Kytril®
Granisetron

ATNAHS

Composition
Active ingredient: granisetron.

Ampoules
Clear glass ampoules, each containing 1 mg granisetron present as the hydrochloride in 1 ml isotonic saline as a clear, colourless liquid.
Clear glass ampoules, each containing 3 mg granisetron present as the hydrochloride in 3 ml isotonic saline as a clear, colourless liquid.

Excipients: ampoules also contain sodium chloride, citric acid monohydrate and water for injections Ph. Eur.

Tablets
White triangular film-coated tablets, each containing 1 mg granisetron present as the hydrochloride.

Excipients: tablets also contain lactose monohydrate, hypromellose, sodium starch glycolate, cellulose, magnesium stearate, titanium dioxide E171, macrogol 400 and polysorbate 80.

Properties and effects
Granisetron is a potent and highly selective 5-hydroxytryptamine (5-HT3) receptor antagonist with anti-emetic activity.

Pharmacokinetics
Absorption
Absorption of Kytril is generally not influenced by food and is rapid and complete, though oral bioavailability is reduced to around 60% as a result of first pass metabolism.

Distribution
Kytril is widely distributed with a mean volume of distribution of approximately 3 liters/kg; plasma protein binding is approximately 65%.

Metabolism
Biotransformation pathways involve N-demethylation and aromatic ring oxidation followed by conjugation.

Elimination
Clearance is predominantly by hepatic metabolism. Urinary excretion of unchanged Kytril averages 12% of dose whilst that of metabolites amounts to about 47% of dose. The remainder is excreted in feces as metabolites. Mean plasma half-life in patients is approximately nine hours, with a wide inter-subject variability.

Indications and usage
Tablets
Kytril is indicated for the prevention of nausea and vomiting induced by cytostatic therapy.

Ampoules
Kytril is indicated for the prevention or treatment of nausea and vomiting induced by cytostatic therapy and for the prevention and treatment of post-operative nausea and vomiting.

Dosage and administration
Cytostatic therapy

Intravenous
Kytril ampoules are for intravenous administration only.

Adults
3mg Kytril which should be administered either in 15ml infusion fluid as an intravenous bolus over not less than 30 seconds or diluted in 20 to 50 ml infusion fluid and administered over five minutes.

Prevention: in clinical trials, the majority of patients have required only a single dose of Kytril to control nausea and vomiting over 24 hours. Up to two additional doses of 3mg Kytril may be administered within a 24-hour period. There is clinical experience in patients receiving daily administration for up to five consecutive days in one course of therapy. Prophylactic administration of Kytril should be completed prior to the start of cytostatic therapy.

Treatment: the same dose of Kytril should be used for treatment as prevention. Additional doses should be administered at least 10 minutes apart.

Maximum daily dosage: up to three doses of 3mg Kytril may be administered within a 24-hour period. The maximum dose of Kytril to be administered over 24 hours should not exceed 9mg.

Concomitant use of dexamethasone
The efficacy of Kytril may be enhanced by the addition of dexamethasone.

Elderly
No special requirements apply to elderly patients.

Children
Prevention: a single dose of 40micrograms/kg body weight (up to 3mg) should be administered as an intravenous infusion, diluted in 10 to 30 ml infusion fluid and administered over five minutes. Administration should be completed prior to the start of cytostatic therapy.

Treatment: the same dose of Kytril as above should be used for treatment as prevention.

One additional dose of 40micrograms/kg body weight (up to 3mg) may be administered within a 24-hour period. This additional dose should be administered at least 10 minutes apart from the initial infusion.

Patients with renal or hepatic impairment
No special requirements apply to those patients with renal or hepatic impairment.

Administration
Adults
To prepare a dose of 3mg, 3ml is withdrawn from the ampoule and diluted either to 15ml with 0.9% w/v Sodium Chloride Injection BP [British Pharmacopeia] (for bolus administration) or in infusion fluid to a total volume of 20 to 50 ml in any of the following solutions: 0.9% w/v Sodium Chloride Injection BP; 0.18% w/v Sodium Chloride and 4% w/v Glucose Injection BP; 5% w/v Glucose Injection BP; Hartmann's Solution for Injection BP; Sodium Lactate Injection BP; or 10% Mannitol Injection BP (for infusion). No other diluents should be used.

Children
To prepare the dose of 40micrograms/kg the appropriate volume (up to 1ml from the 1mg ampoule or up to 3ml from the 3mg ampoule) is withdrawn and diluted with infusion fluid (as for adults) to a total volume of 10 to 30ml.

Oral
The tablet is only indicated for use in the prevention of nausea and vomiting induced by cytostatic therapy.

Adults (Tablets)
Prevention: 1mg twice a day or 2mg once a day during cytostatic therapy.

The first dose should be administered within one hour before the start of cytostatic therapy.

Kytril is also available as ampoules for intravenous administration. The maximum dose of Kytril administered over 24 hours should not exceed 9mg.

Treatment: There is insufficient information to recommend the oral administration of Kytril in the treatment of nausea and vomiting induced by cytostatic therapy.

Concomitant use of dexamethasone
The efficacy of Kytril may be enhanced by the addition of dexamethasone.

Elderly
No special requirements apply to elderly patients.

Children
There is insufficient information to recommend the oral administration of Kytril in the prevention and treatment of nausea and vomiting induced by cytostatic patients.

Patients with renal or hepatic impairment
No special requirements apply to those patients with renal or hepatic impairment.

Post-operative nausea and vomiting

Intravenous

Adults

Prevention: for prevention in adults, a single dose of 1mg of Kytril should be diluted to 5ml and administered as a slow intravenous injection (over 30 seconds). Administration should be completed prior to induction of anesthesia.

Treatment: for the treatment of established post-operative nausea and vomiting in adults, a single dose of 1mg of Kytril should be diluted to 5ml and administered by slow intravenous injection (over 30 seconds).

Maximum dose and duration of treatment: two doses (2mg) in one day.

Administration

Adults

To prepare a dose of 1mg, 1ml should be withdrawn from the ampoule and diluted to 5ml with 0.9% w/v Sodium Chloride Injection BP. No other diluents should be used.

Children

There is no experience in the use of Kytril in the prevention and treatment of post-operative nausea and vomiting in children. Kytril is not therefore recommended for the treatment of post-operative nausea and vomiting in this age group.

Elderly patients

As for adults.

Renally impaired and hepatically impaired patients

As for adults.

Contraindications

Kytril is contraindicated in patients with known hypersensitivity to granisetron or to any of its excipients.

Precautions

As Kytril may reduce lower bowel motility, patients with signs of sub-acute intestinal obstruction should be monitored following administration of Kytril.

As with other 5-HT3 antagonists, cases of ECG modifications including QT prolongation have been reported with Kytril. These ECG changes with Kytril were minor and generally not of clinical significance, specifically with no evidence of proarrhythmia. However, in patients with pre-existing arrhythmias or cardiac conduction disorders, this might lead to clinical consequences. Therefore, caution should be exercised in patients with cardiac comorbidities, on cardio-toxic chemotherapy and/or with concomitant electrolyte abnormalities.

Cross-sensitivity between 5-HT_3 antagonists has been reported.

Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take this medicine.

As with other 5-HT_3 antagonists, cases of serotonin syndrome (including altered mental status, autonomic dysfunction and neuromuscular abnormalities) have been reported following the concomitant use of Kytril and other serotonergic drugs. If concomitant treatment with granisetron and other serotonergic drugs is clinically warranted, appropriate observation of this patient is advised.

There has been no evidence from human studies that Kytril has any adverse effect on alertness.

As a general precaution, Kytril should not be mixed in solution with other drugs. Prophylactic administration of Kytril should be completed prior to the start of cytostatic therapy or induction of anesthesia.

Data from two-year carcinogenicity studies have shown an increase in hepatocellular carcinoma and/or adenoma in rats and mice of both sexes given 50mg/kg (rat dosage reduced to 25mg/kg/day at week 59). Increases in hepatocellular neoplasia were also detected at 5mg/kg in male rats. In both species, drug-induced effects (hepatocellular neoplasia) were not observed in the low-dose group (1mg/kg). In several *in vitro* and *in vivo* assays, Kytril was shown to be non-genotoxic in mammalian cells.

Interactions

In studies in healthy subjects, no evidence of any interaction has been indicated between Kytril and cimetidine or lorazepam. No evidence of drug interactions has been observed in clinical studies conducted.

No specific interaction studies have been conducted in anesthetized patients, but Kytril has been safely administered with commonly used anesthetic and analgesic agents. In addition, *in vitro* human microsomal studies have shown that the cytochrome P_{450} subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by Kytril.

As for other 5-HT3 antagonists, cases of ECG modifications including QT prolongation have been reported with Kytril. These ECG changes with Kytril were minor and generally not of clinical significance, specifically with no evidence of proarrhythmia. However, in patients concurrently treated with drugs known to prolong QT interval and/or are arrhythmogenic, this may lead to clinical consequences.

As with other 5-HT_3 antagonists, cases of serotonin syndrome have been reported following the concomitant use of Kytril and other serotonergic drugs. If concomitant treatment with granisetron and other serotonergic drugs is clinically warranted, appropriate observation of this patient is advised.

Pregnancy, nursing mothers

Whilst animal studies have shown no teratogenic effects, there is no experience of Kytril in human pregnancy. Therefore, Kytril should not be administered to women who are pregnant unless there are compelling clinical reasons. There are no data on the excretion of Kytril in breast milk. Breast-feeding should therefore be discontinued during therapy.

Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions for Kytril are headache and constipation which may be transient. ECG changes include QT prolongation have been reported with Kytril.

The following table of listed adverse reactions is derived from clinical trials and post-marketing data associated with Kytril.

Frequecy categories are as follows:
Very common: ≥ 1/10;
Common: ≥ 1/100 to < 1/10;
Uncommon: ≥ 1/1,000 to < 1/100;
Rare: ≥ 1/10,000 to < 1/1,000;
Very rare: < 1/10,000

Table 1 Tabulated List of Adverse Reactions

Immune system disorders	
Uncommon	Hypersensitive reactions e.g. anaphylaxis, urticaria
Nervous system disorders	
Very common	Headache
Uncommon	Serotonin Syndrome
Cardiac disorders	
Uncommon	QT prolongation
Gastrointestinal disorders	
Very common	Constipation
Hepatobiliary disorders	
Common	Elevated hepatic transaminases*
Skin and subcutaneous tissue disorders	
Uncommon	Rash

*Occurred at a similar frequency in patients receiving comparator therapy

Kytril has been generally well-tolerated in human studies. As reported with other drugs of this class, headache and constipation have been the most frequently noted adverse events, but the majority have been mild or moderate in nature. Cases of hypersensitivity reaction, occasionally severe (e.g. anaphylaxis) have been reported. Other allergic reactions including minor skin rashes have also been reported. In clinical trials transient increases in hepatic transaminases, generally within the normal range, have been seen.

As for other 5-HT3 antagonists, cases of ECG modifications including QT prolongation have been reported with Kytril. These ECG changes with Kytril were minor and generally not of clinical significance, specifically with no evidence of proarrhythmia. (See Precautions and Interactions)

As with other 5-HT_3 antagonists, cases of serotonin syndrome (including altered mental status, automonic dysfunction and neuromuscular abnormalities) have been reported following the concomitant use of Kytril and other serotonergic drugs.

Overdosage
There is no specific antidote for Kytril. In the case of overdosage, symptomatic treatment should be given. One patient has received 30mg of Kytril intravenously. The patient reported a slight headache but no other sequelae were observed.

Stability
Special Precautions for Handling
Ideally, intravenous infusions of Kytril should be prepared at the time of administration. After dilution (see Dosage and administration), or when the container is opened for the first time, the shelf-life is 24 hours when stored at ambient temperature in normal indoor illumination protected from direct sunlight. It must not be used after 24 hours. If to be stored after preparation, Kytril infusions must be prepared under appropriate aseptic conditions.

See also outer pack for storage remark.

Storage condition for tablet
Do not store above 30°C.

Packs

Ampoules, 1mg, 3mg	5, 5
Tablets, 1mg	10

Medicine: Keep out of reach of children

Current at March 2022

ATNAHS

Ampoules:
Made for Atnahs Pharma UK Limited
Sovereign House,
Miles Gray Road, Basildon, Essex
SS14 3FR, United Kingdom
By CENEXI SAS,
Fontenay-sous-Bois, France

Film-coated tablets:
Made for Atnahs Pharma UK Limited
Sovereign House,
Miles Gray Road, Basildon, Essex
SS14 3FR, United Kingdom
By Delpharm Milano s.r.l. ,
Via Carnevale,1-20054,
Segrate (MI), Italy