For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

PACKAGE INSERT

RANTAC DOM TABLET

GENERIC NAME

Ranitidine Hydrochloride and Domperidone Tablets

COMPOSITION

Each Film Coated Tablet Contains:

Ranitidine Hydrochloride IP equivalent to Ranitidine	150 mg
Domperidone IP	10mg.
Excipients	q.s

DOSAGE FORM

Film Coated Tablet

DOSAGE

Adult and Children over 12 year: 1 tablet bid or as directed by the physician

METHOD OF ADMINISTRATION

The Tablet administered orally.

INDICATIONS

For the treatment of GERD not responding adequately to Ranitidine

USE IN SPECIAL POPULATIONS

Pregnancy-
The FDC of Ranitidine & Domperidone should only be used during pregnancy when justified by the anticipated therapeutic benefit.
Lactation-
The FDC of Ranitidine & Domperidone is excreted in human breast milk. A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. Caution should be exercised in case of QTc prolongation risk factors in breast-fed infants.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients
- Prolactin-releasing pituitary tumour (prolactinoma).

- When stimulation of the gastric motility could be harmful e.g in patients with gastro-intestinal haemorrhage, mechanical obstruction or perforation.
- In patients with moderate or severe hepatic impairment.
- In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure.
- Co-administration with QT-prolonging drugs, at the exception of apomorphine.
- Co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects).

WARNING & PRECAUTIONS

- The possibility of malignancy should be excluded before commencement of therapy in patients with gastric ulcer and in patients of middle age and over with new or recently changed dyspeptic symptoms) as treatment may mask symptoms of gastric carcinoma.
- Ranitidine present in fixed dose combination of Ranitidine and Domperidone is excreted via the kidney and so plasma levels of the drug are increased in patients with renal impairment. The elimination half-life of domperidone is prolonged in severe renal impairment.
- Regular supervision of patients who are taking non-steroidal anti-inflammatory drugs concomitantly with fixed dose combination of Ranitidine and Domperidone is recommended, especially in the elderly and in those with a history of peptic ulcer.
- Fixed dose combination of Ranitidine and Domperidone should be avoided in patients with a history of acute porphyria as it may precipitate attacks of porphyria.
- In patients such as the elderly, persons with chronic lung disease, diabetes or the immune compromised, there may be an increased risk of developing community acquired pneumonia.
- QT interval on the electrocardiogram has been reported with Domperidone
- Epidemiological studies showed that domperidone present in fixed dose combination of Ranitidine and Domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death.
- FDC of Ranitidine and Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia. Treatment should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should consult their physician. Patients should be advised to promptly report any cardiac symptoms.
- Domperidone present in fixed dose combination of Ranitidine and Domperidone is contra-indicated with QT prolonging drugs including apomorphine, unless the benefit of the co-administration with apomorphine outweighs the risks,

DRUG INTERACTIONS

Ranitidine
Ranitidine has the potential to affect the absorption, metabolism or renal excretion of other drugs. The altered pharmacokinetics may necessitate dosage adjustment of the affected drug or discontinuation of treatment

Interactions occur by several mechanisms including:

1) Inhibition of cytochrome P450-linked mixed function oxygenase system: Ranitidine at usual therapeutic doses does not potentiate the actions of drugs which are inactivated by this enzyme system such as diazepam, lidocaine, phenytoin, propanolol and theophylline.
There have been reports of altered prothrombin time with coumarin anticoagulants (e.g. warfarin). Due to the narrow therapeutic index, close monitoring of increased or decreased prothrombin time is recommended during concurrent treatment with ranitidine.

2) Competition for renal tubular secretion:
Since ranitidine is partially eliminated by the cationic system, it may affect the clearance of other drugs eliminated by this route. High doses of ranitidine (e.g. such as those used in the treatment of Zollinger-Ellison syndrome) may reduce the excretion of procainamide and N-acetylprocainamide resulting in increased plasma level of these drugs.

3) Alteration of gastric pH:
The bioavailability of certain drugs may be affected. This can result in either an increase in absorption (e.g. triazolam, midazolam, glipizide) or a decrease in absorption (e.g. ketoconazole, atazanavir, delaviridine, gefitnib).
There is no evidence of an interaction between ranitidine and -amoxicillin or metronidazole. If high doses (2 g) of sucralfate are co-administered with ranitidine the absorption of the latter may be reduced. This effect is not seen if sucralfate is taken after an interval of 2 hours.

Domperidone
The main metabolic pathway of domperidone is through CYP3A4. In vitro data suggest that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone.
Increased risk of occurrence of QT-interval prolongation, due to pharmacodynamic and/or pharmacokinetic interactions.

Concomitant use of the following substances is contraindicated
QTc prolonging medicinal products

- anti-arrhythmics class IA (e.g., disopyramide, hydroquinidine, quinidine)
- anti-arrhythmics class III (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol)
- certain anti-psychotics (e.g., haloperidol, pimozide, sertindole)
- certain anti-depressants (e.g., citalopram, escitalopram)
- certain antibiotics (e.g. , erythromycin, levofloxacin, moxifloxacin, spiramycin)
- certain antifungal agents (e.g., pentamidine)
- certain antimalarial agents (in particular halofantrine, lumefantrine)
- certain antihistaminics (e.g., mequitazine, mizolastine)
- certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine)

- certain other medicines (e.g., bepridil, diphemanil, methadone)
- apomorphine, unless the benefit of the co-administration outweighs the risks, and only if the recommended precautions for co-administration are strictly fulfilled.

Potent CYP3A4 inhibitors (regardless of their QT prolonging effects), i.e.:
- protease inhibitors
- systemic azole antifungals
- some macrolides (erythromycin, clarithromycin, telithromycin)

Concomitant use of the following substances is not recommended
Moderate CYP3A4 inhibitors i.e. diltiazem, verapamil and some macrolides.
Concomitant use of the following substances requires caution in use
Caution with bradycardia and hypokalaemia-inducing drugs, as well as with the following macrolides involved in QT-interval prolongation: azithromycin and roxithromycin (clarithromycin is contraindicated as it is a potent CYP3A4 inhibitor).

UNDESIRABLE EFFECTS:

FDC of Ranitidine and Domperidone
Blood & Lymphatic System Disorders
Blood count changes (leucopenia, thrombocytopenia). These are usually reversible. Agranulocytosis or pancytopenia, sometimes with marrow hypoplasia or marrow aplasia.
Immune System Disorders
Hypersensitivity reactions (urticaria, angioneurotic oedema, fever, bronchospasm, hypotension and chest pain).
Anaphylactic reaction (including anaphylactic shock)
Dyspnoea.
Psychiatric Disorders
Reversible mental confusion, depression, loss of libido, anxiety, agitation, nervousness and hallucinations.
Nervous System Disorders
Headache (sometimes severe), somnolence, convulsion, dizziness, reversible involuntary movement disorders, extrapyramidal disorder.
Eye Disorders
Reversible blurred vision, oculogyric crisis
Cardiac Disorders
As with other H_2 receptor antagonists bradycardia, A-V block and tachycardia, ventricular arrhythmias, Sudden cardiac death, QTc prolongation, Torsade de Pointes
Vascular Disorders
Vasculitis.
Gastrointestinal Disorders
Abdominal pain, constipation, dry mouth, diarrhoea, nausea (these symptoms mostly improved during continued treatment), acute pancreatitis
Hepatobiliary Disorders
Transient and reversible changes in liver function tests.
Hepatitis (hepatocellular, hepatocanalicular or mixed) with or without jaundice, these were usually reversible.
Skin and Subcutaneous Tissue Disorders
Rash, Pruritus, Urticaria, Angioedema Erythema multiforme, alopecia.

Musculoskeletal and Connective Tissue Disorders
Musculoskeletal symptoms such as arthralgia and myalgia.
Renal and Urinary Disorders
Elevation of plasma creatinine (usually slight; normalised during continued treatment), acute interstitial nephritis, urinary retention.
Reproductive System and Breast Disorders
Reversible impotence, breast symptoms and breast conditions (such as gynaecomastia and galactorrhoea), galactorrhoea, Breast pain, Breast tenderness, amenorrhoea.
Investigations
Liver function test abnormal, Blood prolactin increased.

OVERDOSE

In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required.

PHARMACODYNAMICS

Pharmacological class: Antacid/Antiemetic

Ranitidine
Mechanism of action
Ranitidine is a specific rapidly acting histamine H -antagonist. It inhibits basal and stimulated secretion of gastric acid, reducing both the volume and the acid and pepsin content of the secretion.
Ranitidine has a relatively long duration of action and so a single 150 mg dose effectively suppresses gastric acid secretion for twelve hours.

Domperidone
Mechanism of action
Domperidone is a dopamine antagonist with anti-emetic properties, Domperidone does not readily cross the blood-brain barrier. In domperidone users, especially in adults, extrapyramidal side effects are very rare, but domperidone promotes the release of prolactin from the pituitary. Its anti-emetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema. Animal studies, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors.
Studies in man have shown oral domperidone to increase lower oesophaegeal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.
In accordance with ICH-E14 guidelines, a thorough QT study was performed. This study included a placebo, an active comparator and a positive control and was conducted in healthy subjects with up to 80 mg per day 10 or 20 mg administered 4 times a day of domperidone. This study found a maximal difference of QTc between domperidone and placebo in LS-means in the change from baseline of 3.4 msec for 20 mg domperidone administered 4 times a day on Day 4. The 2-sided 90 % CI (1.0 to 5.9 msec) did not exceed 10 msec. No clinically relevant QTc effects were observed in this study when domperidone was administered at up to 80 mg/day (i.e., more than twice the maximum recommended dosing).

However, two previous drug-drug interaction studies showed some evidence of QTc prolongation when domperidone was administered as monotherapy (10 mg 4 times a day).The largest time matched mean difference of QTcF between domperidone and placebo was 5.4 msec (95 % CI: -1.7 to 12.4) and 7.5 msec (95 % CI: 0.6 to 14.4), respectively.

PHARMACOKINETICS

Ranitidine

Absorption

Following oral administration of 150 mg ranitidine, maximum plasma concentrations (300 to 550 ng/mL) occurred after 1-3 hours. Two distinct peaks or plateau in the absorption phase result from reabsorption of drug excreted into the intestine. The absolute bioavailability of ranitidine is 50-60% and plasma concentrations increase proportionally with increasing dose up to 300 mg.

Distribution

Ranitidine is not extensively bound to plasma proteins (15%), but exhibits a large volume of distribution ranging from 96 to 142 L.

Metabolism

Ranitidine is not extensively metabolised. The fraction of the dose recovered as metabolites is similar after both oral and i.v. dosing; and includes 6% of the dose in urine as the N-oxide, 2% as the S-oxide, 2% as desmethylranitidine and 1 to 2% as the furoic acid analogue.

Elimination

Plasma concentrations decline bi-exponentially, with a terminal half-life of 2-3 hours. The major route of elimination is renal. After IV administration of 150 mg 3H-ranitidine, 98% of the dose was recovered, including 5% in faeces and 93% in urine, of which 70% was unchanged parent drug. After oral administration of 150 mg 3H-ranitidine, 96% of the dose was recovered, 26% in faeces and 70% in urine of which 35% was unchanged parent drug. Less than 3% of the dose is excreted in bile. Renal clearance is approximately 500 mL/min, which exceeds glomerular filtration indicating net renal tubular secretion.

Domperidone

Absorption

Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations occurring at approximately 1hr after dosing. The C_{max} and AUC values of domperidone increased proportionally with dose in the 10 mg to 20 mg dose range. A 2- to 3-fold accumulation of domperidone AUC was observed with repeated four times daily (every 5 hr) dosing of domperidone for 4 days.

The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut wall and liver. Although Domperidone's bioavailability is enhanced in normal subjects when taken after a meal, patients with gastro-intestinal complaints should take domperidone 15-30 minutes before a meal. Reduced gastric acidity impairs the absorption of domperidone. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate. The time of peak absorption is slightly delayed and the AUC somewhat increased when the oral drug is taken after a meal.

Distribution

Oral domperidone does not appear to accumulate or induce its own metabolism; a peak plasma level after 90 minutes of 21 ng/ml after two weeks oral administration of 30 mg per day was almost the same as that of 18 ng/ml after the first dose. Domperidone is 91-93% bound to plasma proteins. Distribution studies with radiolabelled drug in animals have shown wide tissue distribution, but low brain concentration. Small amounts of drug cross the placenta in rats.

Metabolism

Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. *In vitro* metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

Excretion

Urinary and faecal excretions amount to 31 and 66% of the oral dose respectively. The proportion of the drug excreted unchanged is small (10% of faecal excretion and approximately 1% of urinary excretion). The plasma half-life after a single oral dose is 7-9 hours in healthy subjects but is prolonged in patients with severe renal insufficiency.

INCOMPATIBILITIES

None known.

PACKAGING INFORMATION

Blister strip of 10 Tablets. Such 3 blisters packed in carton.

STORAGE AND HANDLING INSTRUCTIONS

Store protected from light and moisture, at a temperature not exceeding 30ºC.

MANUFACTURED BY

Acme Life Tech-LLP
Plot No. 103, 104, 105- EPIP,
Phase I, Jharmajri, Baddi
Dist. Solan (H.P) 173 205

MARKETED BY

J. B. Chemicals & Pharmaceuticals Ltd.
Neelam Centre, 'B' Wing, Hind Cycle Road,
Worli, Mumbai – 400 030