KYTRON TABLET 1 MG

372593

DESCRIPTION: Kytron Tablet 1 mg : White triangular shaped, biconvex, film coated tablets with debossing of "1GN"on one side and plain surface on the other side.

COMPOSITION: Kytron Tablet 1 mg : Each film-coated tablet contains 1 mg of granisetron (free base equivalent)

PHARMACODYNAMICS:
Pharmacotherapeutic group: protein-tyrosine kinase inhibitor. ATC code: A04AA02

Mechanism of action
Serotonin receptors of the 5-HT3 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-HT3 receptors. This invokes vagal afferent discharge, inducing vomiting. Kytron is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine (5-HT3) receptors. Radioligand binding studies have demonstrated that Kytron has negligible affinity for other receptor types including 5-HT and dopamine D2 binding sites.

PHARMACOKINETICS:
Absorption
Absorption of Kytron 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
Kytron 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 Kytron 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 route is approximately 9 hours, with a wide inter-subject variability.
The pharmacokinetics of oral Kytron 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.

Pharmacokinetics in Special Populations
Renal failure: No dosage adjustments required.
Hepatic impairment: No dosage adjustments required.
Elderly: No dosage adjustments required.

INDICATIONS:
Kytron tablet is indicated for the prevention and treatment (control) of acute and delayed nausea and vomiting associated with chemotherapy and radiotherapy.

RECOMMENDED DOSAGE:
Chemotherapy Induced Nausea and Vomiting (CINV)
Adults:
Prevention: 1 mg twice a day or 2 mg once a day for up to one week following chemotherapy. The first dose of Kytron tablet should be administered within 1 hour before the start of therapy.
Treatment: There is insufficient information to recommend the oral administration of Kytron in the treatment of CINV in adult patients.

Pediatrics:
There is insufficient information to recommend the oral administration of Kytron in the prevention and treatment of CINV in pediatric patients.

Radiotherapy Induced Nausea and Vomitting (RINV)
Adults:
Prevention and treatment: 2 mg once a day for up to one week following radiotherapy. The first dose of Kytron tablet should be administered within 1 hour before the start of therapy.

Pediatrics:
There is insufficient information to recommend the oral administration of Kytron tablet in the prevention and treatment of RINV in children.

Special populations
Geriatrics: No dosage adjustments required.
Renal impairment: No dosage adjustments required.
Hepatic impairment: No dosage adjustments required.

ROUTE OF ADMINISTRATION: Oral

CONTRAINDICATIONS: Kytron tablet is contraindicated in patients with known hypersensitivity to granisetron or to any of the excipients.

WARNING AND PRECAUTIONS:
As Kytron tablet may reduce lower bowel motility, patients with signs of sub-acute intestinal obstruction should be monitored following administration of Kytron tablet.

As with other 5-HT3 antagonists, cases of ECG modifications including QT prolongation have been reported with Kytron tablet. These ECG changes with Kytron tablet 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.

Cross-sensitivity between 5-HT3 antagonists has been reported.

It is recommended that Kytron tablets are not taken by patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption.
As with other 5-HT3 antagonists, cases of serotonin syndrome (including altered mental status, autonomic dysfunction and neuromuscular abnormalities) have been reported following the concomitant use of Kytron tablet and other serotonergic drugs. If concomitant treatment with granisetron and other serotonergic drugs is clinically warranted, appropriate observation of this patient is advised.

INTERACTIONS WITH OTHER MEDICAMENTS:
Granisetron tablet did not induce or inhibit the cytochrome P450 drug metabolising enzyme in rodent studies or inhibit the activity of any well characterized P450 sub-families studied in in vitro investigations.
In human, hepatic enzyme induction with phenobarbital resulted in an increase in total plasma clearance of intravenous Granisetron of approximately one-quarter. In in vitro human microsomal studies, ketoconazole inhibited ring oxidation of Granisetron. However, given the absence of pK/pD relationship with granisetron, these changes are believed to have no clinical consequences.

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

No specific interaction studies have been conducted in anaesthetised patients, but Kytron tablet has been safely administered with commonly used anesthetic and analgesic agents. In addition, the activity of the cytochrome P450 subfamily 3A4 (involved in the metabolistm of some of the main narcotic analgesic agents) is not modified by Kytron tablet.
As for other 5-HT3 antagonists, cases of ECG modifications including QT interval prolongation have been reported with Kytron. These EGC changes with KYTRON 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 for other 5-HT3 antagonists, cases of serotonin syndrome have been reported following the concomitant use of KYTRON and other serotonergic drugs. If concomitant treatment with granisetron and other serotonergic drugs is clinically warranted, appropriate observation of this patient is advised (Warning and Precautions).

USE IN PREGNANCY AND LACTATION:

There are no studies in pregnant women and it is not known whether granisetron is excreted in human milk. Use of Kytron 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 (Preclinical Safety).

SIDE EFFECTS/ADVERSE EFFECTS:

Effects on ability to drive and use machines

There are no data on the effect of Kytron tablets on the ability to drive or use machinery.

Undesirable effects

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

The following table of listed adverse reactions with granisetron hydrochloride tablets and other 5-HT3 antagonists.

Table 1 Tabulated List of Adverse Reactions

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

*Occurred at a similar frequency in patients receiving comparator therapy

In common with other drugs of this class, headache and constipation have been reported. 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-HT3 antagonists, ECG modifications including QT prolongation have been reported with Kytron tablets. These ECG changes with Kytron tablets were minor and generally not of clinical significance, specifically with no evidence of proarrhythmia. (Warnings and Precautions and Interactions with other Medicaments).

As with other 5-HT3 antagonists, cases of serotonin syndrome (including altered mental status, autonomic dysfunction and neuromuscular abnormalities) have been reported following the concomitant use of Kytron tablets and other serotonergic drugs (Warnings and Precautions and Interactions with other Medicaments).

SYMPTOMS AND TREATMENT OF OVERDOSAGE:

There is no specific antidote for Kytron tablets. In the case of overdose with Kytron tablets, symptomatic treatment should be given.

STORAGE CONDITIONS:

Store below 30°C in original package. Protect from light and moisture. Retain in carton until time of use.
Keep out of the reach of children. Jauhi daripada kanak- kanak.

SHELF LIFE: Please refer outer package

DOSAGE FORM & PACKING AVAILABLE:

Tablet: Blister pack of 1x10's tablets/ box, 2x10's tablets/ box and 3x10's tablets/ box.

PRODUCT REGISTRATION HOLDER:
DUOPHARMA (M) SDN BHD
Lot 2599, Jalan Seruling 59, Kawasan 3,
Taman Klang Jaya, 41200 Klang, Selangor, Malaysia.

Manufactured by:
Natco Pharma Limited (Pharma-Division)
Kothur - 509 228
Rangareddy District,
Telangana, India

Date of revision of text
May 2019

372593

Changes:
1. Remove company registration number (42491-M) in product registration holder address.
2. To follow product PI template from manufacturer. No others change in the package insert info.