New code	00000000	735-3253 EFA	Size:	148 x 594 mm		PAGE 1 of 2	Technical approval
Date:	14.12.16	Version 6	B/code:		Information:	Kytril 1 mg tablets	Date:.....
Update:	09.06.17	12.01.17	26.01.18	29.01.18	07.02.18		Signed:.....
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Previous ref:	10164074 EFA						

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Kytril®

ATNAHS

Granisetron

Composition

Active substance: granisetron as granisetron hydrochloride

Excipients:
Film-coated tablets: lactose monohydrate, hypromellose, sodium starch glycolate, cellulose microcrystalline, magnesium stearate, titanium dioxide, macrogol 400, polysorbate 80
Concentrate for solution for infusion: sodium chloride, citric acid monohydrate, hydrochloric acid, sodium hydroxide, water for injection q.s. 1 ml/3 ml

Pharmaceutical form and quantity of active substance per unit

Film-coated tablets containing 1 mg or 2 mg granisetron.
Concentrate for solution for infusion containing 1 mg granisetron in 1 ml or 3 mg granisetron in 3 ml.

Indications and potential uses

Cytostatic chemotherapy
In adults for the prevention (oral, intravenous) and treatment (intravenous) of nausea and vomiting induced by cytostatic chemotherapy.
In children aged 2 years and above for the prevention (intravenous) and treatment (intravenous) of nausea and vomiting induced by cytostatic chemotherapy.

Radiotherapy
In adults for the prevention (oral, intravenous) and treatment (intravenous) of nausea and vomiting induced by radiotherapy.

Postoperative nausea and vomiting
In adults for the treatment (intravenous) of postoperative nausea and vomiting.

Dosage and administration

Standard dosage in adults

Cytostatic chemotherapy (prevention)
Oral:
One 1 mg Kytril film-coated tablet twice daily or one 2 mg tablet once daily during and for up to a week after cytostatic therapy. The first dose of Kytril should be taken within one hour before the start of cytostatic therapy.

Intravenous:
Patients weighing over 50 kg: One ampoule (granisetron 3 mg/3 ml) is diluted in 20–50 ml infusion solution and administered over 5 minutes before cytostatic therapy. This 3 mg dose ampoule can also be given as a bolus injection over 30 seconds.
Patients weighing under 50 kg: 20–40 µg/kg body weight; the appropriate volume of Kytril solution should preferably be diluted in 20–50 ml infusion solution and administered over 5 minutes before cytostatic therapy. Alternatively, the appropriate volume of Kytril solution can also be given as a bolus injection over 30 seconds. Ampoules containing 3 mg/3ml and 1 mg/1 ml are available for this purpose.
The infusion should be completed before cytostatic therapy is started.
In clinical trials the majority of patients have required only a single dose to control nausea and vomiting over 24 hours.

Cytostatic chemotherapy (treatment)
Intravenous:
Breakthrough nausea and vomiting may occur in a small number of patients. If necessary, up to two additional 5-minute infusions of no more than 3 mg, given at least 10 minutes apart, may be administered within 24 hours. The maximum dose is 9 mg/24 hours.

Radiotherapy (prevention)
Oral:
One 2 mg film-coated tablet once daily. The first dose should be administered within one hour before the start of radiotherapy.

Intravenous:
The same dosage recommendations apply as for the indication Cytostatic chemotherapy (prevention).

Radiotherapy (treatment)
Intravenous:
Breakthrough nausea and vomiting may occur in a small number of patients. If necessary, up to two additional 5-minute infusions of no more than 3 mg, given at least 10 minutes apart, may be administered within 24 hours. The maximum dose is 9 mg/24 hours.

Postoperative nausea and vomiting (treatment)
Intravenous:
For the treatment of postoperative nausea and vomiting, a single dose of 1 mg of Kytril should be administered by slow intravenous injection (over 30 seconds). Experience exists with intravenous Kytril doses of up to 3 mg in patients undergoing elective surgery under anesthesia.

Special dosage instructions

Children
Cytostatic therapy (prevention)
Intravenous: A single dose of 20 µg/kg body weight, diluted in 10–30 ml infusion solution, should be administered by intravenous infusion 5 minutes before cytostatic therapy.

Cytostatic therapy (treatment)
Intravenous:
Up to two additional 5-minute infusions of 20 µg/kg body weight, given at least 10 minutes apart, may be administered.
The maximum dose is 3 times 20 µg/kg per 24-hour period.

Postoperative nausea and vomiting
No experience is available on the use of i.v. or oral Kytril to prevent or treat postoperative nausea and vomiting in children.

Geriatrics, liver failure, renal failure:
No dosage adjustment required (see "Dosage and administration, Standard dosage in adults").

Contraindications

Known hypersensitivity to granisetron or any of the constituent excipients.
There is evidence of a possible hypersensitivity reaction in patients who have shown a hypersensitivity reaction to other selective 5-HT_3 receptor antagonists.

Warnings and precautions

As Kytril may reduce lower bowel motility, patients with signs of subacute intestinal obstruction should be monitored closely following treatment with Kytril.
No special precautions are required in elderly patients or in patients with renal or hepatic impairment.
In healthy subjects no clinically relevant effects on resting EEG or performance in psychometric tests were observed after intravenous administration at any dose tested (up to 200 µg/kg).
Cases of ECG changes, including QT prolongation, have occurred on treatment with Kytril. These ECG abnormalities on Kytril use were mild and generally of no clinical relevance, there being in particular no evidence of proarrythmia. However, patients with pre-existing arrhythmias or cardiac conduction disorders could develop clinical complications. Caution is therefore required in patients with cardiac comorbidities, patients receiving cardiotoxic chemotherapy and/or those with concomitant electrolyte abnormalities. Clinical complications could occur if drugs known to prolong the QT interval and/or to be arrhythmogenic are coadministered to patients treated with Kytril.
Cross-reactivity between 5-HT_3 antagonists has occurred.
Kytril film-coated tablets contain lactose and use of Kytril film-coated tablets is therefore not recommended in patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption.
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 required, appropriate monitoring of the patient is advised.

Interactions

The efficacy of Kytril may be enhanced by intravenous administration of a single dose of dexamethasone (8–20 mg) before chemotherapy. In *in vitro* studies the metabolism of Kytril was inhibited by ketoconazole. This suggests involvement of a cytochrome P450 3A isoenzyme. Other *in vitro* studies have definitively excluded involvement of the cytochrome P450 3A4 subfamily.
No specific interaction studies have been conducted in anesthetised patients, but Kytril has been safely administered with commonly used anesthetic and analgesic agents.
In vitro studies have shown that cytochrome P450 3A4, which is involved in the metabolism of the most common narcotic analgesic agents, is not influenced by Kytril.
In healthy human subjects, hepatic enzyme induction with phenobarbital increased total plasma clearance of intravenous Kytril by approximately a quarter.
Kytril has been safely used in humans receiving benzodiazepines, neuroleptics, and anti-ulcer drugs, which are commonly prescribed with antiemetics.
Similarly, no interactions with emetogenic cytostatic drugs have been observed.
As with other 5-HT_3 antagonists, cases of serotonin syndrome have occurred following the concomitant use of Kytril and other serotonergic drugs. If concomitant treatment with granisetron and other serotonergic drugs is clinically warranted, appropriate monitoring of the patient is advised (see "Warnings and precautions").

Pregnancy and lactation

Pregnancy
Animal experiments have not revealed any teratogenic effects; however, no studies are available on pregnant and breastfeeding women.
Kytril must not be used in pregnancy unless clearly needed.

Lactation
There are no data on the excretion of granisetron in breast milk. Women should therefore not breastfeed while receiving Kytril.

Effects on ability to drive and use machines

There are no data on the effects of Kytril on the ability to drive. Somnolence was occasionally reported during clinical trials, and this should be borne in mind. A relationship to treatment with Kytril has not been established.

Undesirable effects

In most cases, the adverse events seen in association with Kytril have not been severe and have been tolerated by patients, so that treatment has not had to be stopped.

The most frequently observed adverse reactions with Kytril were headache and constipation, which may be transient. ECG changes including QT prolongation have also been observed with Kytril.
The following adverse reactions, based on clinical studies and post-marketing experience, have been observed in association with Kytril:
Very common (≥1/10), common (>1/100 to <1/10), uncommon (>1/1000 to <1/100), rare (>1/10,000 to <1/1000) and very rare (<1/10,000).

Immune system
Uncommon: hypersensitivity reactions (which have sometimes been severe, e.g. anaphylaxis).

Nervous system
Very common: headache (14%).

Heart
Uncommon: QT prolongation.
Isolated serious adverse events (hypotension, cardiac arrhythmias) have been reported. Cases of ECG changes, including QT prolongation, have occurred (see "Warnings and precautions").

Gastrointestinal disorders
Very common: constipation.

Hepatobiliary system
Common: transaminase elevation (same frequency as with placebo).

Skin
Uncommon: rash, edema/facial edema.

General disorders
Uncommon: flu-like symptoms including fever and chills.

Overdosage

There is no specific antidote to Kytril.
In the event of overdosage, symptomatic treatment should be given.
Overdosage with single intravenous doses of more than 38 mg granisetron has occurred without symptoms or with only slight headache.

Properties and effects

ATC code: A04AA02

Mechanism of action/Pharmacodynamics
Kytril is a selective 5-HT_3 receptor antagonist.
Binding studies have demonstrated that Kytril has negligible affinity for other receptor types including 5-HT and dopamine D_2 binding sites.
Kytril has no effect on plasma levels of prolactin or aldosterone.

Chemotherapy-induced nausea and vomiting (CINV)
Adults: Kytril administered intravenously or orally has been shown to be effective for prevention and/or treatment of nausea and vomiting associated with cancer chemotherapy in adults.
Children aged 2 years and above: Kytril administered intravenously has been shown to be effective for prevention and treatment of acute nausea and vomiting induced by chemotherapy in children aged 2 years and above. There are insufficient data to recommend oral use of Kytril for prevention and treatment of nausea and vomiting induced by chemotherapy in pediatric patients.

Radiotherapy-induced nausea and vomiting (RINV)
Kytril has been shown to be effective for prevention and treatment of nausea and vomiting associated with total body irradiation or fractionated abdominal irradiation in adults. Efficacy in children has not been evaluated in controlled clinical trials.

Postoperative nausea and vomiting (PONV)
Kytril administered intravenously has been shown to be effective for treatment of postoperative nausea and vomiting in adults.
A prospective, multicentre, randomised, double-blind, parallel-group study evaluated a single dose of granisetron (20 or 40 µg/kg) in 157 children aged 2 to 16 years undergoing elective surgery. Total control of postoperative nausea and vomiting in the first 2 hours after surgery was observed in most patients.

Pharmacokinetics

Absorption
Absorption of granisetron after oral administration is rapid and complete, though absolute bioavailability is reduced to about 60% as a result of first-pass metabolism. Oral bioavailability is generally not influenced by food.

Distribution
Granisetron is distributed throughout the body, with a mean volume of distribution of 3 l/kg.
Plasma protein binding is approximately 65%.

Metabolism
Biotransformation occurs principally via N-demethylation and aromatic ring oxidation followed by conjugation.
In *in vitro* studies the metabolism of Kytril was inhibited by ketoconazole. This suggests involvement of a cytochrome P450 3A isoenzyme. Other *in vitro* studies have definitively excluded involvement of the cytochrome P450 3A4 subfamily.

Elimination
Clearance is predominantly by hepatic metabolism. Urinary excretion of unchanged granisetron averages 12% and that of metabolites 47% of dose. The remaining 41% is excreted in the feces as metabolites.
The plasma elimination half-life in patients after oral and intravenous administration is 9 hours, with wide interindividual variability.
The plasma concentration of granisetron is not clearly correlated with antiemetic efficacy. The therapeutic effect can still be present even when granisetron is no longer detectable in plasma.
The pharmacokinetics of orally and intravenously administered granisetron are essentially linear at oral doses up to 2.5 times and intravenous doses up to 4 times the recommended clinical dose.

Pharmacokinetics in special patient populations
In elderly patients, pharmacokinetic parameters after single intravenous doses were within the range found in younger patients.
In patients with severe renal failure, pharmacokinetic parameters after single intravenous doses were generally similar to those in normal patients.
In patients with hepatic impairment due to neoplastic changes, total plasma clearance of an intravenous dose was approximately half that of patients with normal liver function. Despite these changes, no dosage adjustment is necessary.
Kinetics in children: When granisetron is administered at a dose of 20 µg/kg body weight, its pharmacokinetics do not differ to any clinically significant extent in adults as compared to children.

PRECLINICAL DATA

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, reproductive toxicity and genotoxicity. Carcinogenicity studies revealed no special hazard for humans when used at the recommended human dose. However, when administered at higher doses and over prolonged periods, the risk of carcinogenicity cannot be ruled out.
A study in cloned human cardiac ion channels has shown that granisetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels. Granisetron has been shown to block both sodium and potassium channels, which potentially affects both depolarisation and repolarisation through prolongation of PR, QRS and QT intervals. These data contribute to an understanding of the molecular mechanisms by which certain ECG changes (particularly QT and QRS prolongation) associated with this class of agents occur. However, there is no modification of heart rate, blood pressure or the ECG trace. If changes do occur, they are generally without clinical significance.

Toxicity
No toxicity was observed in rats and dogs treated orally with Kytril once daily for 12 months at dosages of 5 mg/kg/day. In summary, Kytril was harmless to rats and dogs when administered for 12 months at dosages of 5 mg/kg/day.

Mutagenicity
In mammalian and non-mammalian in vivo and in vitro test systems, Kytril was found to be non-mutagenic and there was no evidence of unscheduled DNA synthesis; these findings indicate that Kytril is non-genotoxic.