

NAVOBAN® (tropisetron)

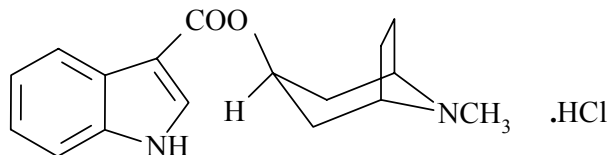
COMPOSITION

Capsules containing 5.64 mg tropisetron hydrochloride (equivalent to 5 mg of the base) and ampoules (2 or 5 mL) containing 2.26 or 5.64 mg tropisetron hydrochloride (equivalent to 2 or 5 mg of the base respectively).

DESCRIPTION

Tropisetron hydrochloride is 1 α H,5 α H-tropan-3 α -yl indole-3-carboxylate hydrochloride.

CAS - 89565-68-4 (tropisetron); CAS - 105826-92-4 (tropisetron hydrochloride).



Tropisetron hydrochloride is a white or off-white crystalline powder. It is soluble >5% in water, 1.6% in ethanol (95% v/v) and poorly soluble (0.02%) in acetone. The molecular weight of the free base is 284.4 and of the hydrochloride salt is 320.8.

PHARMACOLOGY

Tropisetron is a highly potent and selective competitive antagonist of the 5-HT₃ receptor, a subclass of serotonin receptors located on peripheral neurons and within the CNS. Surgery and treatment with certain substances, including some chemotherapeutic agents, may trigger the release of serotonin (5-HT) from enterochromaffin-like cells in the visceral mucosa and initiate the emesis reflex and its accompanying feeling of nausea. Tropisetron selectively blocks the excitation of the presynaptic 5-HT₃ receptors of the peripheral neurons in this reflex, and may exert additional direct actions within the CNS on 5-HT₃ receptors mediating the actions of vagal input to the area postrema. These effects are considered to be the underlying mechanism of action of the anti-emetic effect of tropisetron.

Navoban has a 24-hour duration of action which allows once-a-day administration.

In studies where Navoban has been administered over multiple chemotherapy cycles, treatment has remained effective.

Navoban prevents nausea and vomiting induced by cancer chemotherapy or surgery without causing extrapyramidal side-effects.

Clinical Trials on Use in Post-operative Nausea and Vomiting

The use of Navoban in the treatment and prevention of post-operative nausea and vomiting (PONV) was supported by the results of three prospective, double-blind, placebo-controlled trials conducted in adult patients. All three studies had one primary endpoint (the proportion of patients without emetic episodes over a 24 h postoperative period, regardless of rescue treatment received) and two secondary endpoints (the proportion of patients without nausea and without rescue treatment over a 24 h period). As patients could receive rescue treatment for nausea and remain free of emetic episodes or receive rescue treatment for vomiting while remaining free of nausea, the rescue treatment endpoint was thus a reflection of a combined response. In the treatment study, only patients who experienced PONV within 2 hours of recovering from anaesthesia were included.

In two of the studies, a 0.5, 2 or 5 mg i.v. dose of Navoban was compared with placebo in the prevention of PONV in women undergoing abdominal and gynaecological surgery (n=385), and in the treatment of PONV in men and women with established PONV (n=314). In the study on the prevention of PONV, 68%, 74%, 70% and 56% of patients had no emetic episodes in the 0.5 mg, 2 mg, 5 mg and placebo groups respectively. Similarly, in the treatment study, 52%, 58%, 60% and 29% of patients responded in the 0.5 mg, 2 mg, 5 mg and placebo groups respectively. The results for the secondary endpoints were in line with the primary endpoint of the studies and indicate that the 2 mg dose is optimal both for prevention and treatment of PONV. Tropisetron did not suppress the retching or vomiting associated with the removal of the endotracheal tube.

In the third study, 2 mg i.v. Navoban, 4 mg i.v. ondansetron and placebo were compared in the prevention of PONV (n=908). This study was prospectively stratified for sex and type of surgery (abdominal versus non-abdominal surgery). Navoban 2 mg and ondansetron 4 mg were shown to have similar efficacy in preventing PONV following abdominal surgery, with response rates of 70 and 72% respectively, compared with 59% for the placebo group. However, in the non-abdominal surgery types tested the efficacy results for both agents were not significantly different from those of the placebo group.

Pharmacokinetics

The absorption of tropisetron from the gastrointestinal tract is rapid (mean half-life of about 20 minutes) and nearly complete (more than 95%). Due to first-pass metabolism in the liver, the absolute bioavailability of a 5 mg oral dose is 60%. As this metabolism is saturable, the absolute bioavailability increases with the dose (up to 100% at a dose of 45 mg). The peak plasma concentration is attained within three hours. Tropisetron is 71% bound to plasma protein in a non-specific manner. The volume of distribution is 400-600 L.

The metabolism of tropisetron occurs by hydroxylation at the 5, 6 or 7 positions of its indole ring, followed by a conjugation reaction to the glucuronide or sulphate and excretion in the urine or bile (urine to faeces ratio 5:1). The metabolites have a greatly reduced potency for the 5-HT₃ receptor and do not contribute to the pharmacological action of the drug. The metabolism of tropisetron is linked to the genetically determined sparteine/debrisoquine polymorphism. About 8% of the Caucasian population are known to be poor metabolisers for the sparteine/debrisoquine pathway. The elimination half-life (beta-phase) is about eight hours in extensive metabolisers; in poor metabolisers this could be extended to 45 hours (see PRECAUTIONS).

In extensive metabolisers, about 8% of tropisetron is excreted in the urine as unchanged drug, 70% as metabolites; 15% is excreted in the faeces, almost entirely as metabolites. In poor metabolisers, a greater proportion of unchanged tropisetron is excreted in the urine than in extensive metabolisers.

INDICATIONS

- For the prevention of nausea and vomiting induced by cytotoxic therapy (5 mg/5 mL ampoule and 5 mg capsule only).
- For the treatment and prevention of post-operative nausea and vomiting in adults (2 mg/2 mL ampoule only).

CONTRAINDICATIONS

Hypersensitivity to tropisetron, other 5-HT₃ receptor antagonists, or any other components of the formulations. Pregnancy and lactation (see PRECAUTIONS).

PRECAUTIONS

Effects on Ability to Drive and Use Machinery

No data exist on the effect of Navoban on the ability to drive or operate machinery. The occurrence of dizziness and fatigue as side effects should be taken into account.

Use in Pregnancy Category B3

Reproductive studies have been performed in rats, rabbits and monkeys at oral doses up to 60, 120 and 180 mg/kg/day, respectively, and have revealed no evidence of a drug related teratogenic effect. In rats and rabbits there were increased incidences of post implantation loss and delayed development of pups at doses greater than 20 and 60 mg/kg/day, respectively. Studies in rats also showed an increased incidence of post-natal loss at doses of 15 mg/kg/day and above.

Use in Lactation

Tropisetron is excreted in the breast milk of rats. It is not known whether tropisetron is excreted into human milk and therefore patients on Navoban should not breast-feed.

Use in Children

Since experience with Navoban in children is still limited, its use cannot be recommended.

Use in the Elderly

There is no evidence that elderly patients require different dosages or experience different side-effects from younger patients.

Use in Poor Metabolisers of Sparteine/Debrisoquine

In patients belonging to this group (about 8% of the Caucasian population) the elimination half-life of tropisetron is prolonged (4-5 times longer than in extensive metabolisers). However, when Navoban was given intravenously at doses up to 40 mg twice a day over a period of seven days to healthy volunteers known to be poor metabolisers, no serious adverse events occurred. These observations indicate that for six-day courses (for the prevention of cancer chemotherapy-induced nausea and vomiting) the usual daily dose of 5 mg does not need to be reduced in patients with poor metabolism.

Use in Patients with Impaired Hepatic or Renal Function

No change in the pharmacokinetics of tropisetron occurs in patients with acute hepatitis or fatty liver disease. In contrast, patients with liver cirrhosis or impaired kidney function may have plasma concentrations up to 50% higher than those found in healthy volunteers belonging to the group of extensive metabolisers of sparteine/debrisoquine. Nevertheless, no dosage reduction is necessary in such patients when the recommended six-day courses of 5 mg Navoban per day are given for the prevention of cancer chemotherapy-induced nausea and vomiting.

In patients who have renal impairment and who are also poor metabolisers of sparteine/debrisoquine, there is a possibility of increased plasma tropisetron levels.

Use in Patients with Uncontrolled Hypertension

In patients with uncontrolled hypertension, daily doses of Navoban higher than 10 mg should be avoided since they may cause a further increase in blood pressure.

Carcinogenicity/Mutagenicity

Carcinogenicity studies showed no evidence of a drug related carcinogenic response at doses up to 45 mg/kg/day in the rat and 90 mg/kg/day in the female mouse. In the male mouse there was a statistically significant increase in the incidence of benign hepatocellular neoplasia at doses of 30 mg/kg/day and above. Tropisetron was not mutagenic in standard tests for mutagenicity.

General

Caution should be exercised in patients with cardiac rhythm or conduction disturbances, or in patients treated with anti-arrhythmic or beta-adrenergic blocking agents since, in these patient groups, limited experience is available with concurrent use of Navoban and anaesthetics.

Prolongations of the QTc interval which were not clinically significant have been observed after high (up to 80 mg) iv doses of tropisetron. Therefore it cannot be excluded that lower doses of tropisetron have also contributed to the QTc interval prolongation seen occasionally in patients undergoing general anaesthesia.

Interactions

Ingestion of the capsule with food results in a slight increase in bioavailability, from approx. 60% to approx. 80%, which is not clinically relevant.

Concomitant administration of Navoban with rifampicin or with other liver enzyme-inducing drugs (e.g. phenobarbital) results in lower plasma concentrations of tropisetron and, therefore, requires an increase in dosage in extensive metabolisers (but not in poor metabolisers). The effects on tropisetron plasma levels of cytochrome P450 enzyme inhibitors such as cimetidine are negligible and do not require dose adjustment.

As a prolongation of the QTc interval has been observed in patients administered Navoban (see PRECAUTIONS - General), care should be taken when other drugs that are likely to prolong the QT interval are taken concomitantly with Navoban.

No interaction studies have been performed with tropisetron and drugs used in anaesthesia (see “PRECAUTIONS-General”).

ADVERSE REACTIONS

In general, Navoban is well tolerated and the side-effects are transient at the recommended dose. The most frequently reported adverse reaction at the 2 mg dose was headache. At the 5 mg dose, constipation and, less frequently, dizziness, fatigue, somnolence, and gastrointestinal disorders, such as abdominal pain, diarrhoea and anorexia were observed as well.

As with other 5-HT₃ receptor antagonists, hypersensitivity reactions (“type 1- reactions”) with one or more of the following symptoms have been observed: flushing and / or generalised urticaria, chest discomfort, dyspnoea, acute bronchospasm, hypotension.

Navoban was found to cause prolongation of the QT interval although this was not of clinical significance.

Listed in the following table are the frequencies of adverse events observed in more than 1% of patients exposed to each treatment in the clinical trials discussed under Clinical trials on use in post-operative nausea and vomiting.

Adverse Event	Placebo (n=473)	NAVOBAN®			Ondansetron
		0.5 mg (n=174)	2 mg (n=485)	5 mg (n= 176)	4 mg (n= 299)
bradycardia	50 (11%)	1 (1%)	50 (10%)	2 (1%)	47 (16%)
hypotension	31 (7%)	0 (0%)	40 (8%)	1 (1%)	27 (9%)
headache	15 (3%)	4 (2%)	19 (4%)	17 (10%)	8 (3%)
shivering	10 (2%)	1 (1%)	15 (3%)	0 (0%)	12 (4%)
hypertension	12 (3%)	2 (1%)	16 (3%)	1 (1%)	17 (6%)
skin reactions	5 (1%)	3 (2%)	7 (1%)	2 (1%)	6 (2%)
bronchospasm	6 (1%)	0 (0%)	5 (1%)	0 (0%)	2 (1%)
dizziness	5 (1%)	2 (1%)	2 (0%)	2 (1%)	1 (0%)

With the exception of headache, the frequency, severity and relationship to the study drug of these events was similar for Navoban and placebo. Therefore it is likely that these events can be attributed to the anaesthesia or the surgical procedures.

The following adverse reactions have been observed in less than 1% of patients exposed to each treatment in the clinical trials: syncope, urticaria generalized.

Post-marketing experience:

The following adverse reactions have been reported during post approval use of Navoban. Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following hypersensitivity reactions have been rarely observed: rash, erythema and anaphylactic reactions/shock. In very rare instances, collapse and cardiovascular arrest have been reported. Some may have been caused by the concomitant chemotherapy or the underlying disease.

DOSAGE AND ADMINISTRATION

Prevention of Nausea and Vomiting Induced by Cytotoxic Therapy

Navoban is recommended as six-day courses of 5 mg per day, given intravenously on Day 1 immediately before cancer chemotherapy either as an infusion given over 15 minutes (see below for dilution instructions) or as a slow injection (not less than 1 minute), followed by oral administration on Days 2 to 6. Capsules should be taken with water in the morning immediately upon rising at least one hour before food intake.

If Navoban alone produces insufficient antiemetic control, its therapeutic efficacy may be enhanced by the addition of dexamethasone.

For infusion, one ampoule can be diluted in 100 mL of sodium chloride 0.9%; glucose 5%; potassium chloride, sodium chloride and calcium chloride intravenous solution (Ringer's solution); fructose intravenous solution (Levulose 5%); mannitol 10%; potassium chloride 0.3% and sodium chloride 0.9%; potassium chloride 0.3% and glucose 5%. The diluted solutions are physically and chemically stable for at least 24 hours. However, considering the risk of microbial contamination during preparation of the infusion, the solution should be used within eight hours of preparation. Any storage should be at 2-8°C.

Treatment and Prevention of Post-operative Nausea and Vomiting

Navoban is recommended as a 2 mg dose given intravenously either as an infusion or as a slow injection (not less than 30 seconds). In the case of prevention of post-operative nausea and vomiting, Navoban should be administered shortly before the induction of anaesthesia.

OVERDOSAGE

Symptoms:

At very high repeated doses, visual hallucinations and, in patients with pre-existing hypertension, an increase in blood pressure, have been observed.

Treatment:

Symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND PACKAGING

Ampoules : 5 mg/5 mL, box of 1 or 10 ampoules.
2 mg/2 mL, box of 1 or 10 ampoules.
Navoban injection is a clear, colourless to very faintly yellow-brown aqueous solution, pH 4.6 - 5.2.
The ampoules contain as excipients, acetic acid - glacial, sodium acetate, sodium chloride and water for injections.

Capsules: 5 mg, packs of 2, 5 or 50 capsules.
Opaque yellow and opaque white, marked with "NVR EA 5 mg" in red.
The capsules contain as excipients, silica - colloidal anhydrous, magnesium stearate, starch - maize, lactose, gelatin, titanium dioxide, shellac, iron oxide yellow CI 77492 and iron oxide red CI 77491.

Storage: Ampoules and capsules: Store below 30°C.
Shelf-life: 5 years

Poison schedule: S4

Novartis Pharmaceuticals Australia Pty Ltd
ABN 18 004 244 160
54 Waterloo Road
NORTH RYDE NSW 2113

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