Destron Tablet 1mg

Granisetron 1mg

COMPOSITION

Each film-coated tablet contains granisetron hydrochloride 1.12 mg equivalent to 1 mg of granisetron.

DESCRIPTION

White to off white, triangular film-coated tablet with 'G1' on one side and plain on the other.

PHARMACODYNAMICS

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 releases serotonin, which stimulates 5-HT_3 receptors. This invokes vagal afferent discharge inducing vomiting. Destron is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine (5-HT_3) receptors. Radioligand binding studies have demonstrated that Destron has negligible affinity for other receptor types including 5-HT and dopamine D_2 binding sites.

PHARMACOKINETICS

Absorption

Absorption of Destron 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

Destron is extensively distributed, with a mean volume of distribution of approximately 31/kg. Plasma protein binding is approximately 65%.

Metabolism

Biotransformation pathways include N-demethylation and aromatic ring oxidation followed by conjugation. In vitro liver microsomal studies show that granisetron 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 Destron averages 12% of dose while that of metabolites amount to about 47% of dose. The remainder is excreted in faeces as metabolites. Mean plasma half-life in patients by the oral route is apparently 9 hours with a wide inter-subject variability. The pharmacokinetics of oral Destron 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.
Pediatrics: No dosage adjustments required.

INDICATION

Destron 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 Destron tablet should be administered within 1 hour before the start of therapy.

Treatment: There is insufficient information to recommend the oral administration of Destron in the treatment of CINV in adult patients.

Paediatrics

There is insufficient information to recommend the oral administration of Destron tablet in the prevention and treatment of CINV in paediatric patients.

Radiotherapy Induced Nausea and Vomiting (RINV)

Adults

Prevention and treatment: 2mg once a day for up to one week following radiotherapy. The first dose of Destron tablet should be administered within 1 hour before the start of therapy.

Paediatrics

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

SPECIAL DOSAGE INSTRUCTIONS

Geriatrics

No dosage adjustments required

Renal Impairment

No dosage adjustments required

Hepatic Impairment

No dosage adjustments required

MODE OF ADMINISTRATION

Oral

CONTRAINDICATIONS

Destron is contraindicated in patients with known hypersensitivity to granisetron or to any of the excipients.

WARNING AND PRECAUTIONS

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

As with other 5-HT_3 antagonists, cases of ECG modifications including QT prolongation have been reported with Destron. These ECG changes with Destron 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-HT_3 antagonists has been reported. It is recommended that Destron tablets are not taken by patients with rare hereditary problems of galactose intolerance, lactose 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 Destron tablet and other serotonergic drugs. If concomitant treatment with granisetron and other serotonergic drugs is clinically warranted, appropriate observations of this patient is advised.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no data on the effect of granisetron on the ability to drive or use machineries.

INTERACTIONS WITH OTHER MEDICAMENTS

Destron tablet did not induce or inhibit the cytochrome P_{450} drug metabolising enzyme in rodent studies or inhibit the activity of any well characterized P_{450} sub-families studied in in vitro investigations. In in vitro human microsomal studies, ketoconazole inhibited ring oxidation of Destron. However, given the absence of pK/pD relationship with granisetron, these changes are believed to have no clinical consequences.

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

No specific interaction studies have been conducted in anaesthetised patients, but Destron tablet 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 Destron tablet.

As for other 5-HT_3 antagonists, cases of ECG modifications including QT interval prolongation have been reported with Destron. These ECG changes with Destron 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-HT_3 antagonists, cases of serotonin syndrome have been reported following the concomitant use of Destron and other serotonergic drugs. If concomitant treatment with granisetron and other serotonergic drugs is clinically warranted, appropriate observation of this patient is advised.

PREGNANCY AND LACTATION

Pregnancy

Use of Destron during pregnancy should be limited to situation where the potential benefits to the mother justifies the potential risk to the fetus.

Lactation

There are no studies in pregnant women and it is not known whether granisetron is excreted in human milk. Use of Destron 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.

ADVERSE EFFECTS

The most frequently reported adverse reactions for Destron tablets are headache and constipation which may be transient. ECG changes including QT

prolongation have been reported with Destron tablets.

The following table of listed adverse reactions with granisetron hydrochloride tablets and other 5-HT_3 antagonists.

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
Uncommon	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-HT_3 antagonists, ECG modifications including QT prolongation have been reported with Destron tablets. These ECG changes with Destron tablets were minor and generally not of clinical significance, specifically with no evidence of proarrhythmia.

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 Destron tablets and other serotonergic drugs.

OVERDOSE AND TREATMENT
There is no specific antidote for granisetron. In the case of over dosage with granisetron, symptomatic treatment should be given.

STORAGE CONDITION
Store below 30°C.
Protect from light.

SHELF LIFE
Product should not be used beyond the expiry date imprinted on the product packaging.

DOSAGE FORMS AND PACKAGING AVAILABLE
In boxes of 10 tablets (1 blister x 10 tablets).

PRODUCT REGISTRATION HOLDER/ MANUFACTURER:
PHARMANIAGA MANUFACTURING BERHAD (198001006232)
No. 11A, Jalan P/1, Kawasan Perusahaan Bangi, 43650 Bandar Baru Bangi, Selangor Darul Ehsan, Malaysia.

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