Tamarind

Tamarindo; West Indian Tamarind.

Индийский Финик; Плоды Тамаринда; Тамаринд

Pharmacopoeias. In *Fr.*

Profile

Tamarind is the fruits of *Tamarindus indica* (Leguminosae) freed from the brittle outer part of the pericarp and preserved with sugar or syrup. It contains tartaric, citric, and malic acid and their salts. Tamarind is used as a laxative with senna.

Preparations

Proprietary Preparations (details are given in Part 3)

Fr.: Delabarre.

Multi-ingredient: ***Arg.:*** Tamarine†; ***Austria:*** Frugelletten; Neda Fruchtewurfel; ***Braz.:*** Fitolax; Florlax; Fontolax; Frutalax†; Laxarine†; Laxtam; Naturetti; Tamanl; Tamarine; Tamarix†; ***Chile:*** Tamarine; ***Fr.:*** Carres Parapsyllium; Laxarine; Tamarine; ***Ital.:*** Ortisan; Tamarine; ***Mex.:*** Naturetti†; ***Spain:*** Dentomicin; Pruina.

Tegaserod Maleate *(BANM, USAN, rINNM)*

HTF-919; Maleato de tegaserod; SDZ-HTF-919; Tégasérod, Maléate de; Tegaserodi Maleas. 1-{[(5-Methoxyindol-3-yl)methylene]amino}-3-pentylguanidine maleate.

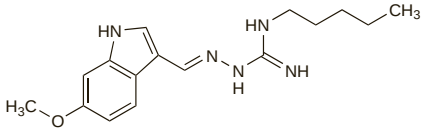
Тегасерода Малеат

$C_{16}H_{23}N_5O,C_4H_4O_4$ = 417.5.

CAS — 145158-71-0 (tegaserod); 189188-57-6 (tegaserod maleate).

ATC — A03AE02.

ATC Vet — QA03AE02.



(tegaserod)

Stability and compatibility. Crushed tablets of tegaserod were found to be stable in water, and apple juice; the latter may mask the taste of the drug. Orange juice, milk, or yogurt were not recommended as vehicles because of incomplete dissolution or uncertainty about stability.[1]

1. Carrier M-N, *et al.* Stability and compatibility of tegaserod from crushed tablets mixed in beverages and foods. *Am J Health-Syst Pharm* 2004; **61:** 1135–42.

Adverse Effects

The most common adverse effects of tegaserod are gastrointestinal disturbances including abdominal pain, diarrhoea, nausea, vomiting, and flatulence. Diarrhoea generally occurs within the first week of treatment and is usually transient but may be severe. Ischaemic colitis has been reported. Headache, dizziness, migraine, insomnia, fatigue, leg or back pain, and arthropathy have also been commonly reported. Cardiovascular adverse effects include hypotension and arrhythmias. Serious cardiovascular ischaemic events such as myocardial infarction, unstable angina pectoris, and stroke have occurred; fatalities have been reported. Other adverse effects include effects on the nervous system such as depression, and other gastrointestinal effects including cholelithiasis and dyspepsia.

◊ References.

1. Hasler WL, Schoenfeld P. Safety profile of tegaserod, a 5-HT receptor agonist, for the treatment of irritable bowel syndrome. *Drug Safety* 2004; **27:** 619–31.
2. Quigley EM, *et al.* Safety and tolerability of tegaserod in patients with chronic constipation: pooled data from two phase III studies. *Clin Gastroenterol Hepatol* 2006; **4:** 605–13.

Effects on the gastrointestinal tract. Severe diarrhoea, leading to hypovolaemia, hypotension, and syncope has been seen occasionally in patients receiving tegaserod. Some patients required hospitalisation for rehydration, and patients should be advised to stop taking the drug and seek medical attention if severe diarrhoea or associated dizziness or lightheadedness develop. In addition, ischaemic colitis has been reported rarely, and the drug should be stopped immediately in patients who develop symptoms such as rectal bleeding, bloody diarrhoea, or new and worsening abdominal pain.[1] The FDA noted that it had received 20 reports of ischaemic colitis in patients taking tegaserod between August 2002 and March 2004; in 3 cases, the effect only developed after several months (7 to 13) of therapy.[2] However, in reply the manufacturer (*Novartis*) suggested that there was no evidence from postmarketing surveillance to support an increased rate of ischaemic colitis over that normally seen in patients with irritable bowel syndrome, who are at increased risk of this diagnosis, nor any obvious pharmacological mechanism for such an adverse effect.[3]

1. Novartis, Canada. Important safety update: diarrhea and ischemic colitis in patients using Zelnorm (tegaserod hydrogen maleate) (issued 28/04/04). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/zelnorm_hpc-cps_e.pdf (accessed 07/07/06)
2. Brinker AD, *et al.* Tegaserod and ischemic colitis. *N Engl J Med* 2004; **351:** 1361–3.
3. Joelsson BE, *et al.* Tegaserod and ischemic colitis. *N Engl J Med* 2004; **351:** 1363–4.

Effects on the heart. In an analysis of pooled data from 29 studies, 13 out of 11 614 patients taking tegaserod had serious cardiovascular ischaemic events, compared with 1 out of 7031 patients taking placebo. Events included unstable angina pectoris, stroke, and myocardial infarction, one of which was fatal.[1-3] Most of these patients had at least one cardiovascular risk factor, but for some, no cardiovascular disease or risk had been diagnosed at the onset of treatment with tegaserod.[2] Patients taking tegaserod should seek medical attention if they have severe chest pain, dyspnoea, dizziness, sudden onset of weakness, difficulty walking or talking, or any other symptoms suggestive of myocardial infarction or stroke.[1]

1. FDA Public Health Advisory. Tegaserod maleate (marketed as Zelnorm) (issued 30th March 2007). Available at: http://www.fda.gov/cder/drug/advisory/tegaserod.htm (accessed 31/05/07)
2. Novartis, Canada. Health Canada endorsed important safety information on Zelnorm (tegaserod hydrogen maleate) (issued 30th March 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/zelnorm_hpc-cps_2_e.pdf (accessed 31/05/07)
3. Novartis, USA. Urgent: marketing and sales suspension notice for Zelnorm® tablets, 2-mg and 6-mg all lots within expiry (issued 30th March 2007). Available at: http://www.zelnorm.com/Dr_Doctor_Letter.pdf (accessed 31/05/07)

Precautions

Tegaserod is contra-indicated in patients with a history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions. Tegaserod should also not be given to patients who have diarrhoea or who frequently experience diarrhoea. It should be stopped in patients with new or sudden worsening of abdominal symptoms, hypotension, or syncope. Tegaserod should not be used in patients with severe renal impairment or moderate to severe hepatic impairment. For the possible cardiovascular risks of tegaserod therapy, see above; in the USA use is restricted, and it is contra-indicated in patients with a history of heart disease or symptoms suggestive of cardiac disorders.

Pharmacokinetics

Tegaserod is rapidly absorbed from the gastrointestinal tract with peak plasma levels occurring after about 1 hour. The absolute bioavailability of an oral dose is 10%; this is reduced by the presence of food. Tegaserod is widely distributed into the tissues and is about 98% bound to plasma proteins. Presystemic acid-catalysed hydrolysis in the stomach, and then oxidation and glucuronidation, produces the main metabolite, which is inactive; direct systemic glucuronidation also occurs. Two-thirds of an oral dose is excreted unchanged in the faeces and one-third excreted in the urine primarily as the main metabolite. The terminal half-life of tegaserod is about 11 hours.

◊ Reviews.

1. Appel-Dingemanse S. Clinical pharmacokinetics of tegaserod, a serotonin 5-HT receptor partial agonist with promotile activity. *Clin Pharmacokinet* 2002; **41:** 1021–42.

Uses and Administration

Tegaserod is a partial agonist at 5-HT_4 receptors and has prokinetic properties. It is used in women for the short-term treatment of irritable bowel syndrome (p.1699), particularly the constipation-predominant form. It has also been used for the treatment of chronic idiopathic constipation (p.1693) in men and women less than 65 years of age.

Tegaserod is given orally as the maleate but doses are expressed in terms of the base; 8.31 mg of tegaserod maleate is equivalent to about 6 mg of tegaserod. It is given in a dose of 6 mg twice daily before food. For irritable bowel syndrome, it is given for 4 to 6 weeks; a further 4 to 6 weeks of treatment may be given if a beneficial response is seen.

In March 2007, marketing of tegaserod was suspended in some countries because of a high incidence of cardiovascular ischaemic events (see Effects on the Heart, above). In the USA, the use of tegaserod was subsequently restricted to women younger than 55 years of age who have either constipation-predominant irritable bowel syndrome or chronic idiopathic constipation, and who meet specific guidelines; patients should have no known or pre-existing cardiac problems.

◊ References.

1. Wagstaff AJ, *et al.* Tegaserod: a review of its use in the management of irritable bowel syndrome with constipation in women. *Drugs* 2003; **63:** 1101–20.
2. Lea R, Whorwell PJ. Benefit-risk assessment of tegaserod in irritable bowel syndrome. *Drug Safety* 2004; **27:** 229–42.
3. Johanson JF, *et al.* Effect of tegaserod in chronic constipation: a randomized, double-blind, controlled trial. *Clin Gastroenterol Hepatol* 2004; **2:** 796–805.
4. Müller-Lissner S, *et al.* Tegaserod is effective in the initial and retreatment of irritable bowel syndrome with constipation. *Aliment Pharmacol Ther* 2005; **21:** 11–20.
5. Kamm MA, *et al.* Tegaserod for the treatment of chronic constipation: a randomized, double-blind, placebo-controlled multinational study. *Am J Gastroenterol* 2005; **100:** 362–72.
6. Tack J, *et al.* A randomised controlled trial assessing the efficacy and safety of repeated tegaserod therapy in women with irritable bowel syndrome with constipation. *Gut* 2005; **54:** 1707–13.
7. Muller-Lissner S, *et al.* Safety, tolerability, and efficacy of tegaserod over 13 months in patients with chronic constipation. *Am J Gastroenterol* 2006; **101:** 2558–69.
8. Baun RF, Levy HB. Tegaserod for treating chronic constipation in elderly patients. *Ann Pharmacother* 2007; **41:** 309–13.
9. Evans BW, *et al.* Tegaserod for the treatment of irritable bowel syndrome and chronic constipation. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 17/03/08).

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Altezerod; Coloserod; Procinet; Tegarod; Zelmac; ***Austral.:*** Zelmac†; ***Braz.:*** Zelmac; ***Canad.:*** Zelnorm; ***Chile:*** Colonaid; Distimax; Tegasir; Ther; Zelmac; ***Cz.:*** Zelmac†; ***Hong Kong:*** Zelmac; ***India:*** Tegibs; Tegod; ***Indon.:*** Zelmac; ***Israel:*** Zelmac; ***Malaysia:*** Zelmac†; ***Mex.:*** Zelmac; ***NZ:*** Zelmac; ***Philipp.:*** Zelnorm; ***Rus.:*** Zelmac (Зелмак)†; ***S.Afr.:*** Zelnorm; ***Singapore:*** Zelmac; ***Switz.:*** Zelmac; ***Thai.:*** Zelmac; ***Turk.:*** Zelmac; ***USA:*** Zelnorm†; ***Venez.:*** Zelmac.

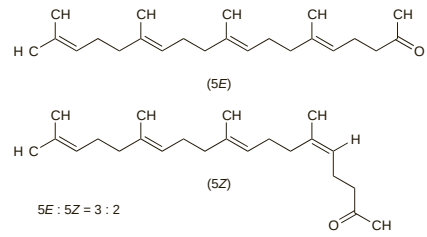
Teprenone *(rINN)*

E-671; Geranylgeranylacetone (5*E*, 9*E*,13*E* isomer); Teprenona; Téprénone; Teprenonum. 6,10,14,18-Tetramethyl-5,9,13,17-nonadecatetraen-2-one, mixture of (5*E*,9*E*,13*E*) and (5*Z*,9*E*,13*E*) isomers.

Тепренон

$C_{23}H_{38}O$ = 330.5.

CAS — 6809-52-5 (teprenone); 3796-63-2 (5E,9E,13E isomer); 3796-64-3 (5Z,9E,13E isomer).



(5*E*)

(5*Z*)

5*E* : 5*Z* = 3 : 2

Profile

Teprenone is a cytoprotective drug that is used in the treatment of gastritis and peptic ulcer disease (p.1702) in a usual oral dose of 50 mg three times daily.

Preparations

Proprietary Preparations (details are given in Part 3)

Indon.: Purubex; ***Jpn:*** Selbex; ***Philipp.:*** Selbex; ***Thai.:*** Selbex.

Tiemonium Iodide *(BAN, rINN)*

Ioduro de tiemonio; TE-114; Tiemonii Iodidum; Tiémonium, Iodure de. 4-[3-Hydroxy-3-phenyl-3-(2-thienyl)propyl]-4-methylmorpholinium iodide.

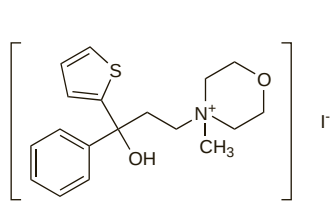
Тиемония Йодид

$C_{18}H_{24}INO_2S$ = 445.4.

CAS — 6252-92-2 (tiemonium); 144-12-7 (tiemonium iodide).

ATC — A03AB17.

ATC Vet — QA03AB17.



Tiemonium Metilsulfate

Tiemonio, metilsulfato de; Tiemonium Methylsulphate. 4-[3-Hydroxy-3-phenyl-3-(2-thienyl)propyl]-4-methyl-morpholinium methylsulphate.

$C_{19}H_{27}NO_6S_2$ = 429.6.

CAS — 6504-57-0.

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.

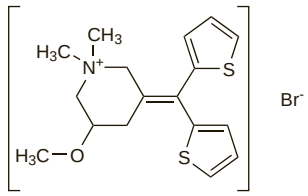
Preparations
Proprietary Preparations (details are given in Part 3)
Belg.: Visceralgine†; ***Fr.:*** Visceralgine; ***Indon.:*** Visceralgine.

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.

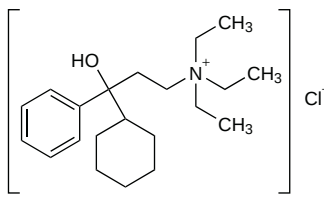
Urinary metabolites of timepidium may cause a reddish coloration of the urine.

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.



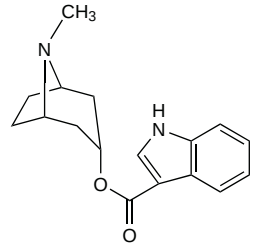
NOTE. Tridihexethyl Iodide is *rINN*.

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.