton; Ome-Puren; Ome-Q; Omebeta; Omedoc; Omegamma; OmeLich; Omelind; Omep; ***Gr.:*** Assoprol; Belifax; Elibactin; Elkostop; Elkotheran; Eselan; Esopraz; Ezipol; Gertalgin; Glaveral; Inhiplex; Kerlofin; Lanex; Lenar; Lomezec; Loproc; Lordin; Losec; Lozaprin; Malortil; Meprolen; Novek; Odamesol; Odasol; Ofnimarex; Omeprol; Penrazol; Pipacid; Prazolin; Probitor; Rythmogastryl; Sedacid; Sieral; Silato; Ufonitren; Veralox; Zolldenol; ***Hong Kong:*** Losec; ***Hung.:*** Losec; Omegen; Omep; Omeprawin; Ulzol; ***India:*** Biocid; Lomac; Nogacid; Ocid; Olit; Omezol; Promisec; Ulzol†; ***Indon.:*** Contral; Dudencer; Loklor; Losec; Meisec; Norsec; Omevell; OMZ; Onic; Opm; Oprezol; Ozid; Prohibit; Promezol; Protop; Pumpitor; Redusec; Regasec; Rocer; Socid; Stomacer; Ulzol; Zepral; Zollocid; ***Irl.:*** BySec; Lopraz; Losamel; Losec; Losepine; Ulcid; ***Israel:*** Losec; Omepradex; ***Ital.:*** Antra; Losec; Mepral; Omeprazen; ***Jpn:*** Omepral; ***Malaysia:*** Gasec; Losec; Medoprazole; Omelon; Omesec; Omez; Omezole; Probitor†; Romesec; Zenpro†; Zimor; ***Mex.:*** Alboz; Aleprozil; Apopraza; Argaryn†; Azoran; Danovag; Domer; Gerdex; Grizol; Hopram†; Ibax; Inhibitron; Logazil; Lopram; Losec; Medral; Mopral; Mornin; Olexin; Omecaps; Ometec; Opramid; Osiren; Ozoken; Panzer; Pastrizol; Pentren; Prazidec; Prazolit; Sarox; Solcer; Suifac; Tarzol; Ucetal; Ulsen; Ultizol; Ultromep; Usaltron; Vulcasid; Zoral; Zulmedx; ***Neth.:*** Losec; Omeprazostad†; Omepstad†; Omezol†; Omolin; Romisan; ***Norw.:*** Losec; ***NZ:*** Losec; Omezol; ***Philipp.:*** Gastriloc; Hovizol; Losec; Mepracid; Omenole; Omepron; Omizac; OMZ; Opehex; Peptisolv; Premio; Promesec; Puroxel; Risek; Tansinel; Ulsek; Zyom; ***Pol.:*** Bioprazol; Gasec; Helicid; Losec; Notis; Omar; Ortanol; Polprazol; Prazol; Ulzol; ***Port.:*** Belmazol; Bloprazol; Eugastrim; Gasec; Losec; Mepraz; Novek; Nuclosina†; Omepra; Omeratio; Omerol†; Ometon; Omezolan; Prazentol; Prazex; Prazolene; Proclor; Proton; ***Rus.:*** Gastrozol (Гастрозол); Helicid (Хеликид); Helol (Хелол); Losec (Лосек); Ocid (Оцид); Omez (Омез); Omipix (Омипикс); Omitox (Омитокс); Omizac (Омизак); Romesec (Ромесек); Sopral (Сопрал)†; Ultop (Ультоп); Ulzol (Улзол); Zerocid (Зероцид); ***S.Afr.:*** Altosec; Losec; Omez; Omiloc; Ulzec; ***Singapore:*** Losec; Ocid; Olit; Omesec; Omezole; Penrazole; Proceptin; Romesec; Zenpro; Zimor; ***Spain:*** Audazol; Aulcer; Belmazol; Ceprandal; Dolintol; Elgam; Emeproton; Gastrimut; Indurgan; Ipirasa; Losec; Miol; Mopral†; Norpramin; Novek; Nuclosina; Omapren; Ompranyt; Parizac; Pepticum; Prysma; Sanamidol; Ulceral; Ulcesep; Ulcometion; Zimor; ***Swed.:*** Losec; ***Switz.:*** Amanol; Antra; Antramups; Gastroprazol; Omed; omepra-basan†; Omezol; Oprazol; ***Thai.:*** Airomet; Desec; Dosate; Duogas; Eselan; Eucid; Gaster; Gomec; Lomac; Losec; Madiprazole; Meiceral; Metsec; Miracid; Nocid; O-Sid; Olit; Omez; Omicap; Oprazole; Probitor; Severon†; Stomec; Ulprazole; Zefxon; Zimor†; ***Turk.:*** Demeprazol; Erbolin; Losec; Omegast; Omeprazid; Omeprol; Prosek; ***UAE:*** Risek; ***UK:*** Heartburn Relief; Losec; Zanprol; ***USA:*** Prilosec; ***Venez.:*** Fordex; Gastronol; Losec; Meprox†; Omebloc; Omevax; Omez†; Omezul; Parsolen; Prazol†; Probitor; Promezol; Tecol†.

Multi-ingredient: ***Austral.:*** Klacid HP 7; Losec Hp 7; ***Braz.:*** Erradic; Helicocid Triplice†; Omepramix; ***Canad.:*** Losec 1-2-3 A; Losec 1-2-3 M; ***Fin.:*** Losec Helira†; ***India:*** Helipac; Nogacid D; Okacid D; OTC HP Kit; ***Malaysia:*** Pylobact Combi; ***NZ:*** Klacid HP 7†; Losec Hp 7; ***Philipp.:*** OAC Hp7; ***Rus.:*** Pylobact (Пилобакт); ***S.Afr.:*** Losec 20 Triple†; ***USA:*** Zegerid.

Ondansetron *(BAN, rINN)*

GR-38032; Ondansétron; Ondansetrón; Ondansetroni; Ondansetronum. (±)-1,2,3,9-Tetrahydro-9-methyl-3-(2-methylimidazol-1-ylmethyl)-carbazol-4(9*H*)-one.

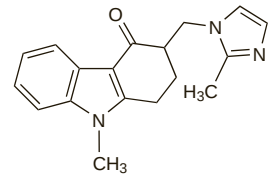
Ондансетрон

$C_{18}H_{19}N_3O$ = 293.4.

CAS — 99614-02-5; 116002-70-1.

ATC — A04AA01.

ATC Vet — QA04AA01.



Pharmacopoeias. In *US*.

USP 31 (Ondansetron). A white to off-white powder. Sparingly soluble in water; very soluble in acid solutions. Store in airtight containers. Protect from light.

Ondansetron Hydrochloride *(BANM, USAN, rINNM)*

GR-38032F; Hidrocloruro de ondansetrón; Ondansétron, chlorhydrate d'; Ondansetron hydrochlorid; Ondansetronhydroklorid; Ondansetroni hydrochloridum; Ondansetronihydrokloridi; Ondansetrono hidrochloridas; Ondanstroni Hydrochloridum; Ondánszetronhidroklorid; SN-307.

Ондансетрона Гидрохлорид

$C_{18}H_{19}N_3O,HCl,2H_2O$ = 365.9.

CAS — 99614-01-4; 103639-04-9.

ATC — A04AA01.

ATC Vet — QA04AA01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US*.

Ph. Eur. 6.2 (Ondansetron Hydrochloride Dihydrate). A white or almost white powder. Sparingly soluble in water and in alcohol; slightly soluble in dichloromethane; soluble in methyl alcohol. Protect from light.

USP 31 (Ondansetron Hydrochloride). A white to off-white powder. Sparingly soluble in water and in alcohol; very slightly soluble in acetone, in chloroform, and in ethyl acetate; slightly soluble in dichloromethane and in isopropyl alcohol; soluble in methyl alcohol. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Ondansetron hydrochloride and dexamethasone sodium phosphate were not compatible when high concentrations were combined in polypropylene syringes.[1] Lower concentrations (up to 640 micrograms/mL of ondansetron and 400 micrograms/mL of dexamethasone phosphate) were stable

in 50 mL containers of infusion fluid for 30 days under refrigeration. Compatibility has been reported for 24 hours in plastic syringes at 4° or 23° with a variety of other drugs,[2] and with several antineoplastics (cytarabine, dacarbazine, doxorubicin, etoposide, or methotrexate) in PVC infusion bags for 48 hours at room temperature.[3]

1. Hagan RL, *et al.* Stability of ondansetron hydrochloride and dexamethasone sodium phosphate in infusion bags and syringes for 32 days. *Am J Health-Syst Pharm* 1996; **53:** 1431–5.
2. Stewart JT, *et al.* Stability of ondansetron hydrochloride and 12 medications in plastic syringes. *Am J Health-Syst Pharm* 1998; **55:** 2630–4.
3. Stewart JT, *et al.* Stability of ondansetron hydrochloride and five antineoplastic medications. *Am J Health-Syst Pharm* 1996; **53:** 1297–1300.

Adverse Effects and Precautions

Ondansetron and other 5-HT_3 antagonists may cause headache, a sensation of flushing or warmth, hiccups, and constipation. A transient rise in liver enzymes has occasionally occurred. There have been rare reports of immediate hypersensitivity reactions, including anaphylaxis. Chest pain, arrhythmias, hypotension, tachycardia, and bradycardia have been reported rarely. Dizziness and transient visual disturbances such as blurred vision (or very rarely, transient blindness) have been reported during rapid intravenous injection. Transient ECG changes including QT interval prolongation have occurred very rarely, mainly with intravenous ondansetron. Seizures and movement disorders, including extrapyramidal reactions such as dystonia, dyskinesia, and oculogyric crisis have been reported. Rashes and urticaria have also occurred. Injection site reactions may develop, and local burning sensations are common after insertion of suppositories.

5-HT_3 antagonists should generally not be used in patients who have had a hypersensitivity reaction to a member of this drug class. They should be used with care in patients with signs of subacute intestinal obstruction or ileus. Ondansetron should be given in reduced doses to patients with moderate to severe hepatic impairment.

Effects on the cardiovascular system. Chest pain and/or cardiac arrhythmias that might have been associated with ondansetron were reported[1] in 4 patients, 2 of whom died. In 3 subsequent patients who developed severe chest or anginal pain, treatment with ondansetron was stopped.

The manufacturers (*Glaxo*) had at that time no evidence of a causal relationship between ondansetron and episodes of chest pain and cardiac abnormalities.[2] Giving ondansetron or granisetron intravenously produced no clinically important cardiovascular changes in a study in 12 healthy subjects.[3] Since then, however, myocardial ischaemia has been reported with both ondansetron[4] and dolasetron;[5] in the latter case this led to an acute myocardial infarction. Supraventricular tachycardia reported with dolasetron was attributed to an interaction with sevoflurane.[6] Another study in healthy subjects found that dolasetron mainly altered ECG parameters indicative of ventricular depolarisation, whereas ondansetron affected mainly ventricular repolarisation.[7] However, ECG changes were transient and asymptomatic. Studies of high-dose intravenous granisetron[8-10] found no significant adverse effects on pulse, blood pressure, or ECG measurements. A review[11] of the electrocardiographic and cardiovascular effects of the 5-HT_3 antagonists concluded that although this class of drugs may cause small, transient ECG changes, the clinical benefits of the drugs outweighed the small theoretical risk of any clinically significant cardiovascular events. Nonetheless, the use of dolasetron in children has been contra-indicated in the UK (see Uses and Administration, p.1726).

1. Ballard HS, *et al.* Ondansetron and chest pain. *Lancet* 1992; **340:** 1107.
2. Palmer JBD, Greenstreet YL. Ondansetron and chest pain. *Lancet* 1992; **340:** 1410.
3. Boike SC, *et al.* Cardiovascular effects of i.v. granisetron at two administration rates and of ondansetron in healthy adults. *Am J Health-Syst Pharm* 1997; **54:** 1172–6.
4. Bosek V, *et al.* Acute myocardial ischemia after administration of ondansetron hydrochloride. *Anesthesiology* 2000; **92:** 885–7.
5. Arole A, *et al.* Coronary vasospasm leading to an acute myocardial infarction after the administration of dolasetron. *J Clin Anesth* 2005; **17:** 72–4.
6. Higgins DJ, Bunker NJ. Dolasetron and peri-operative cardiac arrhythmia. *Anaesthesia* 2005; **60:** 936–7.
7. Benedict CR, *et al.* Single-blind study of the effects of intravenous dolasetron mesylate versus ondansetron on electrocardiographic parameters in normal volunteers. *J Cardiovasc Pharmacol* 1996; **28:** 53–9.
8. Carmichael J, Harris AL. High-dose i.v. granisetron for the prevention of chemotherapy-induced emesis: cardiac safety and tolerability. *Anticancer Drugs* 2003; **14:** 739–44.
9. Carmichael J, Harris AL. The cardiovascular safety of high-dose intravenous granisetron in cancer patients receiving highly emetogenic chemotherapy. *Cancer Chemother Pharmacol* 2004; **53:** 123–8.
10. Aapro M, Bourke JP. Rapid intravenous administration of granisetron prior to chemotherapy is not arythmogenic [sic]: results of a pilot study. *Eur J Cancer* 2003; **39:** 927–31.
11. Navari RM, Koeller JM. Electrocardiographic and cardiovascular effects of the 5-hydroxytryptamine receptor antagonists. *Ann Pharmacother* 2003; **37:** 1276–86.

Effects on the eyes. Blurring followed by transient loss of vision has been reported after rapid intravenous injection of ondansetron.[1] Oculogyric crisis may occur as part of extrapyramidal reactions seen with ondansetron, see Effects on the Nervous System, below.

1. Cherian A, Maguire M. Transient blindness following intravenous ondansetron. *Anaesthesia* 2005; **60:** 938–9.

Effects on the liver. Although disturbances in liver enzyme values have been reported in patients given ondansetron, more severe symptoms of liver disorder appear to be very rare; however, there is a report of severe jaundice associated with ondansetron as an antiemetic for chemotherapy.[1] Symptoms did not recur when the patient received granisetron.

1. Verrill M, Judson I. Jaundice with ondansetron. *Lancet* 1994; **344:** 190–1.

Effects on the nervous system. Tonic-clonic movements and frothing at the mouth occurred in a patient 90 minutes after an infusion of ondansetron;[1] the patient responded to diazepam intravenously. The manufacturers had seen 10 patients who developed *seizures* during initial clinical studies, but considered that, unlike this case, all these patients had predisposing factors. Hypotension and generalised tonic-clonic seizures were reported in a patient with metastatic breast cancer given ondansetron as an intravenous bolus.[2] Although seizures might have been due to brain metastases, the authors concluded that ondansetron had been the likely cause, since the patient experienced no further problems when antiemetic therapy was changed to metoclopramide. *Extrapyramidal reactions* in patients given ondansetron as part of a chemotherapy regimen[3,4] and for postoperative nausea and vomiting[5-7] have also been reported. In one case,[7] transient multifocal encephalopathy developed. Clinical manifestations such as clonus, oculogyric crisis, and oromandibular and limb dystonia resembled those of structural brain injury, and response to diphenhydramine was poor; despite this, the patient made a full neurological recovery over the course of 12 hours.

1. Sargent AI, *et al.* Seizure associated with ondansetron. *Clin Pharm* 1993; **12:** 613–15.
2. Sharma A, Raina V. Generalised seizures following ondansetron. *Ann Oncol* 2001; **12:** 131–2.
3. Krstenansky PM, *et al.* Extrapyramidal reaction caused by ondansetron. *Ann Pharmacother* 1994; **28:** 280.
4. Mathews HG, Tancil CG. Extrapyramidal reaction caused by ondansetron. *Ann Pharmacother* 1996; **30:** 196.
5. Stonell C. An extrapyramidal reaction to ondansetron. *Br J Anaesth* 1998; **81:** 658.
6. Tolan MM, *et al.* Perioperative extrapyramidal reactions associated with ondansetron. *Anesthesiology* 1999; **90:** 340–1.
7. Ritter MJ, *et al.* Ondansetron-induced multifocal encephalopathy. *Mayo Clin Proc* 2003; **78:** 1150–2.

Hypersensitivity. Anaphylactoid reactions have been reported in patients given ondansetron injections. The FDA stated in October 1993 that it had received 24 reports of such reactions,[1] mostly occurring after the first ondansetron dose of the second or third chemotherapy cycle, and characterised by urticaria, angioedema, hypotension, bronchospasm, and dyspnoea. Similar effects have been reported in a patient with no prior exposure to ondansetron.[2]

Cross-sensitivity between 5-HT_3 antagonists has been reported;[3] 2 patients who had had a mild hypersensitivity reaction to one 5-HT_3 antagonist developed a more severe reaction after exposure to another. In the first case severe acute asthma, cyanosis, and loss of consciousness developed after ondansetron in a patient who had previously experienced an asthmatic reaction after tropisetron. The second patient had developed pruritus after a tropisetron injection and urticaria after ondansetron, and subsequently developed anaphylactic shock 5 minutes after a further dose of tropisetron. It was recommended that another 5-HT_3 antagonist should not be given as a replacement to patients who developed a hypersensitivity reaction to a drug of this class.

1. Chen M, *et al.* Anaphylactoid-anaphylactic reactions associated with ondansetron. *Ann Intern Med* 1993; **119:** 862.
2. Weiss KS. Anaphylactic reaction to ondansetron. *Arch Intern Med* 2001; **161:** 2263.
3. Kataja V, de Bruijn KM. Hypersensitivity reactions associated with 5-hydroxytryptamine -receptor antagonists: a class effect? *Lancet* 1996; **347:** 584–5.

Interactions

Ondansetron does not appear to induce or inhibit the cytochrome P450 isoenzyme system, but it is itself metabolised by multiple hepatic isoenzymes, including CYP3A4, CYP2D6, and CYP1A2. US licensed product information states that inducers or inhibitors of these isoenzymes may change the clearance and half-life of ondansetron, but that on the basis of available data, no dose adjustments are recommended. UK licensed product information states that enzyme inhibition of one isoenzyme is usually compensated for by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement. Potent inducers of CYP3A4, such as phenytoin, carbamazepine, and rifampicin, have been reported to increase ondansetron clearance and reduce ondansetron plasma concentrations.

Because of the reports of transient ECG changes in some patients taking 5-HT_3 antagonists (see above), there is a theoretical need for caution if given with other drugs that prolong QT-interval; however, clinical evidence of a significant interaction seems to be mostly lacking.

Analgesics. For evidence of reduced analgesic efficacy of *tramadol* in patients also given 5-HT_3-receptor antagonists, such as ondansetron, see p.131.

Antibacterials. *Rifampicin* pretreatment reduced the area under the plasma concentration-time curve of oral ondansetron by 65% and of intravenous ondansetron by 48% in healthy subjects.[1] Use of rifampicin, or other potent inducers of cytochrome P450 isoenzyme CYP3A4, with ondansetron may reduce antiemetic efficacy.

1. Villikka K, *et al.* The effect of rifampin on the pharmacokinetics of oral and intravenous ondansetron. *Clin Pharmacol Ther* 1999; **65:** 377–81.

Antineoplastics. For mention of retrospective studies suggesting a change of pharmacokinetic parameters of high-dose cyclophosphamide and cisplatin when given with an ondansetron-containing antiemetic regimen, see Gastrointestinal Drugs, p.703.

Pharmacokinetics

Peak plasma concentrations of ondansetron occur about 1.5 hours after an oral dose of 8 mg, and about 6 hours after a rectal dose. The absolute bioavailability is about 60%, mainly because of hepatic first-pass metabolism. In elderly subjects, bioavailability may be somewhat higher (65%) and clearance lower, presumably due to reduced hepatic first-pass metabolism.

Ondansetron is extensively distributed in the body; about 70 to 75% of the drug in plasma is protein bound. It is metabolised in the liver through multiple enzymatic pathways; ondansetron is a substrate for cytochrome P450 isoenzymes, primarily CYP3A4, but also CYP1A2 and CYP2D6. Less than 5% of a dose is excreted unchanged in the urine.

The terminal elimination half-life is about 3 hours after oral or parenteral doses, and about 6 hours after rectal use. The terminal elimination half-life is prolonged to about 5 hours in the elderly and in those with renal impairment. These differences are not considered sufficient to warrant dosage adjustment. However, in patients with severe hepatic impairment, bioavailability may approach 100% and clearance is markedly reduced, with elimination half-lives of 15 to 32 hours; dosage restriction is advisable (see Administration in Hepatic Impairment, below). In general, children have a higher clearance than adults, although age-related reductions in clearance have also been reported, with younger children having lower clearances. Use of weight-based doses compensates for these changes and normalises exposure in paediatric patients.

◊ References.

1. Roila F, Del Favero A. Ondansetron clinical pharmacokinetics. *Clin Pharmacokinet* 1995; **29:** 95–109.
2. Figg WD, *et al.* Pharmacokinetics of ondansetron in patients with hepatic insufficiency. *J Clin Pharmacol* 1996; **36:** 206–15.
3. Van Den Berg CM, *et al.* Pharmacokinetics of three formulations of ondansetron hydrochloride in healthy volunteers: 24-mg oral tablet, rectal suppository, and iv infusion. *Am J Health-Syst Pharm* 2000; **57:** 1046–50.

Uses and Administration

Ondansetron is a 5-HT_3 antagonist (5-HT_3-receptor antagonist) with antiemetic activity. It is used in the management of **nausea and vomiting** induced by cytotoxic chemotherapy and radiotherapy. It is also used for the prevention and treatment of postoperative nausea and vomiting. For the management of nausea and vomiting, and the important role of 5-HT_3 antagonists, see p.1700.

Ondansetron is given by intramuscular or slow intravenous injection or infusion as the hydrochloride, by mouth as the hydrochloride or base, or rectally as the base. Doses are expressed in terms of the base. On-

dansetron hydrochloride 4.99 mg is equivalent to about 4 mg of ondansetron base.

Numerous dosing schedules of ondansetron have been used; some typical examples are cited below.

For *highly emetogenic* **chemotherapy** the following dose schedules appear to be equally effective in *preventing* acute emesis:

- a single dose of 8 mg by slow intravenous or intramuscular injection immediately before treatment

or

- 8 mg by slow intravenous or intramuscular injection immediately before treatment, either followed by a continuous intravenous infusion of 1 mg/hour for up to 24 hours, or by a further two doses of 8 mg two to four hours apart

or

- a single dose of 32 mg given by intravenous infusion over at least 15 minutes immediately before treatment

or

- 150 micrograms/kg by intravenous infusion over 15 minutes, beginning 30 minutes before chemotherapy, and repeated 4 and 8 hours after the first dose

or

- a 16-mg suppository rectally, given 1 to 2 hours before treatment

or

- a single oral dose of 24 mg taken 30 minutes before the start of single-day chemotherapy

The efficacy of ondansetron in highly emetogenic chemotherapy may be enhanced by giving intravenous dexamethasone sodium phosphate 20 mg before chemotherapy.

Similar regimens to those given above are used for preventing acute emesis with *less emetogenic chemotherapy* and/or **radiotherapy** and also include:

- 8 mg can be given orally up to 2 hours before treatment followed by 8 mg 8 to 12 hours later

To protect against delayed emesis these regimens are followed by oral ondansetron 8 mg twice daily, or 16 mg rectally once daily, for up to 5 days after the end of a course of chemotherapy.

For children the licensed dose in the UK is 5 mg/m^2 intravenously immediately before chemotherapy, followed by 4 mg orally 12 hours later. A dose of 4 mg orally twice daily may be continued for up to 5 days after the end of chemotherapy. The *BNFC* allows (in children aged 1 to 12 years) for 5 mg/m^2 intravenously before chemotherapy (up to a maximum single dose of 8 mg), which can be repeated every 8 to 12 hours during chemotherapy and for at least 24 hours afterwards; alternatively oral doses of 4 mg can be given every 8 to 12 hours for up to 5 days after intravenous use. In the USA a licensed regimen in children over 6 months of age is 150 micrograms/kg by intravenous infusion 30 minutes before chemotherapy, repeated 4 and 8 hours after the first dose. Alternatively, for children aged 4 to 11 years, an oral dose of 4 mg may be given 30 minutes before the start of chemotherapy, with subsequent 4-mg doses given 4 and 8 hours thereafter. An oral dose of 4 mg three times daily may be given for 1 to 2 days after the end of chemotherapy.

To *prevent* **postoperative nausea and vomiting** adults may be given:

- 16 mg orally an hour before anaesthesia

or

- 8 mg orally an hour before anaesthesia followed by 2 further doses of 8 mg at 8-hour intervals

or

- a single dose of 4 mg by intramuscular or slow intravenous injection at induction of anaesthesia

For the *treatment* of postoperative nausea and vomiting a single 4-mg dose by intramuscular or slow intravenous injection is recommended.

In the UK, children aged 2 years and over may be given 100 micrograms/kg by slow intravenous injection, up to a maximum dose of 4 mg, both for the prevention and treatment of postoperative nausea and vomiting; in the USA this dose is licensed from 1 month of age.

In patients with moderate or severe *hepatic impairment* it is recommended that the total daily dose of ondansetron should not exceed 8 mg (see below).

◊ Reviews.

1. Perez EA. A risk-benefit assessment of serotonin 5-HT receptor antagonists in antineoplastic therapy-induced emesis. *Drug Safety* 1998; **18:** 43–56.
2. Gregory RE, Ettinger DS. 5-HT receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting: a comparison of their pharmacology and clinical efficacy. *Drugs* 1998; **55:** 173–89.
3. Lindley C, Blower P. Oral serotonin type 3-receptor antagonists for prevention of chemotherapy-induced emesis. *Am J Health-Syst Pharm* 2000; **57:** 1685–97.
4. Culy CR, *et al.* Ondansetron: a review of its use as an antiemetic in children. *Paediatr Drugs* 2001; **3:** 441–79.
5. Gridelli C. 5-HT -receptor antagonists in the control of delayed-onset emesis. *Anticancer Res* 2003; 23: 2773–82.
6. Constenla M. 5-HT receptor antagonists for prevention of late acute-onset emesis. *Ann Pharmacother* 2004; **38:** 1683–91.
7. Aapro M. 5-HT -receptor antagonists in the management of nausea and vomiting in cancer and cancer treatment. *Oncology* 2005; **69:** 97–109.
8. Anonymous. 5HT -receptor antagonists as antiemetics in cancer. *Drug Ther Bull* 2005; **43:** 57–62.

Administration. Ondansetron has been successfully used by continuous *subcutaneous* infusion to control intractable nausea and vomiting.[1] Despite concern about the low pH of ondansetron injection there was no problem with the skin at the infusion site. An *oral* protocol for chemotherapy-induced emesis in children has been described;[2] efficacy was similar to intravenous use.

1. Mulvenna PM, Regnard CFB. Subcutaneous ondansetron. *Lancet* 1992; **339:** 1059.
2. Walker PC, *et al.* Promoting the use of oral ondansetron in children receiving cancer chemotherapy. *Am J Health-Syst Pharm* 2001; **58:** 598–602.

Administration in hepatic impairment. Licensed drug information recommends that the dose of ondansetron should not exceed 8 mg daily in patients with moderate or severe hepatic impairment. When this dose was given intravenously to patients with hepatic impairment, those with severe impairment showed an increase in the area under the plasma concentration/time curve and in the terminal plasma half-life, and a decrease in plasma clearance.[1] The authors of this study, some of whom worked for the manufacturers (*Glaxo*), considered that ondansetron should be restricted to once daily dosage in severe hepatic impairment.

1. Blake JC, *et al.* The pharmacokinetics of intravenous ondansetron in patients with hepatic impairment. *Br J Clin Pharmacol* 1993; **35:** 441–3.

Bulimia nervosa. A combination of counselling, support, psychotherapy, and antidepressants is the usual treatment of bulimia nervosa. Preliminary reports have indicated that ondansetron may be of benefit in the treatment of this disorder.[1,2]

1. Faris PL, *et al.* Effect of decreasing afferent vagal activity with ondansetron on symptoms of bulimia nervosa: a randomised, double-blind trial. *Lancet* 2000; **355:** 792–7.
2. Fung SM, Ferrill MJ. Treatment of bulimia nervosa with ondansetron. *Ann Pharmacother* 2001; **35:** 1270–3.

Fatigue. Preliminary results indicated that treatment with 5-HT$_3$ antagonists such as ondansetron and tropisetron may be of benefit in patients with chronic fatigue.[1] Ondansetron 4 mg twice daily by mouth was reported[2] to resolve fatigue in a woman with chronic hepatitis C. In a randomised study in 36 patients with chronic hepatitis C, this dose of ondansetron given for 1 month significantly improved fatigue scores at day 15 and day 60 (beyond the treatment period) when compared with placebo.[3] The authors noted that patient awareness that constipation was a possible effect of active treatment may have potentially unblinded the study. Further confirmation by larger studies is needed.

1. Späth M, *et al.* Treatment of chronic fatigue syndrome with 5-HT receptor antagonists—preliminary results. *Scand J Rheumatol* 2000; **113** (suppl): 72–7.
2. Jones EA. Relief from profound fatigue associated with chronic liver disease by long-term ondansetron therapy. *Lancet* 1999; **354:** 397.
3. Piche T, *et al.* Effect of ondansetron, a 5-HT receptor antagonist, on fatigue in chronic hepatitis C: a randomised, double blind, placebo controlled study. *Gut* 2005; **54:** 1169–73.

Pain. Preliminary results from a small crossover study[1] indicated that oral ondansetron was more effective than paracetamol in relieving the pain of fibromyalgia, a chronic disorder that responds poorly to conventional analgesics. A single bolus of ondansetron given to patients with chronic neuropathic pain significantly reduced pain scores 2 hours after injection in a placebo-controlled study;[2] this effect may be due to an action on 5-HT$_3$ receptors in the spinal cord.

Other 5-HT$_3$ antagonists such as granisetron[3-5] and tropisetron[6-8] have also been investigated in various painful syndromes.

1. Hrycaj P, *et al.* Pathogenetic aspects of responsiveness to ondansetron (5-hydroxytryptamine type 3 receptor antagonist) in patients with primary fibromyalgia syndrome—a preliminary study. *J Rheumatol* 1996; **23:** 1418–23.
2. McCleane GJ, *et al.* Does a single intravenous injection of the 5HT3 receptor antagonist ondansetron have an analgesic effect in neuropathic pain? A double-blinded, placebo-controlled cross-over study. *Anesth Analg* 2003; **97:** 1474–8.
3. Voog O, *et al.* Immediate effects of the serotonin antagonist granisetron on temporomandibular joint pain in patients with systemic inflammatory disorders. *Life Sci* 2000; **68:** 591–602.
4. Dubey PK, Prasad SS. Pain on injection of propofol: the effect of granisetron pretreatment. *Clin J Pain* 2003; **19:** 121–4.
5. Ernberg M, *et al.* Effects on muscle pain by intramuscular injection of granisetron in patients with fibromyalgia. *Pain* 2003; **101:** 275–82.
6. Farber L, *et al.* Short-term treatment of primary fibromyalgia with the 5-HT3-receptor antagonist tropisetron: results of a randomized, double-blind, placebo-controlled multicenter trial in 418 patients. *Int J Clin Pharmacol Res* 2001; **21:** 1–13.
7. Stratz T, *et al.* Local treatment of tendinopathies: a comparison between tropisetron and depot corticosteroids combined with local anesthetics. *Scand J Rheumatol* 2002; **31:** 366–70.
8. Spath M, *et al.* Efficacy and tolerability of intravenous tropisetron in the treatment of fibromyalgia. *Scand J Rheumatol* 2004; **33:** 267–70.

Pruritus. There are several case reports[1,2] of cholestatic pruritus (p.1582) responding to intravenous or oral ondansetron, including one in pregnancy.[3] However, results from controlled studies[4-6] have been mixed. It is similarly unclear if ondansetron is of benefit in pruritus due to renal failure,[7-9] and results have been conflicting from controlled studies evaluating its use in opioid-induced pruritus.[10-15] There are reports of ondansetron ameliorating the pruritus associated with some skin disorders.[16] Other 5-HT$_3$ antagonists such as tropisetron[9] and dolasetron[14] have also been investigated.

1. Schwörer H, Ramadori G. Improvement of cholestatic pruritus by ondansetron. *Lancet* 1993; **341:** 1277.
2. Raderer M, *et al.* Ondansetron for pruritus due to cholestasis. *N Engl J Med* 1994; **330:** 1540.
3. Schumann R, Hudcova J. Cholestasis of pregnancy, pruritus and 5-hydroxytryptamine 3 receptor antagonists. *Acta Obstet Gynecol Scand* 2004; **83:** 861–2.
4. Müller C, *et al.* Treatment of pruritus in chronic liver disease with the 5-hydroxytryptamine receptor type 3 antagonist ondansetron: a randomized, placebo-controlled, double-blind cross-over trial. *Eur J Gastroenterol Hepatol* 1998; **10:** 865–70.
5. O'Donohue JW, *et al.* A controlled trial of ondansetron in the pruritus of cholestasis. *Aliment Pharmacol Ther* 2005; **21:** 1041–5.
6. Jones EA, *et al.* Ondansetron and pruritus in chronic liver disease: a controlled study. *Hepatogastroenterology* 2007; **54:** 1196–9.
7. Balaskas EV, *et al.* Histamine and serotonin in uremic pruritus: effect of ondansetron in CAPD-pruritic patients. *Nephron* 1998; **78:** 395–402.
8. Murphy M, *et al.* A randomized, placebo-controlled, double-blind trial of ondansetron in renal itch. *Br J Dermatol* 2003; **148:** 314–7.
9. Weisshaar E, *et al.* Antipruritic effects of two different 5-HT3 receptor antagonists and an antihistamine in haemodialysis patients. *Exp Dermatol* 2004; **13:** 298–304.
10. Borgeat A, Stirnemann H-R. Ondansetron is effective to treat spinal or epidural morphine-induced pruritus. *Anesthesiology* 1999; **90:** 432–6.
11. Korhonen AM, *et al.* Ondansetron does not prevent pruritus induced by low-dose intrathecal fentanyl. *Acta Anaesthesiol Scand* 2003; **47:** 1292–7.
12. Wells J, *et al.* Intrathecal fentanyl-induced pruritus during labour: the effect of prophylactic ondansetron. *Int J Obstet Anesth* 2004; **13:** 35–9.
13. Waxler B, *et al.* Prophylactic ondansetron does not reduce the incidence of itching induced by intrathecal sufentanil. *Can J Anesth* 2004; **51:** 685–9.
14. Iatrou CA, *et al.* Prophylactic intravenous ondansetron and dolasetron in intrathecal morphine-induced pruritus: a randomized, double-blinded, placebo-controlled study. *Anesth Analg* 2005; **101:** 1516–20.
15. Siddik-Sayyid SM, *et al.* Does ondansetron or granisetron prevent subarachnoid morphine-induced pruritus after cesarean delivery? *Anesth Analg* 2007; **104:** 421–4.
16. Zenker S, *et al.* Behandlung von Pruritus als Symptom von Hauterkrankungen mit dem Serotonin-Rezeptorantagonisten Ondansetron. *J Dtsch Dermatol Ges* 2003; **1:** 705–10.

Psychiatric disorders. Ondansetron has been tried experimentally in a number of psychiatric disorders including schizophrenia,[1-3] and psychosis in patients with parkinsonism,[4] and may be of value in moderating tardive dyskinesia.[5] A reduction in tic severity in Tourette's syndrome (p.954) has been reported,[6] and preliminary results have suggested benefit in obsessive-compulsive disorder,[7] and bulimia nervosa (see above). It is also reported to be under investigation in the management of panic attacks (p.952). For the more conventional management of schizophrenia, parkinsonism, and obsessive-compulsive disorder see p.955, p.791, and p.952, respectively.

1. White A, *et al.* Ondansetron in the treatment of schizophrenia. *Lancet* 1991; **337:** 1173.
2. Adler LE, *et al.* Improved P50 auditory gating with ondansetron in medicated schizophrenia patients. *Am J Psychiatry* 2005; **162:** 386–8.
3. Levkovitz Y, *et al.* The effect of ondansetron on memory in schizophrenic patients. *Brain Res Bull* 2005; **65:** 291–5.
4. Zoldan J, *et al.* Psychosis in advanced Parkinson's disease: treatment with ondansetron, a 5-HT receptor antagonist. *Neurology* 1995; **45:** 1305–8.
5. Sirota P, *et al.* Use of the selective serotonin 3 receptor antagonist ondansetron in the treatment of neuroleptic-induced tardive dyskinesia. *Am J Psychiatry* 2000; **157:** 287–9.

6. Toren P, *et al.* Ondansetron treatment in Tourette's disorder: a 3-week, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2005; **66:** 499–503.
7. Hewlett WA, *et al.* Pilot trial of ondansetron in the treatment of 8 patients with obsessive-compulsive disorder. *J Clin Psychiatry* 2003; **64:** 1025–30.

Substance dependence. Ondansetron is being studied in the management of alcohol dependence (p.1626). However, in one study[1] a significant reduction in alcohol consumption was found only in lighter drinkers after subgroup analysis. Another study[2] found a reduction in alcohol consumption by patients with early-onset alcoholism (onset before age 25) who took ondansetron compared with placebo. No such effect was seen, however, in patients with late-onset alcoholism. Further study found that ondansetron also effectively ameliorated mood disturbances including symptoms of depression, anxiety, and hostility, in early-onset alcoholics.[3] Self-reported alcohol consumption also reduced in adolescents (between ages 14 and 20) with alcohol dependence who were given ondansetron in an open study.[4]

1. Sellers EM, *et al.* Clinical efficacy of the 5-HT antagonist ondansetron in alcohol abuse and dependence. *Alcohol Clin Exp Res* 1994; **18:** 879–85.
2. Johnson BA, *et al.* Ondansetron for reduction of drinking among biologically predisposed alcoholic patients. *JAMA* 2000; **284:** 963–71.
3. Johnson BA, *et al.* Ondansetron reduces mood disturbance among biologically predisposed, alcohol-dependent individuals. *Alcohol Clin Exp Res* 2003; **27:** 1773–9.
4. Dawes MA, *et al.* A prospective, open-label trial of ondansetron in adolescents with alcohol dependence. *Addict Behav* 2005; **30:** 1077–85.

Preparations

USP 31: Ondansetron Hydrochloride Oral Suspension; Ondansetron Injection; Ondansetron Oral Solution; Ondansetron Orally Disintegrating Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Cetron; Dantenk; Dismolan; Emivox†; Espasevit; Finaber; Finoxi; Tiosalis; Zofran; ***Austral.:*** Ondaz; Onsetron; Zofran; ***Austria:*** Glaxosetron; Ondanoglax; Ondensan; Zofran; ***Belg.:*** Zofran; ***Braz.:*** Ansentron; Injectrax; Modifical; Nausedron; Ontrax; Vonau; Zofran; ***Canad.:*** Zofran; ***Chile:*** Amilene; Gardoton; Izofran; Odanex; Oncoemet; Trorix; ***Cz.:*** Danemet; Emeset; Emetron†; Novetron; Ondemet; Setron†; Setronon; Zofran; ***Denm.:*** Hexatron; Zofran; ***Fin.:*** Zofran; ***Fr.:*** Zophren; ***Ger.:*** Zofran; ***Gr.:*** Biosetron; Cruzafen; Dentron; Fedral; Odnatron; Onda; Ondameton; Ondaren; Ondaseprol; Setrodan; Vefron; Zetron; Zodatron; Zofron; Zophralen; ***Hong Kong:*** Zofran; ***Hung.:*** Antivom; Emetron; Ondagen; Zofran; ***India:*** Emeset; Periset; Vomiof; ***Indon.:*** Cedantron; Dantroxal; Entron; Frazon; Invomit; Narfoz; Ondavell; Onetic 4; Vomceran; Zantron; Zofran; ***Irl.:*** Emital; Zofran; ***Israel:*** Zofran; ***Ital.:*** Zofran; ***Malaysia:*** Osetron; Zofran; ***Mex.:*** Danac; Modifical; Precirux; Zofran; ***Neth.:*** Zofran; ***Norw.:*** Zofran; ***NZ:*** Onsetron; Zofran; ***Philipp.:*** Emodan; Zofran; ***Pol.:*** Atossa; Emetron; Setronon; Zofran; ***Port.:*** Nausiend; Otobrol; Zofran; ***Rus.:*** Emetron (Эметрон); Setronon (Сетронон); Zofran (Зофран); ***S.Afr.:*** Dantron; Nausetron; Zofran; ***Singapore:*** Zofran; ***Spain:*** Fixca†; Yatrox; Zofran; ***Swed.:*** Zofran; ***Switz.:*** Zofran; ***Thai.:*** Dantron; Emeset; Onsia; Vomitron†; Zetron; Zofran; ***Turk.:*** Zofer; Zofran; Zoltem; ***UK:*** Ondemet; Zofran; ***USA:*** Zofran; ***Venez.:*** Dismolan; Emeset; Tructum; Zofran.

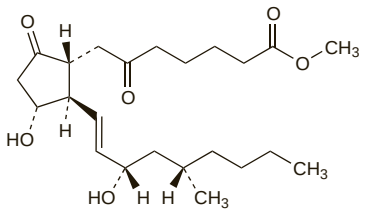
Ornoprostil *(rINN)*

Ornoprostilo; Ornoprostilum; OU-1308. Methyl (–)-(1*R*,2*R*,3*R*)-3-hydroxy-2-[(*E*)-(3*S*,5*S*)-3-hydroxy-5-methyl-1-nonenyl]-ε,5-dioxocyclopentaneheptanoate.

Орнопростил

$C_{23}H_{38}O_6$ = 410.5.

CAS — 70667-26-4.



Profile

Ornoprostil is a synthetic prostaglandin analogue that has been used in the treatment of peptic ulcer disease.

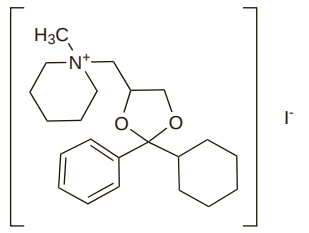
Oxapium Iodide *(rINN)*

Ciclonium Iodide; Cyclonium Iodide; Ioduro de oxapio; Oxapii Iodidum; Oxapium, Iodure d'; SH-100. 1-(2-Cyclohexyl-2-phenyl-1,3-dioxolan-4-ylmethyl)-1-methylpiperidinium iodide.

Оксапия Йодид

$C_{22}H_{34}INO_2$ = 471.4.

CAS — 6577-41-9.



NOTE. Distinguish from ciclonium bromide, p.1716, an unrelated antispasmodic.

Pharmacopoeias. In *Jpn.*

Profile

Oxapium iodide is an antimuscarinic that has been used as an antispasmodic in the treatment of gastrointestinal disorders and renal calculi.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Esperan.

Oxyphencyclimine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de oxifenciclimina; Oksifensiklimin Hidroklorür; Oxyphencyclimine, Chlorhydrate d'; Oxyphencyclimini Hydrochloridum. 1,4,5,6-Tetrahydro-1-methylpyrimidin-2-ylmethyl α-cyclohexylmandelate hydrochloride.

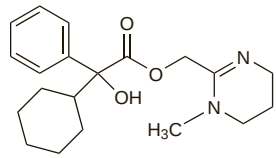
Оксифенциклимина Гидрохлорид

$C_{20}H_{28}N_2O_3$,HCl = 380.9.

CAS — 125-53-1 (oxyphencyclimine); 125-52-0 (oxyphencyclimine hydrochloride).

ATC — A03AA01.

ATC Vet — QA03AA01.



(oxyphencyclimine)

Profile

Oxyphencyclimine hydrochloride is a tertiary amine antimuscarinic with effects similar to those of atropine (p.1219). It has been used as an adjunct in the treatment of peptic ulcer disease and for the relief of smooth muscle spasms in gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Part 3)

Hong Kong: Daricon; ***Thai.:*** Daricon†; Med-Spastic†; Oxyno; Proclimine.

Multi-ingredient: ***Hong Kong:*** Rudd-U†; ***Turk.:*** Spazmo-Valibrin.

Oxyphenonium Bromide *(BAN, rINN)*

Bromuro de oxifenonio; Oksyfenoniowy bromek; Oxphenonii Bromidum; Oxyphenonii Bromidum; Oxyphenonium Bromatum; Oxyphénonium, Bromure d'. 2-(α-Cyclohexylmandeloyloxy)ethyldiethylmethylammonium bromide.

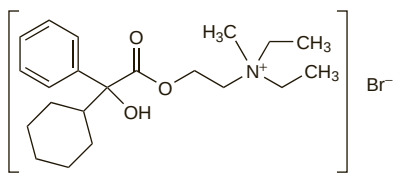
Оксифенония Бромид

$C_{21}H_{34}BrNO_3$ = 428.4.

CAS — 14214-84-7 (oxyphenonium); 50-10-2 (oxyphenonium bromide).

ATC — A03AB03.

ATC Vet — QA03AB03.



Pharmacopoeias. In *Pol.*

Profile

Oxyphenonium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1219). It has been given orally to relieve visceral spasms.

Preparations

Proprietary Preparations (details are given in Part 3)

India: Antrenyl; ***Pol.:*** Spasmophen; ***S.Afr.:*** Spastrex†.

Multi-ingredient: ***Cz.:*** Endiform†.

Palonosetron Hydrochloride

(USAN, rINNM)

Hidrocloruro de palonosetrón; Palonosétron, Chlorhydrate de; Palonosetroni Hydrochloridum; RS-25259-197. (3a*S*)-2,3,3a,4,5,6-Hexahydro-2-[(3*S*)-3-quinuclidinyl]-1*H*-benz[*de*]isoquinolin-1-one hydrochloride.

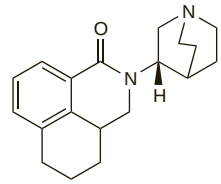
Палоносетрона Гидрохлорид

$C_{19}H_{24}N_2O$,HCl = 332.9.

CAS — 135729-56-5 (palonosetron); 135729-55-4 (palonosetron hydrochloride); 135729-62-3 (palonosetron hydrochloride).

ATC — A04AA05.

ATC Vet — QA04AA05.



(palonosetron)

Stability. The stability of palonosetron hydrochloride at concentrations of 5 and 30 micrograms/mL was assessed in polyvinyl chloride bags of the following 4 infusion solutions: glucose 5%, sodium chloride 0.9%, glucose 5% in sodium chloride 0.45%, and glucose 5% in lactated Ringer's solution. All solutions were considered to be physically and chemically stable for at least 48 hours at room temperature exposed to light, and for 14 days under refrigeration.[1]

Palonosetron 50 micrograms/mL was found to be physically and chemically stable during simulated Y-site administration with the following drugs: fentanyl citrate 50 micrograms/mL, hydromorphone hydrochloride 500 micrograms/mL, morphine sulfate 15 mg/mL, pethidine hydrochloride 10 mg/mL, and sufentanil citrate (12.5 micrograms/mL of sufentanil).[2]

1. Trissel LA, Xu QA. Physical and chemical stability of palonosetron HCl in 4 infusion solutions. *Ann Pharmacother* 2004; **38:** 1608–11.
2. Trissel LA, *et al.* Physical and chemical stability of palonosetron hydrochloride with five opiate agonists during simulated Y-site administration. *Am J Health-Syst Pharm* 2007; **64:** 1209–13.

Adverse Effects and Precautions

As for Ondansetron, p.1757, although no dosage reduction is considered necessary in hepatic impairment. Diarrhoea, fatigue, and abdominal pain may also occur. Patients with a history of constipation or signs of subacute intestinal obstruction should be monitored if given palonosetron.

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.

Interactions

As for Ondansetron, p.1757.

Pharmacokinetics

Palonosetron has a volume of distribution of around 7 to 8 litres/kg; plasma protein binding is about 62%. About 50% of a dose is metabolised in the liver by cytochrome P450 isoenzymes (notably CYP2D6, but also CYP3A4 and CYP1A2). About 80% of a dose is recovered in the urine within 144 hours, as palonosetron and its metabolites. The mean elimination half-life is reported to be about 40 hours.

◊ References.

1. Hunt TL, *et al.* Evaluation of safety and pharmacokinetics of consecutive multiple-day dosing of palonosetron in healthy subjects. *J Clin Pharmacol* 2005; **45:** 589–96.
2. Shah A, *et al.* Pharmacokinetic evaluation and safety profile of a 15-minute versus 30-second infusion of palonosetron in healthy subjects. *J Clin Pharmacol* 2006; **46:** 1139–45.