OD-PEP™
Fixed Dose Combination of Pantoprazole and Domperidone

DESCRIPTION

OD-PEP™ (a Fixed dose combination of Pantoprazole and Domperidone) contains Pantoprazole which is chemically sodium 5-(difluoromethoxy)-2-[[3,4-dimethoxy-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole sesquihydrate and Domperidone which is chemically 5-chloro-1-[1-[3-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)propyl]-piperidin-4-yl]-1,3-dihydro-2H-benzimidazol-2-one. OD-PEP™ capsule is Transparent/Transparent size "1" hard gelatin capsule filled with one yellow colored, round, beveled, biconvex, enteric coated tablet of Pantoprazole and one each of white/ red colored, round, beveled, biconvex, film coated tablet of immediate-release/ delayed-release tablet of Domperidone.

COMPOSITION

Each hard gelatin capsule of OD-PEP™ contains three smartlets:

Each white film coated smartlet contains:

Domperidone BP .........................10mg
Colour : Titanium Dioxide

Each yellow enteric-coated smartlet contains:

Pantoprazole Sodium Sesquihydrate equivalent to Pantoprazole ...............40mg
Colours : Ferric Oxide and Titanium Dioxide.

Each red delayed-release smartlet contains:

Domperidone BP ..........................10mg
Colours : Ferric Oxide and Titanium Dioxide

CLINICAL PHARMACOLOGY
Mechanism of Action

Pantoprazole, a benzimidazole sulfoxide derived prodrug, is an irreversible proton pump inhibitor. Pantoprazole, being a weak base, is highly ionized at low pH and readily accumulated in the highly acidic canalicular lumen of the stimulated parietal cell in the stomach. In this acidic environment, it is protonated and rapidly converted to a cationic cyclic...
sulphonamide. The sulphonamide binds covalently to cysteine residues on the luminal (acidic) surface of H⁺ / K⁺-ATPase to form a mixed disulphide; thus causing irreversible inhibition of the gastric proton pump. This inhibition of the gastric proton pump or H⁺ / K⁺ -ATPase (which represents the final step in the secretory process), suppresses gastric acid secretion.¹ ²

Domperidone, a benzimidazole derivative (structurally related to the butyrophenones), acts by selectively antagonizing the peripheral dopaminergic D₂ receptors in the gastrointestinal (G.I.) wall, thereby enhancing gastrointestinal peristalsis and motility and increasing Lower Esophageal Sphincter (LES) tone.³

RATIONALE OF COMBINATION
The mode of action of both Pantoprazole and Domperidone are different and complimentary to each other. Upper G.I. disorders are frequently associated with a combination of hyperacidity and dysmotility. As a result, acidic chyme may either stagnate in stomach and duodenum or may be evacuated by reverse peristalsis (vomiting or nausea). Reflux of acid contents of stomach cause erosions of lower part of esophagus which may further aggravate nausea and vomiting. Since both hyperacidity and dysmotility are present at the same time in disorders like Gastro Esophageal Reflux Disease (GERD) and Non Ulcer Dyspepsia (NUD), a combination of drugs which will take care of both would be ideal. Pantoprazole is a potent gastric acid inhibitor that blocks the final stage of acid secretion. Hence, whatever may be the stimulus, hyperacidity will be controlled by Pantoprazole. In contrast, Domperidone increases G.I. motility, thereby facilitating the movement of acid contents further down in the intestine preventing reflux esophagitis and thereby controlling nausea and vomiting. Hence, the pharmacology of Pantoprazole and Domperidone corroborates their use in combined form for the treatment of GERD, NUD and related disorders.

Domperidone is usually administered at a dose of 10-20 mg, 2-3 times daily before meals. In order to enhance patient compliance, OD-PEP™ has been designed for single dose administration, which contains two smartlets of Domperidone, each containing 10 mg of Domperidone. One of the smartlets (white film coated tablet) provides immediate release of Domperidone whereas the other is in delayed release form. Bioavailability studies conducted on human volunteers have shown biphasic release profile of Domperidone, which allows once daily administration. This helps in improving patient compliance without compromising on the efficacy.

PHARMACOKINETICS
Pantoprazole
Pantoprazole is rapidly absorbed after oral administration, with peak plasma concentrations (Cₘₐₓ) of 1.1 to 3.1. (mean 2.1) mg/L occurring within 2 to 4 (mean 2.7) hours (tₘₐₓ) after ingestion of an enteric coated 40 mg tablet. The volume of distribution is low (mean 0.16 L/kg at steady state) due to high degree of plasma protein binding (~98%). Plasma Pantoprazole concentrations decline monophonically after oral administration, with a mean plasma terminal half-life (t₁/₂ₚ) of 0.9 to 1.9 hours. However, since inhibition of acid secretion is non-competitive or irreversible, there is no correlation between plasma levels and the duration of action of Pantoprazole. Concomitant intake of food has no influence on the bioavailability of Pantoprazole, and any possible retardant effect of food on the rate of drug absorption is not of clinical relevance, considering the prolonged antisecretory action of Pantoprazole. The enteric coating does not influence the bioavailability of Pantoprazole.²

Pantoprazole undergoes extensive hepatic metabolism via cytochrome P450 oxidase followed by sulphate conjugation. Elimination of Pantoprazole is predominantly renal, with ~80% of an oral dose being excreted as urinary metabolite; the remainder is excreted in the faeces and originates primary from biliary secretion.

Domperidone
Domperidone is rapidly and almost completely (93%) absorbed after oral administration. Peak plasma concentrations occur within 30 min. after oral administration. The peak plasma
concentration value after a 20mg oral dose is in the range of 15 to 19 ng/ml. The mean elimination half life ranges from 12 - 16 hours for an oral dose. Oral bioavailability of Domperidone is 13 - 17% because of extensive presystemic metabolism in gut wall and liver. Administration of Domperidone 90 minutes after a meal increases bioavailability whereas Cimetidine or alkali pretreatment reduces bioavailability. Domperidone is strongly bound to plasma proteins (90-93%). Domperidone undergoes extensive biotransformation with <1% excreted unchanged in urine.\textsuperscript{3,4}

**Special populations**

**Pantoprazole**

**Hepatic impairment:** There is a slight increase (1.5 fold) in maximum drug concentrations in patients with mild to severe hepatic impairment. No dosage adjustment is needed in patients with mild to severe hepatic impairment.

**Renal impairment:** Pharmacokinetic parameters for Pantoprazole in patients with severe renal impairment are similar to those of healthy subjects. No dosage adjustment is needed in patients with renal impairment.

**Gender:** No dosage adjustment is needed based on gender.

**Pediatrics:** The pharmacokinetics of Pantoprazole have not been investigated in patients <18 years of age.

**Geriatrics:** No dosage adjustment is recommended based on age.

**Domperidone**

**Hepatic impairment:** There is no published pharmacokinetic data in patients with hepatic impairment. Because Domperidone is extensively metabolized, response to the drug should be carefully monitored in this patient population.

**Neonates:** Domperidone is not recommended for use in neonates.

**Breast milk:** Domperidone may precipitate galactorrhea and improve postnatal lactation. It is secreted in breast milk in very small quantities and thus insufficient to be considered harmful.

**Pediatrics:** Domperidone is not recommended other than for treatment of nausea and vomiting in patients undergoing cancer therapy. There may be an increased risk for extrapyramidal reactions in young children because of an incompletely developed blood brain barrier.

**Pregnant women:** The safety of Domperidone has not been proven, therefore its use is not recommended in pregnant women.

**Geriatrics:** No special precautions are necessary in older patients.

OD-PEPTM should be used with caution in conditions where the individual drugs have been used with precautionary approach.

**INDICATIONS**

OD-PEPTM is indicated in the management of gastroesophageal reflux disease; gastritis, non-ulcer dyspepsia, gastric or duodenal ulcer, dyspepsia, bloating, fullness, belching, NSAID-induced dyspepsia.

**CONTRAINDICATIONS**

OD-PEPTM is contraindicated in patients with known hypersensitivity to Pantoprazole or Domperidone.

**Pregnancy and Lactation**

Due to lack of controlled studies in pregnant and lactating women, use of OD-PEPTM is contraindicated in this group of patients.

**WARNINGS AND PRECAUTIONS**

OD-PEPTM shall be given with care to patients with renal dysfunction or hepatic dysfunction.

**DRUG INTERACTIONS**

**Pantoprazole**

Pantoprazole is metabolized through the cytochrome P450 system, primarily the CYP2C19
and CYP3A4 isoenzymes, and subsequently undergoes phase II conjugation. Based on studies evaluating possible interactions of Pantoprazole with other drugs metabolized by the cytochrome P450 system, no dosage adjustment is needed with concomitant use of the following drugs: theophylline, cisapride, antipyrine, caffeine, carbamezapine diazepam, diclofenac, digoxin, ethanol, glyburide, oral contraceptives (levonorgestrel / ethynylestradiol), metoprolol, nifedipine, phenytoin or warfarin. Clinically relevant interactions of Pantoprazole with other drugs with the same metabolic pathways are not expected. Therefore, when co-administered with Pantoprazole, adjustment of the dosage of Pantoprazole with such drugs may not be necessary. There was also no interaction with concomitantly administered antacids.

Because of profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that Pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g. Ketoconazole, Ampicillin esters, and iron salts).

**Domperidone**

Anti-cholinergic drugs may inhibit the anti-dyspeptic effects of Domperidone. Antimuscarinic agents and opioid analgesics may antagonise the effect of Domperidone. Domperidone suppresses the peripheral effects (digestive disorders, nausea and vomiting) of dopaminergic agonists. Since Domperidone has gastro-kinetic effects, it could influence the absorption of concomitant orally administered drugs, particularly those with sustained release or enteric coated formulations.

As Domperidone interferes with serum prolactin levels, it may interfere with other hypoprolactinaemic agents and with some diagnostic tests.

Antacids and anti-secretory agents lower the oral bioavailability of Domperidone. They should be taken after meals and not before meals, i.e. they should not be taken simultaneously with Domperidone. Reduced gastric acidity impairs the absorption of Domperidone.

Oral bioavailability is decreased by prior administration of Cimetidine or Sodium Carbonate.

**ADVERSE REACTIONS**

**Pantoprazole**

the adverse reactions associated with Pantoprazole include Headache, Diarrhoea, Skin rash, Pruritus and Dizziness.

**Domperidone**

Serum prolactin level may rise resulting in galactorrhea in females and less frequently gynaecomastia in males due to Domperidone. Dry mouth, Thirst, Headache, Nervousness, Drowsiness, Diarrhoea, Skin rashes and Itching may follow treatment with Domperidone.

**OVERDOSAGE AND TREATMENT**

In the event of overdosage, gastric lavage should be performed. Symptomatic and supportive measures are recommended.

**DOSAGE AND ADMINISTRATION**

The usual recommended dose of OD-PEP™ is one capsule daily before breakfast. Swallow capsule as a whole, do not chew the capsule.

**STORAGE INSTRUCTIONS**

Store at a temperature below 25°C, protect from light and moisture.

Keep the medicine out of reach of children.
*The brand name has now been changed to OD-PEP™*

REFERENCES