NOVARTIS

Drug Regulatory Affairs

NAVOBAN®

(tropisetron)

5 mg Capsules

2 mg/2 mL or 5 mg/5 mL Solution for injection and infusion

Basic Prescribing Information

NOTICE

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.

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1 Name of the medicinal product

NAVOBAN®

2 Qualitative and quantitative composition

The active ingredient is ((1 alphaH, 5 alphaH)-8-Methyl-8-azabicyclo(3.2.1)oct-3-alphayl) 1H-indole-3-carboxylate hydrochloride (= tropisetron hydrochloride).

One capsule contains 5.64 mg tropisetron hydrochloride (= 5 mg tropisetron base).

One ampoule contains 2.26 mg tropisetron hydrochloride (= 2 mg tropisetron base) per 2 mL, or 5.64 mg tropisetron hydrochloride (= 5 mg tropisetron base) per 5 mL.

For a full list of excipients, see section 6.1 List of excipients.

3 Pharmaceutical form

Capsule: hard gelatine capsules for oral administration;

Ampoule: glass ampoule containing an aqueous-solution for intravenous administration (adults and children) and oral administration (children).

Information might differ in some countries.

4 Clinical particulars

4.1 Therapeutic indications

- Prevention of cancer-chemotherapy-induced nausea and vomiting.
- Treatment of post-operative nausea and vomiting.
- Prevention of post-operative nausea and vomiting in patients undergoing intra-abdominal gynaecological surgery. In order to optimise the benefit-risk ratio, use should be limited to patients with a known history of post-operative nausea and vomiting.

4.2 Posology and method of administration

Prevention of cancer chemotherapy-induced nausea and vomiting

Children

The recommended dose for Navoban® in children over two years of age is 0.2 mg/kg, up to a maximum daily dose of 5 mg per day. It is recommended that Navoban be given intravenously on day 1, shortly before cancer chemotherapy, either as an infusion (diluted in a common infusion fluid such as normal saline, Ringer's solution, glucose 5%, or levulose 5%) or as a slow injection (not less than 1 minute), followed by oral administration on days 2 up to 6.

Navoban can be given as a drink solution immediately after diluting the appropriate amount of tropisetron from the ampoule in orange juice or cola, and should be taken in the morning, one hour before food intake.

Adults

Navoban is recommended in adults as 6-day courses of 5 mg per day, given intravenously on day 1 shortly before cancer chemotherapy either as an infusion (diluted in a common infusion fluid such as normal saline, Ringer's solution, glucose 5%, or levulose 5%) or as a slow injection (not less than 1 minute), followed by oral administration on days 2 to 6.

If tropisetron alone produces insufficient anti-emetic control, its therapeutic efficacy can be enhanced by dexamethasone.

Capsules should be taken with water in the morning immediately upon rising, one hour before food intake.

Treatment and prevention of post-operative nausea and vomiting

Adults

Navoban is recommended as a 2 mg dose given intravenously either as an infusion (diluted in a common infusion fluid such as normal saline, Ringer's solution, glucose 5% or levulose 5%), 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.

4.3 Contraindications

Known hypersensitivity to tropisetron, other 5-HT_3 receptor antagonists, or any other components of the formulations (see section 6.1 List of excipients).

Navoban must not be given to pregnant women (see section 4.6 Pregnancy and lactation).

4.4 Special warnings and precautions for use

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 7 days to healthy volunteers known to be poor metabolisers, no serious adverse events occurred. These observations indicate that, for 6-day courses in patients with poor metabolism, the usual daily dose of 5 mg does not need to be reduced.

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 6-day courses of 5 mg Navoban per day are given.

Use in patients with 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.

Use in cardiac patients

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.

Use in children

In children above two years of age, Navoban has been found to be well tolerated (see section 4.2 Posology and method of administration: children).

Use in the elderly

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

4.5 Interactions with other medicinal products and other forms of interaction

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 necessitates an increase in dosage for extensive metabolisers (but not for poor metabolisers). The effects on tropisetron plasma levels of cytochrome P450 enzyme inhibitors such as cimetidine are negligible and do not require dose adjustment.

No interaction studies were performed with tropisetron and drugs used in anaesthesia.

Prolongation of the QTc interval has been observed in a few patients where Navoban has been used in conjunction with drugs known to cause such an effect. QTc prolongation has not been reported in studies where Navoban was used alone in therapeutic doses. Nevertheless, care should be taken when Navoban is used together with other drugs that are likely to prolong the QTc interval.

4.6 Use during pregnancy and lactation

Tropisetron toxicity in female rats was demonstrated by a decreased pregnancy rate and effects on gestation length at doses $\geq$ 15 mg/kg. In pregnant rats and rabbits embryotoxicity was observed at doses of tropisetron that caused maternal toxicity. There was no evidence of

a teratogenic effect. Peri- and post-natal development were impaired in offspring of rats treated with high doses (≥ 15 mg/kg). Since Navoban has not been studied in human pregnancy, it must not be given to pregnant women.

In the rat, after administration of radiolabelled tropisetron, radioactivity was excreted in the milk. It is not known whether tropisetron is excreted into human milk and therefore patients on Navoban should not breast-feed.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The undesirable effects are transient at the recommended dose. The most frequently reported at the 2-mg dose was headache, whereas at the 5-mg dose constipation and, less frequently, dizziness, fatigue, and gastrointestinal disorders such as abdominal pain and diarrhoea were observed as well.

As with other 5-HT_3 receptor antagonists, hypersensitivity reactions ('type I-reactions') with one or more of the following symptoms have been observed: flushing and/or generalised urticaria, chest discomfort, dyspnoea, and hypotension.

The following adverse drug reactions, listed in Table 1, have been accumulated from clinical studies with tropisetron.

Adverse drug reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: *very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10,000, < 1/1000) very rare (< 1/10,000),* including isolated reports

Table 1 Adverse reactions reported in clinical studies

Immune system disorders		
	Uncommon:	Hypersensitivity.
Nervous system disorders		
	Very common:	Headache.
	Common:	Dizziness.
	Uncommon:	Syncope.
Vascular disorders		
	Uncommon:	Hypotension, flushing.
Respiratory, thoracic and mediastinal disorders		
	Uncommon:	Dyspnoea.
Gastrointestinal disorders		
	Very common:	Constipation.
	Common:	Diarrhoea, abdominal pain.
Skin and subcutaneous tissue disorders		
	Uncommon:	Urticaria generalized.

General disorders and administration site conditions	
Common:	Fatigue.
Uncommon:	Chest discomfort.

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

4.9 Overdose

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.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 5-HT_3 receptor antagonist (ATC code A04A A03).

Mechanism of action

Tropisetron is a highly potent and selective competitive antagonist of the 5-HT_3 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-HT_3 receptors of the peripheral neurons in this reflex, and may exert additional direct actions within the CNS on 5-HT_3 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.

5.2 Pharmacokinetic properties

Absorption

Navoban is nearly completely absorbed (more than 95%) from the gastrointestinal tract, with a mean half-life of about 20 minutes.

Distribution

Tropisetron is 71% bound to plasma proteins (particularly $alpha_1$-glycoproteins) in a non-specific manner. The volume of distribution in adults is 400 to 600 L; in children aged 3-6 years it is about 145 L, and in children aged 7-15 about 265 L.

Biotransformation

The peak plasma concentration is attained within 3 hours. The absolute bioavailability is dependent on the dose and amounts to approx. 60% at a dose of 5 mg and is higher (up to 100%) at a dose of 45 mg. The absolute bioavailability and terminal half-life in children was similar to those in healthy volunteers.

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 sulfate and excretion in the urine or bile (urine to feces ratio 5:1). The metabolites have a greatly reduced potency for the 5-HT_3 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.

During repeated administration of Navoban at doses higher than 10 mg twice a day saturation of the hepatic enzyme system involved in the metabolism of tropisetron may occur and result in dose-dependent increases of the plasma levels. However, even in poor metabolisers the exposure to such doses remains well within the tolerated levels. Therefore, at the recommended dose of 5 mg once a day given for 6 days for the prevention of cancer chemotherapy-induced nausea and vomiting, drug accumulation is not thought to be of clinical concern.

Elimination

The elimination half-life (beta-phase) is about 8 hours in extensive metabolisers; in poor metabolisers this could be extended to 45 hours (see section 4.4. Special warnings and precautions for use).

The total clearance of tropisetron is about 1 L/min, with the renal clearance contributing approx. 10%. In patients who are poor metabolisers, the total clearance is reduced to 0.1-0.2

L/min although the renal clearance remains unchanged. This reduction in non-renal clearance results in an approximately 4 to 5-fold longer elimination half-life and in 5 to 7-fold higher AUC values. C_{max} and volume of distribution are not different when compared to extensive metabolisers. In poor metabolisers, a greater proportion of unchanged tropisetron is excreted in the urine than in extensive metabolisers.

5.3 Preclinical safety data

Acute toxicity

The minimal lethal dose was 30 mg/kg for mice and rats after i.v. administration, and 420 mg/kg for mice and 180 mg/kg for rats after oral administration. The corresponding non-lethal doses were 18 and 24 mg i.v. in mice and rats, and 300 and 100 mg/kg p.o. in mice and rats respectively.

Chronic and subchronic toxicity

Oral administration

Tolerability has been investigated with oral administration for up to 6 months in chronic toxicity studies in rats and dogs.

With high doses of up to 100 times the human dose recommended for prevention and treatment of post-operative nausea and vomiting, a slight decrease in body weight and a reduction in food intake were observed. The no-toxic-effect levels were 16 mg/kg per day for rats and 20 mg/kg per day for dogs.

Intravenous administration

In dogs the i.v. administration of tropisetron over a period of 6 and 26 weeks caused slight clinical alterations such as vomiting, increased salivation, excitation and diarrhoea. These undesirable effects, which have also been observed, though less pronounced, in the placebo control groups, were reversible after termination of treatment.

The no-toxic-effect dose in dogs on the basis of the studies ranges between 3 and 10 mg/kg per day (bolus administration).

Carcinogenicity

In 2-year carcinogenicity studies in mice and rats the incidence of liver adenomas was increased only in male mice which received 30 and 90 mg/kg per day. Additional *in vitro* and *in vivo* investigative studies supported the view that the observed effects in the liver of male mice were species- and sex-specific.

Reproductive toxicity

The reproductive toxicity was studied with oral administration in rats and rabbits. Embryofoetal development was also examined in monkeys.

The reproductive parameters of male rats were not influenced by tropisetron at doses of up to 45 mg/kg per day. In female rats the maternally toxic doses of 15 mg/kg per day (about 400 times the human dose recommended for prevention and treatment of post-operative nausea and vomiting) impaired the reproduction performance. No embryotoxic effects were observed with doses up to 20 mg/kg per day in rats and 60 mg/kg per day in rabbits. At extremely high doses of 60 mg/kg per day in rats - they were also toxic for the dams - death of the embryos have been observed. Comparable results were obtained with rabbits which received 120 mg/kg per day. The foetal body weight was reduced and the peri- and post-natal mortality was increased as a consequence of prolonged pregnancy in rats treated with 60 mg/kg/day.

In cynomolgus monkeys administered tropisetron at doses up to 18 mg/kg/day, no adverse effects were observed in the females or foetuses. Foetal exposure was confirmed by measurements of tropisetron in placental tissue, foetal serum and liver.

Mutagenicity

Neither *in vitro* nor *in vivo* mutagenicity investigations yielded any evidence of a mutagenic effect of tropisetron.

6 Pharmaceutical particulars

6.1 List of excipients

Capsules: silica colloidal, anhydrous; magnesium stearate; maize starch; lactose monohydrate; iron oxide yellow; iron oxide red; titanium dioxide; gelatine; shellac.

Ampoules: acetic acid, glacial; sodium acetate trihydrate; sodium chloride; water for injection.

6.2 Incompatibilities

Solutions for injection shown to be compatible with Navoban ampoule solution are listed under 6.6. Instructions for use/handling.

6.3 Shelf life

The shelf life for both the ampoules and capsules is 5 years

The expiry date is mentioned on the package material. On the ampoules the expiry date is preceded by the characters EXP.

The diluted solutions are physically and chemically stable for at least 24 hours. From a microbiological point of view, the product should be used immediately. 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.

6.4 Special precautions for storage

The ampoules should be stored at 15 to 30° C. Special protection from light is not necessary.

Navoban should be kept out of reach and sight of children.

6.5 Nature and content of container

Navoban 5 mg capsules are made of No. 3 size hard gelatine with an opaque yellow upper part with a NVR sign imprinted in red and an opaque white lower part with EA and the dose strength of 5 mg imprinted in red.

They are available in ALU/PVC/PVDC or ALU/PVC blister packs or in glass bottles of 100 capsules.

Navoban ampoules are made of uncoloured glass, containing clear, colourless to very faintly brown-yellow solution and are coded with two blue colour rings. They are available in packs of one and packs of five.

Country specific.

6.6 Instructions for use/handling

Navoban glass ampoules contain a 2 mg/2 mL, or a 5 mg/5 mL aqueous solution. The ampoule solution is compatible with the following solutions for injection (1 mg tropisetron diluted in 20 mL): glucose 5% (w/v); mannitol 10% (w/v); Ringer's solution; sodium chloride 0.9% (w/v) and potassium chloride 0.3% (w/v); and laevulose 5% (w/v). The ampoule solution is also compatible with the usual types of containers (glass, PVC) and their infusion sets.