PACKAGE INSERT

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

KYTRIL® 1 mg ORAL (Tablet)

KYTRIL® 2 mg ORAL (Tablet)

KYTRIL® 3 mg/3 mλ (Injection)

KYTRIL®1 mg/1 mλ (Injection)

COMPOSITION

1 mg and 2 mg Tablets:

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

Injection:

Ampoules contain sterile, clear solution equivalent to 1 mg of granisetron (free base equivalent) in 1 mλ or 3 mg of granisetron (free base equivalent) in 3 mλ.

PHARMACOLOGICAL CLASSIFICATION

A 5.7.2 Anti-emetics and anti-vertigo preparations.

PHARMACOLOGICAL ACTION

Pharmacodynamics

Granisetron is an anti-emetic and selective antagonist of 5-hydroxytryptamine 5-HT_3 -

receptors. Radioligand binding studies have demonstrated that granisetron has negligible affinity for other receptor types including 5-HT and dopamine D2 binding sites.

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, which triggers a response from the vagal afferent receptors and the emetic centre is then stimulated, inducing vomiting.

Pharmacokinetics

Absorption:

Absorption in granisetron 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.

Distribution:

Granisetron is extensively distributed, with a mean volume of distribution of approximately 3 L/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.

Elimination:

Clearance is predominantly by hepatic metabolism. Urinary excretion of unchanged granisetron averages 12 % of dose while that of metabolites amounts to about 47 % of dose.

The remainder is excreted in faeces as metabolites. Mean plasma half-life (t½) in patients by the oral and intravenous route is approximately 9 hours, with a wide inter-subject variability.

The pharmacokinetics of oral and intravenous granisetron 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.

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.

Paediatrics:

In children, after single intravenous doses, pharmacokinetics are similar to those in adults when appropriate parameters (volume of distribution, total plasma clearance) are normalised

for body weight.

INDICATIONS

KYTRIL is indicated for the prevention and treatment (control) of:

a) acute and delayed nausea and vomiting associated with chemotherapy (CINV) and radiotherapy (RINV).

b) post-operative nausea and vomiting (PONV).

CONTRAINDICATIONS

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

Children under the age of 2 years.

WARNINGS AND SPECIAL PRECAUTIONS

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

The maximum dose of KYTRIL to be administered over 24 hours should not exceed 9 mg (120 µg/kg).

Effects on ability to drive and use machines

There have been reports of somnolence in clinical studies and this should be taken into account.

INTERACTIONS

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 administered in humans with benzodiazepines, neuroleptics and anti-ulcer medications commonly prescribed with anti-emetic treatments. Additionally, KYTRIL has shown no apparent interaction with emetogenic cancer chemotherapies.

No specific interaction studies have been conducted in anaesthetised patients, but KYTRIL has been safely administered with commonly used anaesthetic and analgesic agents. In addition, *in vitro* human microsomal studies have shown that the cytochrome P450 subfamily 3A4 (involved in the metabolism of some of the main narcotic analgesic agents) is not modified by KYTRIL.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established.

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 foetus or nursing infant.

DOSAGE AND DIRECTIONS FOR USE

Chemotherapy Induced Nausea and Vomiting (CINV)

Adults

Tablets:

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 µg/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 mλ infusion fluid and administered over 5 minutes, prior to the start of chemotherapy.

Treatment: A dose of 1 - 3 mg (10 - 40 µg/kg) KYTRIL should be administered either as a slow intravenous injection (over 30 seconds) or as an intravenous infusion diluted in 20 to 50 mλ 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.

Paediatrics

Intravenous: A dose of 10 - 40 µg/kg body weight (up to 3 mg) should be administered as an intravenous infusion, diluted in 10 to 30 mλ 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

Tablets: 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 µg/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 mλ infusion fluid and administered over 5 minutes, prior to the start of radiotherapy.

Paediatrics

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 µg/kg) of KYTRIL should be administered as a slow intravenous injection (over 30 seconds) prior to induction of anaesthesia.

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

Paediatrics

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

Special Dosage Instructions

***Geriatrics*:** No dosage adjustments required.

Renal impairment: No dosage adjustments required.

Hepatic Impairment: No dosage adjustments required.

Preparing the injection

Adults: To prepare the dose of KYTRIL 3 mg, the contents of one ampoule (3 mg) or 40 µg/kg is withdrawn from the ampoule and diluted with infusion fluid, to a total volume of 20 to 50 mλ in any of the following solutions: 0,9 % m/v sodium chloride, 0,18 % m/v sodium chloride and 4 % m/v dextrose, 5 % m/v dextrose, Hartmann's solution, sodium lactate and 10 % m/v mannitol.

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

Stability

Ideally, intravenous injections of KYTRIL should be prepared at the time of administration. However, the recommended solutions of KYTRIL have been shown to be stable for at least 24 hours in the following solutions when stored at room temperature: 0,9 % m/v sodium chloride, 0,18 % m/v sodium chloride and 4 % m/v dextrose, 5 % m/v dextrose, Hartmann's solution, sodium lactate and 10 % m/v mannitol.

Compatibility

As a general precaution, KYTRIL should not be mixed in solution with other medicines. Prophylactic administration of KYTRIL should be completed prior to the start of cytostatic therapy or induction of anaesthesia. No interactions with KYTRIL have been recorded with multiple chemotherapy regimes, including cisplatin up to 120 mg/m².

SIDE-EFFECTS

All side effects were reported as very rare (< 1/10 000)

Nervous system disorders: Headache

Gastrointestinal disorders: Constipation

Skin disorders: Skin rashes

General disorders: Allergic reactions and anaphylaxis

Liver and Biliary System Disorders: A rise in hepatic transaminases may occur.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Headache may occur. There is no specific antidote for KYTRIL. In the case of overdosage, symptomatic treatment should be given.

IDENTIFICATION

KYTRIL 1 mg Oral: each tablet is presented as a white to almost white, triangular, biconvex, film-coated tablet, embossed with "K1" on one face.

KYTRIL 2 mg Oral: each tablet is presented as a white to almost white, triangular, biconvex, film-coated tablet, embossed with "K2" on one face.

KYTRIL 3 mg/3 mλ: each ampoule contains a clear, colourless sterile solution.

KYTRIL 1 mg/1 mλ: each ampoule contains a clear, colourless sterile solution.

PRESENTATION

KYTRIL 1 mg Oral is supplied in blister strips, containing 10 tablets per pack.

KYTRIL 2 mg Oral is supplied in blister strips, containing 5 tablets per pack.

KYTRIL 3 mg/3 mλ is supplied in cartons containing 5 ampoules.

KYTRIL 1 mg/1 mλ is supplied in cartons containing 5 ampoules.

STORAGE INSTRUCTIONS

Store below 30 °C.

Ampoules removed from the pack should be stored protected from direct sunlight. Do not freeze.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

KYTRIL 1 mg Oral: 28/5.7.2/0162

KYTRIL 2 mg Oral: 30/5.7.2/0346

KYTRIL 3 mg/3 mλ: Y/5.7.2/0272

KYTRIL 1 mg/1 mλ: 31/5.7.2/0082

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharmaco Distribution (Pty) Ltd.

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