DRUG PROFILE
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PANTOPRAZOLE

Pantoprazole Sodium is chemically sodium 5- (difluoro methoxy)-2-[(3, 4-dimethoxy-2-pyridyl) methyl] sulphinyl] 1H- benzimidazole sesquihydrate which has been widely used in the treatment of peptic ulcer. Wide varieties of Pantoprazole tablets are available in the market. Pantoprazole sodium comes under the class of proton pump inhibitor.

Chemical Formula:

Sodium 5-(difluoromethoxy)-2-[(RS)-[(3,4-dimethoxypyridin-2-yl) methyl] sulphinyl] benzimidazol-1-ide sesquihydrate.

Structure:

![Fig. 8: Structure of Pantoprazole](image)

Solubility:

Freely soluble in water and in ethanol (96 percent), practically insoluble in hexane. Solubility is low at neutral pH and increases with increasing pH.

Dose:

Adult dose is 40 mg.

Stability:

A suspension of pantoprazole 2 mg/ml in sterile water and sodium bicarbonate was deemed to be physically and chemically stable in amber polyethylene terephthalate bottles for 62 days at 2 ° to 8 °C.

Storage: Stable at 20 – 25°C
**Pharmacology:**

**Pharmacodynamics:**

Pantoprazole is a proton pump inhibitor. It inhibits specifically and dose-proportionately H⁺/K⁺-ATPase, the enzyme which is responsible for gastric acid secretion in the parietal cells of the stomach.

The substance is a substituted benzimidazole which accumulates in the acidic environment of the parietal cells after absorption. There, it is converted into the active form, a cyclic sulphonamide which binds to the H⁺/K⁺-ATPase, thus inhibiting the proton pump and causing potent and long-lasting suppression of basal and stimulated gastric acid secretion. As pantoprazole acts distal to the receptor level, it can influence gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, and gastrin).

Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH < 3), remaining mostly inactive at higher pH values. As a result, its complete pharmacological, and thus therapeutic effect, can only be achieved in the acid secretory parietal cells. By means of a feedback mechanism this effect is diminished at the same rate as acid secretion is inhibited.

As with other proton pump inhibitors and H2 receptor inhibitors treatment with Pantoprazole causes a reduced acidity in the stomach and thereby increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible.

**Pharmacokinetics:**

Pantoprazole is rapidly absorbed and the maximal plasma concentration appears after one single oral dose. After single and multiple oral doses, the median time to reach maximum serum concentrations was approximately 2.5 h. In the fasted state, it was found that the C max of Pantoprazole-GA 40mg tablets was 3.6 microgram/ml. Terminal half-life is approximately 1h.

Volume of distribution is approximately 0.15 L/kg and clearance is approximately 0.1 L/h/kg. Pharmacokinetics does not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear (in the dose range of 10 to 80mg) after both oral and intravenous (IV) administration.
**Absorption**

Pantoprazole is completely absorbed after oral administration. The absolute bioavailability of the tablet is approximately 77%. Concomitant intake of food had no influence on AUC, maximum serum concentrations and thus bioavailability. Pantoprazole is rapidly absorbed and peak plasma-pantoprazole concentrations are achieved about 2 to 2.5 hours after an oral dose. The oral bioavailability is about 77% with the enteric-coated tablet formulation, and does not vary after single or multiple doses.

**Distribution:**

The serum protein binding of pantoprazole is approximately 98%. Pantoprazole is rapidly eliminated from serum and is almost exclusively metabolised in the liver. Renal elimination represents the most important route of excretion (approximately 80%) for the metabolites of pantoprazole, the rest are excreted with the faeces. The main metabolite in both the serum and urine is dimethyl-pantoprazole which is conjugated with the sulphate. The half-life of the main metabolites (approximately 1.5 h) is not much longer than that of pantoprazole.

**Elimination:**

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity.

CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow Pantoprazole metabolisers have elimination half life values of 3.5 to 10.0 hours, they still have minimal accumulation (= 23%) with once daily dosing.
Table 1: Various pharmacokinetic parameters of Pantoprazole

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKa</td>
<td>8.35</td>
</tr>
<tr>
<td>pH</td>
<td>Between 9.0 and 11.5 (2% w/v solution in water)</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>77%</td>
</tr>
<tr>
<td>Absorption</td>
<td>It is rapidly absorbed</td>
</tr>
<tr>
<td>Peak plasma concentration</td>
<td>2.52 mcg/ml</td>
</tr>
<tr>
<td>T max</td>
<td>2.5 hours (under fasting conditions)</td>
</tr>
<tr>
<td>T1/2</td>
<td>The mean elimination half-life is 1 hour</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>0.151/kg</td>
</tr>
<tr>
<td>Excretion</td>
<td>Through renal excretion</td>
</tr>
</tbody>
</table>

**Adverse Effects:**

The most commonly reported adverse actions associated with oral Pantoprazole in short term clinical trial for GERD are headache, diarrhoea, flatulence, abdominal pain, eructation, nausea and rash. The severity of adverse events was not reported. In patients with hepatic impairment Pantoprazole dosage should be monitored closely due to accumulation of drug\(^5^0\).

**Indications and Uses:**

Pantoprazole is a proton pump inhibitor with actions and uses similar to those of omeprazole. It is given as the sodium salt but doses are expressed in terms of the base. Pantoprazole sodium 11.28 mg is equivalent to about 10 mg of pantoprazole. Once-daily doses should be taken in the morning. In the treatment of gastro-oesophageal reflux disease, the usual oral dose is 20 to 40 mg once daily for 4 weeks, increased to 8
weeks if necessary; in the USA, up to 16 weeks of therapy is permitted for healing of erosive oesophagitis. For maintenance therapy, treatment can be continued with 20 to 40 mg daily. Alternatively, for recurring symptoms, an on-demand regimen of 20 mg daily may be given \(^5^1\).

The usual dose for the treatment of peptic ulcer disease is 40 mg once daily. Treatment is usually given for 2 to 4 weeks for duodenal ulceration, or 4 to 8 weeks for benign gastric ulceration. For the eradication of Helicobacter pylori pantoprazole may be combined with two antibacterial in a 1-week triple therapy regimen. Effective regimens include pantoprazole 40 mg twice daily combined with clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily, or combined with clarithromycin 250 mg twice daily and metronidazole 400 mg twice daily \(^5^2\).

Patients who require prophylaxis for NSAID-associated ulceration may take 20 mg daily. In the treatment of pathological hyper secretory states such as the Zollinger-Ellison syndrome, the initial dose is 80 mg daily, adjusted as required. Doses of up to 240 mg daily have been used. Daily doses greater than 80 mg should be given in 2 divided doses.

The safety and tolerability profiles of intravenous pantoprazole given in 10 mL of sodium chloride 0.9% over 2 minutes were similar to those given over 15 minutes in 100 mL \(^5^3\).