Profile
Tiemonium iodide and tiemonium metilsulfate are quaternary ammonium antimuscarinics with peripheral effects similar to those of atropine (p.1219) and are used in the relief of visceral spasms.

Tiemonium metilsulfate is given in an oral dose of 100 to 300 mg daily in divided doses. A dose of 5 mg has been given three times daily by intramuscular or slow intravenous injection. Tiemonium metilsulfate has also been given as a rectal suppository in daily doses of 20 to 40 mg.

Tiemonium iodide has been used similarly.

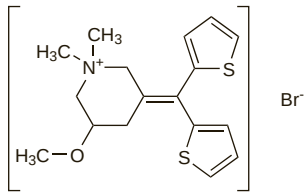
Preparations
Proprietary Preparations (details are given in Part 3)
Belg.: Visceralgine†; ***Fr.:*** Visceralgine; ***Indon.:*** Visceralgine.

Multi-ingredient: ***Belg.:*** Asodal; ***Fr.:*** Colchimax; Visceralgine Forte†; ***Venez.:*** Bort†.

Timepidium Bromide *(rINN)*
Bromuro de timepidio; SA-504; Timepidii Bromidum; Timépidium, Bromure de. 3-[Di-(2-thienyl)methylene]-5-methoxy-1,1-dimethylpiperidinium bromide monohydrate.

Тимепидия Бромид

$C_{17}H_{22}BrNOS_2,H_2O$ = 418.4.
CAS — 35035-05-3.
ATC — A03AB19.
ATC Vet — QA03AB19.



Pharmacopoeias. In *Jpn.*

Profile
Timepidium bromide is a quaternary ammonium antimuscarinic with peripheral actions similar to those of atropine (p.1219). It has been given for the symptomatic treatment of visceral spasms in usual oral doses of 30 mg three times daily. It has also been given by subcutaneous, intramuscular, and intravenous injection in a dose of 7.5 mg.

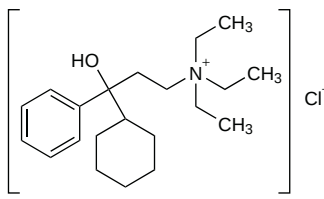
Urinary metabolites of timepidium may cause a reddish coloration of the urine.

Preparations
Proprietary Preparations (details are given in Part 3)
Indon.: Sesden; ***Jpn:*** Sesden; ***Singapore:*** Sesden†.

Tridihexethyl Chloride *(BAN, rINNM)*
Cloruro de tridihexetilo; Tridihexéthyl, Chlorure de; Tridihexethyli Chloridum. (3-Cyclohexyl-3-hydroxy-3-phenylpropyl)triethylammonium chloride.

Тридигексетила Хлорид

$C_{21}H_{36}ClNO$ = 354.0.
CAS — 60-49-1 (tridihexethyl); 4310-35-4 (tridihexethyl chloride); 125-99-5 (tridihexethyl iodide).
ATC — A03AB08.
ATC Vet — QA03AB08.



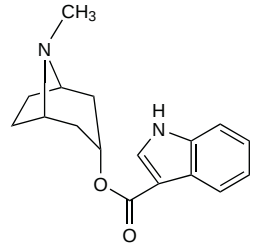
NOTE. Tridihexethyl Iodide is *rINN*.

Profile
Tridihexethyl chloride is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1219). It has been used as an adjunct in the treatment of peptic ulcer disease.

Tropisetron *(BAN, rINN)*
Tropisétron; Tropisetrón; Tropisetroni; Tropisetronum. 1α*H*,5α*H*-Tropan-3α-yl indole-3-carboxylate.

Трописетрон

$C_{17}H_{20}N_2O_2$ = 284.4.
CAS — 89565-68-4.
ATC — A04AA03.
ATC Vet — QA04AA03.



Tropisetron Hydrochloride *(BANM, rINNM)*
Hidrocloruro de tropisetrón; ICS-205-930; Tropisétron, chlorhydrate de; Tropisetroni hydrochloridum.

Трописетрона Гидрохлорид

$C_{17}H_{20}N_2O_2$,HCl = 320.8.
CAS — 105826-92-4.
ATC — A04AA03.
ATC Vet — QA04AA03.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Tropisetron Hydrochloride). A white or almost white powder. Freely soluble or soluble in water; sparingly soluble in alcohol; very slightly soluble in dichloromethane.

Adverse Effects and Precautions
As for Ondansetron, p.1757. Fatigue, abdominal pain, and diarrhoea may also occur. Visual hallucinations, and an increase in blood pressure in patients with pre-existing hypertension, have been noted at high repeated doses. ECG changes such as prolongation of QT interval have been noted with high-dose intravenous tropisetron. The drug should therefore be used with caution in patients with cardiac rhythm or conduction disturbances. Care should be taken when driving or operating machinery. No dosage reduction is considered necessary in renal or hepatic impairment despite possible reductions in clearance.

Carcinogenicity. The manufacturer (*Novartis, UK*) has reported an increased incidence of hepatic neoplasms in male *mice* given high doses of tropisetron but it is suggested that these effects are both species and sex specific.

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
Drugs that induce or inhibit hepatic enzymes may affect plasma concentrations of tropisetron. Licensed product information considers that any changes are usually unlikely to be clinically relevant with the recommended doses.

Tropisetron should be used with caution with antiarrhythmics, beta blockers, or drugs likely to prolong the QT interval, including those likely to cause electrolyte disturbances (see also p.1757).

Pharmacokinetics
Tropisetron is well absorbed after oral doses. Peak plasma concentrations are achieved within 3 hours. Absolute bioavailability depends on the dose since first-pass metabolism is saturable. It is 71% bound to plasma proteins. Tropisetron is metabolised by hydroxylation and conjugation, and metabolites are excreted mainly in the urine with a small amount in the faeces. The cytochrome P450 isoenzyme CYP2D6 is involved in tropisetron metabolism, and shows genetic polymorphism. The elimination half-life is about 8 hours in extensive metabolisers and up to 45 hours in poor metabolisers. Clearance is also reduced in patients with renal impairment.

Uses and Administration
Tropisetron is a 5-HT_3 antagonist with an antiemetic action similar to that of ondansetron (p.1757). It is used in the prevention of nausea and vomiting induced by cytotoxic therapy and in the treatment and prevention of postoperative nausea and vomiting (p.1700).

Tropisetron is given as the hydrochloride by slow intravenous injection or infusion, or orally. Doses are expressed in terms of tropisetron base; 5.64 mg of tropisetron hydrochloride is equivalent to about 5 mg of tropisetron base.

For the *prophylaxis* of acute **nausea and vomiting** associated with cytotoxic **chemotherapy** a single dose of 5 mg may be given by slow intravenous injection or infusion on the day of treatment, shortly before chemotherapy. The injection is given over not less than 1 minute; it may be given into a running infusion. For infusion, it is diluted into 100 mL of a suitable infusion fluid (such as sodium chloride 0.9% or glucose 5%), and given over 15 minutes. Subsequent doses of 5 mg daily are given orally, in the morning at least one hour before food, for a further 5 days.

Children over 2 years of age may be given 200 micrograms/kg (maximum dose 5 mg) before chemotherapy, by intravenous injection over at least 1 minute, or by infusion (at a concentration of 50 micrograms/mL in a suitable infusion fluid). In children weighing less than 25 kg the same dose may be given intravenously once daily for up to a further 4 days as required. In those weighing more than 25 kg, a dose of 5 mg may be given orally once daily for up to a further 5 days; if oral dosage is not possible the same dose may be given intravenously.

For the *treatment* of **postoperative** nausea and vomiting in adults 2 mg may be given by slow intravenous injection (over not less than 30 seconds), or by infusion (over 15 minutes), within 2 hours of the end of anaesthesia. For *prophylaxis*, the same dose may be given shortly before induction of anaesthesia.

◊ References.

1. Lee CR, *et al.* Tropisetron: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential as an antiemetic. *Drugs* 1993; **46:** 925–43.
2. Simpson K, *et al.* Tropisetron: an update of its use in the prevention of chemotherapy-induced nausea and vomiting. *Drugs* 2000; **59:** 1297–1315.

Anxiety disorders. A dose-dependent anxiolytic effect was reported for tropisetron when studied in patients with generalised anxiety,[1] but clinical evidence for the benefit of 5-HT_3 antagonists in anxiety disorders is lacking.[2]

1. Lecrubier Y, *et al.* A randomized double-blind placebo-controlled study of tropisetron in the treatment of outpatients with generalized anxiety disorder. *Psychopharmacology (Berl)* 1993; **112:** 129–33.
2. Greenshaw AJ, Silverstone PH. The non-antiemetic uses of serotonin 5-HT receptor antagonists: clinical pharmacology and therapeutic applications. *Drugs* 1997; **53:** 20–39.

Fatigue. Tropisetron has been reported to be of benefit in patients with chronic fatigue, see under Uses and Administration of Ondansetron, p.1758.

Pain. For reference to the use of tropisetron in various painful syndromes, see under Uses and Administration of Ondansetron, p.1758.

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

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Navoban; ***Austral.:*** Navoban; ***Austria:*** Navoban; ***Belg.:*** Novaban; ***Braz.:*** Navoban†; ***Chile:*** Navoban; ***Cz.:*** Navoban†; ***Denm.:*** Navoban; ***Fin.:*** Navoban; ***Fr.:*** Navoban; ***Ger.:*** Navoban; ***Gr.:*** Navoban; ***Hong Kong:*** Navoban; ***Hung.:*** Navoban; ***Indon.:*** Navoban; Setrovel; ***Israel:*** Navoban†; ***Ital.:*** Navoban; ***Jpn:*** Navoban; ***Malaysia:*** Navoban; ***Mex.:*** Navoban; ***Neth.:*** Novaban; ***Norw.:*** Navoban; ***NZ:*** Navoban; ***Philipp.:*** Navoban; ***Pol.:*** Navoban; ***Port.:*** Navoban; ***Rus.:*** Navoban (Навобан); Tropindol (Тропиндол)†; ***S.Afr.:*** Navoban; ***Spain:*** Navoban; Saronil; ***Swed.:*** Navoban; ***Switz.:*** Navoban; ***Thai.:*** Navoban; ***Turk.:*** Navoban; ***UK:*** Navoban; ***Venez.:*** Navoban.

Troxipide *(rINN)*

Troxipida; Troxipidum. (±)-3,4,5-Trimethoxy-*N*-3-piperidylbenzamide.

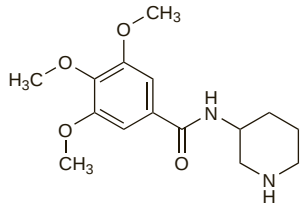
Троксипид

$C_{15}H_{22}N_2O_4$ = 294.3.

CAS — 30751-05-4.

ATC — A02BX11.

ATC Vet — QA02BX11.



Profile

Troxipide is used for its cytoprotective properties in the treatment of gastritis and peptic ulcer disease (p.1702) in a usual oral dose of 100 mg three times daily, after food.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Aplace.

Urogastrone

Anthelone; EGF-URO; Epidermal Growth Factor; Murodermina; Uroanthelone; Uroenterone; Urogastrona.

Урогастрон

CAS — 9010-53-1.

Pharmacopoeias. *Chin.* includes monographs for recombinant human epidermal growth factor suitable for external use.

Uses

Urogastrone is a polypeptide first isolated from human urine. Two forms have been identified, β and γ urogastrone. The β form consists of 53 amino acids and is distinguishable from the γ form by an additional terminal arginine residue. The β form is reported to be identical to human epidermal growth factor and this term is widely used in the literature.

Urogastrone inhibits gastric acid secretion and has been tried in the treatment of peptic ulcer disease and other gastrointestinal disorders but its rapid destruction in the stomach has limited its clinical use.

It is a potent stimulator of cellular proliferation and has also been used as an aid to wound healing.

◊ Reviews.

1. Burgess AW. Epidermal growth factor and transforming growth factor α. *Br Med Bull* 1989; **45:** 401–24.
2. Miyazawa K. Role of epidermal growth factor in obstetrics and gynecology. *Obstet Gynecol* 1992; **79:** 1032–40.
3. Grazul-Bilska AT, *et al.* Wound healing: the role of growth factors. *Drugs Today* 2003; **39:** 787–800.
4. Klenkler B, Sheardown H. Growth factors in the anterior segment: role in tissue maintenance, wound healing and ocular pathology. *Exp Eye Res* 2004; **79:** 677–88.

Gastrointestinal disorders. Intravenous infusion of urogastrone 250 nanograms/kg over 1 hour has been reported[1,2] to reduce the secretion of gastric acid in patients with duodenal ulcer (p.1702) or the Zollinger-Ellison syndrome (p.1704). Ulcer pain was relieved 30 to 60 minutes after the start of the infusion.[2] A dose of 100 nanograms/kg per hour by intravenous infusion has been used with partial success in an infant with microvillous atrophy[3] and was apparently beneficial in an infant with necrotising enteritis.[4]

Human epidermal growth factor has also shown some promise in the treatment of active ulcerative colitis. In a small study,[5] patients received daily enemas containing either recombinant human epidermal growth factor (5 micrograms in 100 mL) or placebo; all patients also received oral mesalazine. Ten of the 12 patients in the urogastrone group were in remission after 2 weeks treatment compared with 1 of the 12 patients in the placebo group, and this benefit was maintained for up to 12 weeks.

1. Koffman CG, *et al.* Effect of urogastrone on gastric secretion and serum gastrin concentration in patients with duodenal ulceration. *Gut* 1982; **23:** 951–6.
2. Elder JB, *et al.* Effect of urogastrone in the Zollinger-Ellison syndrome. *Lancet* 1975; **ii:** 424–7.
3. Walker-Smith JA, *et al.* Intravenous epidermal growth factor/urogastrone increases small-intestinal cell proliferation in congenital microvillous atrophy. *Lancet* 1985; **ii:** 1239–40.
4. Sullivan PB, *et al.* Epidermal growth factor in necrotising enteritis. *Lancet* 1991; **338:** 53–4.
5. Sinha A, *et al.* Epidermal growth factor enemas with oral mesalamine for mild-to-moderate left-sided ulcerative colitis or proctitis. *N Engl J Med* 2003; **349:** 350–7.

Wound healing. For a general discussion of the management of wounds and ulcers, see p.1585.

In a randomised double-blind study in 61 patients with diabetic foot ulcers, adding human epidermal growth factor 0.04% to an ulcer cream containing protein-free bovine blood extract was shown to significantly enhance wound healing and reduce healing time compared with either the cream alone or the cream plus human epidermal growth factor 0.02%.[1] Topical application of recombinant human epidermal growth factor 0.02% has also been reported to reduce pain and promote healing of exfoliated skin lesions in a patient with drug-induced Stevens-Johnson syndrome.[2]

The effect on the rate of wound healing of a cream containing sulfadiazine silver plus recombinant human epidermal growth factor (10 micrograms/mL) was compared with sulfadiazine silver alone in 12 patients each requiring skin grafts at 2 donor sites.[3] The cream containing epidermal growth factor accelerated the rate of epidermal regeneration in all patients and reduced the average time to 100% healing by about 1.5 days. Patients were followed up for a maximum of 1 year after cessation of therapy and no complications or clinical evidence of neoplasia at the healed donor sites occurred.

In contrast, recombinant human epidermal growth factor as an ophthalmic solution containing 30 or 100 micrograms/mL was investigated in patients who had undergone keratoplasty, but the weaker solution had no effect on the rate of re-epithelialisation, and the more concentrated one was actually associated with slower healing.[4]

1. Tsang MW, *et al.* Human epidermal growth factor enhances healing of diabetic foot ulcers. *Diabetes Care* 2003; **26:** 1856–61.
2. Tsang MW, *et al.* The use of recombinant human epidermal growth factor (rhEGF) in a gentleman with drug-induced Steven Johnson syndrome. *Dermatol Online J* 2004; **10:** 25.
3. Brown GL, *et al.* Enhancement of wound healing by topical treatment with epidermal growth factor. *N Engl J Med* 1989; **321:** 76–9.
4. Dellaert MMMJ, *et al.* Influence of topical human epidermal growth factor on postkeratoplasty re-epithelialisation. *Br J Ophthalmol* 1997; **81:** 391–5.

Preparations

Proprietary Preparations (details are given in Part 3)

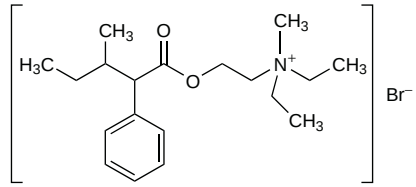
Multi-ingredient: ***Chile:*** FCE; Hebermin†.

Valethamate Bromide

Valetamat Bromür; Valetamato, bromuro de. Diethylmethyl[2-(3-methyl-2-phenylvaleryloxy)ethyl]ammonium bromide.

$C_{19}H_{32}BrNO_2$ = 386.4.

CAS — 16376-74-2 (valethamate); 90-22-2 (valethamate bromide).



Profile

Valethamate bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine (p.1219). It has been given orally, by injection or rectally in the symptomatic treatment of visceral spasms.

Preparations

Proprietary Preparations (details are given in Part 3)
India: Epidosin; Valosin; ***Indon.:*** Epidosin; ***Turk.:*** Epidosin.

Multi-ingredient: ***Turk.:*** Epidosin Compozitum.

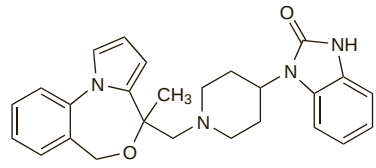
Zaldaride *(rINN)*

CGS-9343B (zaldaride maleate); Zaldarida; Zaldaridum. (±)-1-{1-[(4-Methyl-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepin-4-yl)methyl]-4-piperidyl}-2-benzimidazolinone.

Зальдарид

$C_{26}H_{28}N_4O_2$ = 428.5.

CAS — 109826-26-8 (zaldaride); 109826-27-9 (zaldaride maleate).



Profile

Zaldaride is a calmodulin antagonist that has been investigated as the maleate for the treatment of diarrhoea.

Diarrhoea. Studies in patients with travellers' diarrhoea (p.1694) have indicated that zaldaride in oral doses of 20 mg as the maleate four times daily is an effective antidiarrhoeal.[1,2] It was somewhat less effective than loperamide when given without a loading dose,[2] but a regimen of 40 mg initially, followed by 20 mg, about every 6 hours was as effective as loperamide 4 mg initially followed by 2 mg after each unformed stool.[3]

1. DuPont HL, *et al.* Zaldaride maleate, an intestinal calmodulin inhibitor, in the therapy of travelers' diarrhea. *Gastroenterology* 1993; **104:** 709–15.
2. Okhuysen PC, *et al.* Zaldaride maleate (a new calmodulin antagonist) versus loperamide in the treatment of traveler's diarrhea: randomized, placebo-controlled trial. *Clin Infect Dis* 1995; **21:** 341–4.
3. Silberschmidt G, *et al.* Treatment of travellers' diarrhoea: zaldaride compared with loperamide and placebo. *Eur J Gastroenterol Hepatol* 1995; **7:** 871–5.