Kytril ®

Granisetron

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Antiemetic

1.2 Type of Dosage Form

Kytril is supplied as film-coated tablets, oral solution, ampoules, vials and prefilled syringes.

1.3 Route of Administration

1.4 Sterile / Radioactive Statement

1.5 Qualitative and Quantitative Composition

Active ingredient: granisetron HCL

Film-coated tablets contain 1 mg or 2 mg of granisetron (free base equivalent).

Oral solution contains 6 mg of granisetron (free base equivalent) in 30 ml. Kytril oral solution contains sodium benzoate.

Ampoules contain 1 mg of granisetron (free base equivalent) in 1 ml or 3 mg of granisetron (free base equivalent) in 3 ml.

Single-dose vials contain 1 mg of granisetron (free base equivalent) in 1 ml.

Multi-dose vials contain 4 mg of granisetron (free base equivalent) in 4 ml.

Prefilled syringes contain 3 mg of granisetron (free base equivalent) in 1 ml.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Kytril is indicated for the prevention and treatment (control) of

a) acute and delayed nausea and vomiting associated with chemotherapy and radiotherapy

b) post-operative nausea and vomiting

2.2 Dosage and Administration

Standard Dosage

Chemotherapy Induced Nausea and Vomiting (CINV)

Adults

Oral Tablets & Oral Solution:

Prevention: 1 mg twice a day or 2 mg once a day for up to one week following chemotherapy. The first dose of Kytril should be administered within 1 hour before the start of therapy.

Intravenous:

Prevention: A dose of 1-3 mg (10-40 mcg/kg) of Kytril should be administered either as a slow intravenous injection (over 30 seconds) or as an intravenous infusion diluted in 20 to 50 ml infusion fluid and administered over 5 minutes, prior to the start of chemotherapy.

Treatment: A dose of 1-3 mg (10-40 mcg/kg) Kytril should be administered either as a slow intravenous injection (over 30 seconds) or as an intravenous infusion diluted in 20 to 50 ml infusion fluid and administered over 5 minutes. Further treatment doses of Kytril may be administered, if required, at least 10 minutes apart. The maximum dose of Kytril to be administered over 24 hours should not exceed 9 mg.

Intramuscular:

Prevention & Treatment: A dose of 3 mg of Kytril should be administered by the intramuscular route, 15 minutes prior to the start of chemotherapy. Two subsequent 3 mg doses of Kytril may be administered, if required, within a 24 hour period.

Pediatrics

Oral Solution:

20 mcg/kg (up to 1 mg) twice a day during chemotherapy. The first dose of Kytril should be administered within one hour before the start of chemotherapy.

Intravenous:

A dose of 10-40 mcg/kg body weight (up to 3 mg) should be administered as an intravenous infusion, diluted in 10 to 30 ml infusion fluid and administered over 5 minutes prior to the start of chemotherapy. One additional dose may be administered within a 24 hour period if required. This additional dose should not be administered until at least 10 minutes after the initial infusion.

Intramuscular:

Insufficient data are currently available to recommend the use of Kytril by the intramuscular route in children.

Radiotherapy Induced Nausea and Vomiting (RINV)

Adults

Oral Tablets & Oral Solution:

2 mg once a day for up to one week following radiotherapy. The first dose of Kytril should be administered within 1 hour before the start of therapy.

Intravenous:

Prevention: A dose of 1-3 mg (10-40 mcg/kg) of Kytril should be administered either as a slow intravenous injection (over 30 seconds) or as an intravenous infusion diluted in 20 to 50 ml infusion fluid and administered over 5 minutes, prior to the start of radiotherapy.

Pediatrics

There is insufficient information to recommend use of Kytril in the prevention and treatment of RINV in children.

Post-operative Nausea and Vomiting (PONV)

Adults

Intravenous

Prevention: A dose of 1 mg (10 mcg/kg) of Kytril should be administered as a slow intravenous injection (over 30 seconds) prior to induction of anesthesia.

Treatment: A dose of 1 mg (10 mcg/kg) of Kytril should be administered by slow intravenous injection (over 30 seconds). The maximum dose for patients undergoing anesthesia for surgery is a total dose of 3 mg of Kytril i.v. in one day.

Pediatrics

There is insufficient information to recommend use of Kytril in the prevention and treatment of postoperative nausea and vomiting in children.

2.2.1 Special Dosage Instructions

Geriatrics: No dosage adjustments required.

Renal impairment: No dosage adjustments required.

Hepatic impairment: No dosage adjustments required.

2.3 Contraindications

Kytril is contraindicated in patients hypersensitive to granisetron or its excipients.

2.4 Warnings and Precautions

2.4.1 General

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

As for other 5-HT_3 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 co-morbidities, on cardio-toxic chemotherapy and/or with concomitant electrolyte abnormalities.

2.4.2 Ability to Drive and Use Machines

In healthy subjects, no clinically relevant effects on resting EEG or on the performance of psychometric tests were observed after i.v. Kytril at any dose tested (up to 200 ug/kg). There are no data on the effect of Kytril on the ability to drive or use machinery.

2.4.3 Interactions with other Medicinal Products and other Forms of Interaction

Kytril did not induce or inhibit the cytochrome P_{450} drug metabolizing enzyme system in rodent studies or inhibit the activity of any well characterized P_{450} sub-families studied in *in vitro* investigations.

In humans, hepatic enzyme induction with phenobarbital resulted in an increase in total plasma clearance of intravenous Kytril of approximately one-quarter. In *in vitro* human microsomal studies, ketoconazole inhibited ring oxidation of Kytril. However, given the absence of pK/pD relationship with granisetron, these changes are believed to have no clinical consequences.

Kytril has been safely administered in humans with benzodiazepines, neuroleptics and anti-ulcer medications, commonly prescribed with antiemetic treatments. Additionally, Kytril has shown no apparent drug interaction with emetogenic cancer chemotherapies.

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, the activity of 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-HT_3 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.

2.5 Use in Special Populations

2.5.1 Pregnancy

There are no studies in pregnant women and it is not known whether granisetron is excreted in human milk. Use of Kytril during pregnancy or lactation should be limited to situations where the potential benefit to the mother justifies the potential risk to the fetus or nursing infant.

2.5.2 Pediatric Use

Kytril multi-dose vials contain benzyl alcohol. Benzyl alcohol should not be used in infants less than 3 months of age.

2.6 Undesirable Effects

2.6.1 Clinical Trials

Kytril has been well tolerated in human studies. In common with other drugs of this class, headache and constipation have been reported. Rare cases of hypersensitivity reactions, including rashes and anaphylaxis have been reported. Elevations in hepatic transaminases have been observed and at similar frequency in patients receiving comparator therapy.

As for other 5-HT_3 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 2.4.1 Warnings and Precautions, General and 2.4.3 Interactions with other Medicinal Products and other Forms of Interaction)

2.6.2 Post Marketing

The post-marketing safety experience in over 4 million patients is consistent with the clinical trial safety information.

For ECG modifications, see 2.6.1 Undesirable Effects, Clinical Trials.

2.7 Overdose

There is no specific antidote for Kytril. In the case of overdosage with Kytril, symptomatic treatment should be given. Overdosage of up to 38.5 mg of granisetron hydrochloride as a single injection has been reported without symptoms or only the occurrence of a slight headache.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

Serotonin receptors of the 5-HT_3 type are located peripherally in vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. During chemotherapy-induced vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT_3 receptors. This invokes vagal afferent discharge, inducing vomiting.

Kytril is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine (5-HT_3) receptors. Radioligand binding studies have demonstrated that Kytril has negligible affinity for other receptor types including 5-HT and dopamine D_2 binding sites.

3.1.2 Clinical / Efficacy Studies

Chemotherapy-induced nausea and vomiting

Kytril administered intravenously or orally has been shown to prevent nausea and vomiting associated with cancer chemotherapy in adults and children 2 to 16 years of age.

Radiation-induced nausea and vomiting

Kytril administered orally has been shown to be effective in preventing nausea and vomiting associated with total body or fractionated abdominal irradiation in adults. Efficacy in children has not been established in controlled clinical trials.

Postoperative nausea and vomiting

Kytril administered intravenously has been shown to be effective for prevention and treatment of post-operative nausea and vomiting in adults. Efficacy in children has not been established in controlled clinical trials.

3.2 Pharmacokinetic Properties

3.2.1 Absorption

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

3.2.2 Distribution

Kytril is extensively distributed, with a mean volume of distribution of approximately 3l/kg. Plasma protein binding is approximately 65%.

3.2.3 Metabolism

Biotransformation pathways involve N-demethylation and aromatic ring oxidation followed by conjugation. In-vitro liver microsomal studies show that granisetron's major route of metabolism is inhibited by ketoconazole, suggestive of metabolism mediated by the cytochrome P-450 3A subfamily.

3.2.4 Elimination

Clearance is predominantly by hepatic metabolism. Urinary excretion of unchanged Kytril averages 12% of dose while that of metabolites amounts to about 47% of dose. The remainder is excreted in feces as metabolites. Mean plasma half-life in patients by the oral and intravenous route is approximately 9 hours, with a wide inter-subject variability.

The pharmacokinetics of oral and intravenous Kytril demonstrate no marked deviations from linear pharmacokinetics at oral doses up to 2.5-fold and intravenous doses up to 4-fold the recommended clinical dose.

The results of a study in healthy male volunteers have demonstrated that systemic delivery of 3 mg granisetron from an intramuscular injection is slower than from a 5 minute intravenous infusion (as indicated by lower C_{max} and later T_{max}). In other respects, the pharmacokinetics of granisetron are virtually indistinguishable when administered by these two different routes.

3.2.5 Pharmacokinetics in Special Populations

Renal failure: In patients with severe renal failure, data indicate that pharmacokinetic parameters after a single intravenous dose are generally similar to those in normal subjects.

Hepatic impairment: In patients with hepatic impairment due to neoplastic liver involvement, total plasma clearance of an intravenous dose was approximately halved compared to patients without hepatic involvement. Despite these changes, no dosage adjustment is necessary.

Elderly: In elderly subjects after single intravenous doses, pharmacokinetic parameters were within the range found for non-elderly subjects.

Pediatrics: In children, after single intravenous doses, pharmacokinetics are similar to those in adults when appropriate parameters (volume of distribution, total plasma clearance) are normalized for body weight.

3.3 Preclinical Safety

Kytril was not mutagenic in mammalian or non-mammalian *in vivo* or *in vitro* test systems and there was no evidence of unscheduled DNA synthesis indicating that Kytril is not genotoxic.

Rats and dogs treated orally with Kytril, once daily for 12 months, were free of toxicity when given dosages that are at least 125 times the intravenous/oral clinical dose.

In rats and mice treated orally for their lifetime (2 years), no adverse findings were observed at dosages 25 times the clinical dose. At higher doses, Kytril induced cell proliferation in the rat liver and hepatocellular tumors in rats and mice. Because of these findings, Kytril should be prescribed only at the doses and for the indications recommended.

3.3.1 Impairment of Fertility

In the rat, Kytril had no untoward effect on reproductive performance, fertility or on pre- and post-natal development.

3.3.2 Teratogenicity

Teratogenic effects were not observed in rats or rabbits.

4. PHARMACEUTICAL PARTICULARS

This medicinal product should not be used after the expiry date (EXP) shown on the outer pack.

4.1 Storage

Ampoules, vials, prefilled syringes: Protect from light. Do not freeze.

Multidose vials: Once penetrated the contents should be used within 30 days.

Admixtures of granisetron hydrochloride and dexamethasone sodium phosphate are compatible at concentrations of 10 to 60 ug/ml granisetron and 80 to 480 ug/ml dexamethasone phosphate in either 0.9% sodium chloride or 5% glucose intravenous infusion fluids. The admixture will have a shelf-life of 24 hours.

Kytril has been shown to be stable for at least 24 hours when stored at ambient temperature in any of the following solutions: 0.9% sodium chloride B.P., 0.18% sodium

chloride and 4% dextrose B.P., 5% dextrose, Hartmann's solution, sodium lactate and mannitol.

4.2 Special Instructions for Use, Handling and Disposal

Multidose vials: Once penetrated the contents should be used within 30 days.

Preparation of Infusion

For adults: The appropriate dose is diluted with infusion fluid, to a total volume of 20 to 50ml in any of the following solutions: 0.9% sodium chloride B.P., 0.18% sodium chloride and 4% dextrose B.P., 5% dextrose, Hartmann's solution, sodium lactate and mannitol.

For children: The appropriate dose is diluted with infusion fluid (as for adults) to a total volume of 10 to 30ml.

4.3 Packs

Ampoules, 1mg/1ml, 3mg/3ml	5, 5
Tablets, 1mg	2, 10

Medicine: keep out of reach of children

Current at January 2009

Ampoules
Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland by CENEXI SAS, Fontenay-sous-Bois, France

Film-coated tablets
Made in Switzerland by F. Hoffmann-La Roche Ltd, Basel