

## 1 PRODUCT NAME

TROPISETRON-AFT

tropisetron hydrochloride (equivalent to 2 mg or 5 mg tropisetron) per ampoule.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 1 mg of tropisetron

1 2 mL ampoule contains 2 mg of tropisetron

1 5 mL ampoule contains 5 mg of tropisetron

Each 1 mL of Tropisetron-AFT solution for injection contains 3.5 mg sodium.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for Injection or Infusion

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Dose and method of administration

#### Prevention of Nausea and Vomiting Induced by Cytotoxic Therapy

Tropisetron 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.

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

For infusion, one ampoule may 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.

Tropisetron-AFT is for single use in one patient only. Discard any residue.

### Treatment and Prevention of Post-operative Nausea and Vomiting

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

#### **4.3 Contraindications**

- Hypersensitivity to tropisetron, other 5-HT<sub>3</sub> receptor antagonists, or any other components of the formulation.
- Pregnancy and lactation (see PRECAUTIONS).

#### **4.4 Special warnings and precautions for use**

##### *General*

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

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

##### *Use in Children*

Since experience with tropisetron 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 to 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 tropisetron was given intravenously at doses of up to 40 mg, twice daily 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 tropisetron per day are given for the prevention of cancer chemotherapy-induced nausea and vomiting.

In patients who have renal impairment and 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 tropisetron above 10 mg should be avoided as they may cause a further increase in blood pressure.

#### *Carcinogenicity/Genotoxicity*

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.

### **4.5 Interaction with other medicines and other forms of interaction**

Concomitant administration of tropisetron with rifampicin or 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 e.g. cimetidine are negligible and do not require dose adjustment.

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

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

### **4.6 Fertility, pregnancy and lactation**

#### *Use in Pregnancy*

##### **Category B3**

Reproductive studies performed in rats, rabbits and monkeys at oral doses up to 60, 120 and 180 mg/kg/day, respectively, 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 of 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 therefore patients on Tropisetron-AFT should not breast- feed.

### **4.7 Effects on ability to drive and use machines**

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

### **4.8 Undesirable effects**

In general Tropisetron 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-HT<sub>3</sub> 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.

Tropisetron 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.

Tropisetron					Ondansetron
Adverse Event	Placebo (n=473)	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 Tropisetron 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 less than 1% of patients in the clinical trials: syncope, urticaria generalised.

#### *Post-marketing experience*

The following adverse reactions have been reported during post approval use of Tropisetron. 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 adverse 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.

## **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.

Contact the Poisons Information Centre on 0800 764 766 (0800 POISON) in New Zealand for advice on management.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Tropisetron is a highly potent and selective competitive antagonist of the 5-HT<sub>3</sub> 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<sub>3</sub> receptors of the peripheral neurons in this reflex, and may exert additional direct actions within the CNS on 5-HT<sub>3</sub> 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.

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

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

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

### Clinical Trials

#### *Use in Post-operative Nausea and Vomiting*

The use of tropisetron in the treatment and prevention of post-operative nausea and vomiting (PONV) is supported by the results from 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 hour postoperative period, irrespective of rescue treatment received) and two secondary endpoints (the proportion of patients without nausea or rescue treatment over a 24 hour 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 tropisetron was compared with placebo in the prevention of PONV in women undergoing abdominal and gynaecological surgery (n=385), and for the treatment of PONV in men and women with established PONV (n=314). In the study on the prevention of PONV (n=314), 68%, 74%, 70% and 56% of patients had no emetic episodes in the 0.5 mg, 2 mg, 5 mg and placebo groups respectively. 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. tropisetron, 4 mg I.V. ondansetron and placebo were compared in the prevention of PONV (n=908). The study was prospectively stratified for sex and type of surgery (abdominal versus non-abdominal surgery). Tropisetron 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.

## 5.2 Pharmacokinetic properties

### Absorption

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.

### Metabolism

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 with excretion in the urine or bile (urine to faeces ratio 5:1). The metabolites have a greatly reduced potency for the 5-HT<sub>3</sub> 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.

## 5.3 Preclinical safety data

No information.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

acetic acid  
sodium acetate trihydrate  
sodium chloride  
water for injections

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf life

24 months stored at or below 30°C

#### **6.4 Special precautions for storage**

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.

#### **6.5 Nature and contents of container <and special equipment for use, administration or implantation>**

For infusion, one ampoule may 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.

#### **6.6 Special precautions for disposal <and other handling>**

Tropisetron-AFT is for single use in one patient only. Discard any residue.

### **7 MEDICINE SCHEDULE**

Prescription Medicine

### **8 SPONSOR**

AFT Pharmaceuticals Ltd  
129 Hurstmere Road  
Takapuna 0622  
AUCKLAND

### **9 DATE OF FIRST APPROVAL**

11/04/2013

### **10 DATE OF REVISION OF THE TEXT**

May 2017

### **SUMMARY TABLE OF CHANGES**

<b>Version</b>	<b>Date</b>	<b>Change</b>	<b>Approval Date</b>
1.0	05/2017	Reformat	06/2017