KYTRIL®

Granisetron

Antiemetic
COMPOSITION
Kytril is supplied as ampoules.

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

PROPERTIES AND EFFECT
Mechanism of Action
Serotonin receptors of the 5-HT3 type are located periphrally in vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. During chemotherapy-induced vomiting, mucosal entereochromaffin cells release serotonin, which stimulates 5-HT3 receptors. This invokes vagal afferent discharge, inducing vomiting.

KYTRIL is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine (5HT3 receptors). Radioligand binding studies have demonstrated that KYTRIL has negligible affinity for other receptor types including 5-HT and dopamine D2 binding sites.

Efficacy / Clinical 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 affective 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.

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

Distribution
KYTRIL is extensively distributed, with a mean volume of ditribution of approximately 3L/kg. Plasma protein binding is approximately 65%.

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.
Animal studies suggest that some of the metabolites may also have 5-HT3 receptor antagonist activity.

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 result of a study in a 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 Cmax and later Tmax). In other respect, the pharmacokinetics of granisetron are virtually indistinguishable when administered by these two different routes.

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

Hepatic impairmant: 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.

Preclinical Safety
KYTRIL was not mutagenik 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 dog 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 dosage 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.

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.

THERAPEUTIC INDICATION

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

DOSAGE AND METHOD OF ADMINISTRATION

Standard Dosage

Chemotherapy Induced Nausea and Vomiting (CINV)

Adults

Intravenous:

Prevention: A dose of 1-3 mg (10-40mcg/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 be start of chemotherapy.
Treatment: a dose of 1-3 mg (10-40mcg/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 t the start of chemotherapy. Two subsequent 3 mg doses of KYTRIL may be administered, within a 24 hour period.

Pediatrics

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

Intravenous:

Prevention: a dose of 1-3 mg (10-40mcg/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 be start of radiotherapy.

Pediatrics

There is insufficient information to recommended 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 (10mcg/kg) of KYTRIL should be adminitered as a slow intravenous injection (over 30 seconds) prior to induction of anesthesia.
Treatment: A dose of 1 mg (10mcg/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.

Maximum Dose and Duration Treatment
Two doses (2mg) in one day.

Special Dosage Instruction
Geriatrics: No dosage adjustments required.
Renal impairment: No dosage adjustments required.
Hepatic impairment: No dosage adjustments required.

CONTRAINDICATIONS
KYTRIL is contraindicated in patient hypersensitive to granisetron or its excipients.

SPECIAL WARNING & SPECIAL PRECAUTIONS FOR USE
As KYTRIL may reduce lower bowel motility, patients with signs of sub-acute intestinal obstruction should monitor closely following administration of KYTRIL.
KYTRIL multi-dose vials contain benzyl alcohol. Benzyl alcohol should not be used in infants less than 3 months of age.

Pregnancy and Lactation
In the rat, KYTRIL had no untoward effect on reproductive performance, fertility or on pre- and post-natal development. Teratogenic effects were not observed in rats or rabbits. 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.

Effects on 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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
KYTRIL did not induce or inhibit the cytochrome P450 drug metabolizing enzyme system in rodent studies or inhibit the activity of any well characterzed P450 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 pf 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 P450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by KYTRIL.

UNDESIRABLE EFFECTS

Experience from Clinical Trials

KYTRIL has been well tolerated in human studies. In common with other drugs of this class, headache and constipation have been reported. Race 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.

Post-Marketing Experience

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

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.

Incompatibilities

Admixtures of granisetron hydrochloride and dexamethasone sodium phosphate are compatible at concentrations of 10 to 60 mcg/mL granisetron and 80 to 480 mcg/mL dexamethasone phosphate in either 0.9% sodium chloride or 5% glucose intravenous infusion fluids.

Stability

Multidosevials: oncepenetrated the contents should be used within 30 days.

Storage condition: Do not store above 300C, keep the container in the outer carton.
This medicinal product should not be use after the expiry date (EXP) shown on the outer pack.

Special Remarks

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.
Special Precautions for Storage Ampoules, vials, prefilled syringes: Protect from light. Do not freeze.
Multidose vials: Once penetrated the contents should be uses within 30 days.

Instructions for Use, Handling and Disposal

Preparation of Infusion

For adults: The appropriate dose is diluted with infusion fluid, to a total volume of 20 to 50 ml 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 30 ml.

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.

PACKS

- Kytril 1mg/ml

  Box, 1 blister@ 5 ampul @ 1ml Reg.No.:

- KYTRIL 3mg/3ml

  Box, 1 blister@ 5 ampul @ 1ml Reg.No.:

Medicine: keep out of reach of children

On medical prescriptions only

Harus dengan resep dokter

Manufactured by

F.Hoffmann-La Roche

Basel, Switzerland

Imported by

PT Roche Indonesia

Jakarta, Indonesia