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.

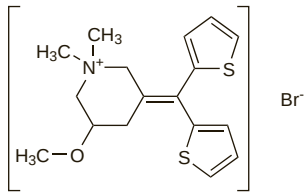
Preparations
Proprietary Preparations (details are given in Part 3)
Belg.: Visceralgine†; ***Fr.:*** Visceralgine; ***Indon.:*** Visceralgine.

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.

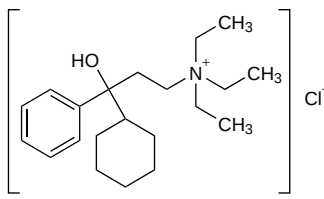
Urinary metabolites of timepidium may cause a reddish coloration of the urine.

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.



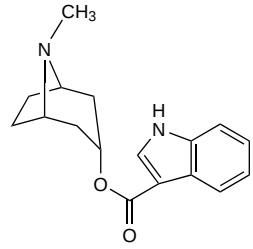
NOTE. Tridihexethyl Iodide is *rINN*.

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.