

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Panrazol 40 mg gastro-resistant tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 40 mg pantoprazole (as 45.16 mg pantoprazole sodium sesquihydrate)

For a full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Gastro-resistant tablet

Panrazol 40 mg: Elliptical, biconvex, dark yellow gastro-resistant tablet

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

For symptomatic improvement and healing of gastrointestinal diseases which require a reduction in acid secretion:

- Duodenal ulcer
- Gastric ulcer
- Moderate and severe reflux oesophagitis
- Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions
- Eradication of *Helicobacter pylori*, in combination with antibiotics in patients with duodenal ulcer or gastric ulcer.

In the case of combination therapy for the eradication of *Helicobacter pylori*, the Summaries of Product Characteristics of the respective antibiotics should be observed.

#### 4.2 Posology and method of administration

Panrazol should not be chewed or crushed, and should be swallowed whole with water one hour before a meal.

Recommended dosage:

#### **Adults and adolescents 12 years of age and above:**

Treatment of moderate and severe reflux oesophagitis

One tablet of Panrazol 40 mg per day.

#### **Adults:**

Treatment of duodenal ulcer and gastric ulcer

One tablet of Panrazol 40 mg per day.

In combination therapy for the eradication of *Helicobacter pylori*, the recommended dose is one tablet taken twice daily. The second Panrazol tablet should be taken one hour before the evening meal. Combination therapy should be implemented for 7 days. At the end of the 7 days' combination period, pantoprazole may be continued to ensure the healing of the ulcer. For duodenal ulcers, this may require an additional 1 to 3 weeks.

The safety of longer-term use is generally well established. Long-term administration of pantoprazole has a safety profile similar to that observed with short-term treatment, and is well tolerated.

In most patients, freedom from symptoms is achieved rapidly. In a few instances, there may be benefit in extending treatment beyond 8 weeks to ensure healing.

#### Duodenal ulcer:

Duodenal ulcers generally heal within 2 weeks. If a 2-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

#### Gastric ulcer:

A 4-week period is usually required for the treatment of gastric ulcers. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

#### Gastro-Oesophageal Reflux:

A 4-week period is usually required for the treatment of gastro-oesophageal reflux. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

#### Long-term treatment of Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions:

Patients should start their treatment with a daily dose of 80 mg (2 tablets of Panrazol 40 mg). Thereafter, the dosage can be titrated up or down as needed using measures of gastric acid secretion to guide. With doses above 80 mg daily, the dose should be divided and given twice daily. A temporary increase of the dosage above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control. Treatment duration in Zollinger-Ellison Syndrome and other pathological hypersecretory conditions is not limited and should be adapted according to clinical needs.

#### Eradication of *Helicobacter pylori* (*H.pylori*):

The recommended dose is 40 mg pantoprazole twice daily in combination with one of the three following combinations:

- a) amoxicillin 1 g twice daily + clarithromycin 500 mg twice daily
- b) clarithromycin 500 mg twice daily + metronidazole 500 mg twice daily
- c) amoxicillin 1 g twice daily + metronidazole 500 mg twice daily

The second Panrazol 40 mg tablet should be taken before the evening meal. Combination therapy should be implemented for 7 days. At the end of the 7 days' combination period, pantoprazole may be continued to ensure the healing of the ulcer. For duodenal ulcers, this may require an additional 1 to 3 weeks. For gastric ulcers, this may require an additional 3 to 7 weeks.

#### Elderly:

The daily dose of 40 mg pantoprazole should not be exceeded. An exception is combination therapy for eradication of *H. pylori*, where elderly patients should receive the usual pantoprazole dose (2 x 40 mg/day) during 1 week treatment.

#### Patients with impaired renal function:

The daily dose of 40mg pantoprazole should not be exceeded. For this reason, *H. pylori* triple therapy is not appropriate in these patients. (see section 4.3).

#### Patients with hepatic cirrhosis:

Patients with severe hepatic impairment should be given 40 mg of pantoprazole every other day (see sections 4.3 and 4.4). In these patients, hepatic enzyme levels should be monitored during the treatment. If hepatic

enzyme levels become elevated, treatment with pantoprazole should be discontinued. For this reason, *H. pylori* triple therapy is not appropriate in these patients.

#### Children:

There is no information on the use of pantoprazole in children. Therefore pantoprazole tablets should not be used in children.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

Pantoprazole like other PPIs should not be administered with atazanavir (see section 4.5).

The preparation should not be used in combination therapy for the eradication of *Helicobacter pylori* in patients with moderate or severe hepatic or renal impairment, since no data is available to date on the efficacy and safety of pantoprazole in the combination therapy of these patients.

### **4.4 Special warnings and precautions for use**

In patients with severe liver impairment, the liver enzymes should be monitored regularly during treatment with pantoprazole, particularly on long-term use. In the case of a rise of the liver enzymes Panrazol should be discontinued.

Decreased gastric acidity due to any means – including proton pump inhibitors – increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with acid-reducing drugs may lead to a slightly increased risk of gastrointestinal infections, such as *Salmonella* and *Campylobacter*.

In patients with Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions requiring long-term treatment, pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered if respective clinical symptoms are observed.

Prior to treatment of gastric ulcer, the possibility of malignancy should be excluded as treatment with Panrazol may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

To date, there has been no experience with treatment in children.

In long term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

### **4.5 Interaction with other medicinal products and other forms of interaction**

Atazanavir: Studies with other PPIs have shown a marked reduction in atazanavir exposure during concomitant PPI treatment. Use of PPIs is contraindicated during atazanavir treatment.

Panrazol may reduce or increase the absorption of drugs whose bioavailability is pH-dependent (e.g. ketoconazole, itraconazole, atazanavir).

Pantoprazole is metabolized in the liver via the cytochrome P450 enzyme system. An interaction of pantoprazole with other drugs or compounds which are metabolized using the same enzyme system cannot be excluded. However, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline and an oral contraceptive.

Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in INR have been reported during concomitant treatment in the post-marketing period. Therefore, in patients treated with coumarin anticoagulants, monitoring of prothrombin time/INR is recommended after initiation, termination or during irregular use of pantoprazole.

There were also no interactions with concomitantly administered antacids.

#### 4.6 Pregnancy and lactation

Clinical experience in pregnant women is limited. In animal reproduction studies, signs of slight fetotoxicity were observed at doses above 5 mg/kg. There is no information on the excretion of pantoprazole into human breast milk. Pantoprazole tablets should only be used when the benefit to the mother is considered greater than the potential risk to the foetus/baby.

#### 4.7 Effects on ability to drive and use machines

There are no known effects on the ability to drive and use machines. Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). Under these conditions the ability to react may be decreased.

#### 4.8 Undesirable effects

Frequency	Common ( $\geq 1/100$ , $< 1/10$ )	Uncommon ( $\geq 1/1000$ , $< 1/100$ )	Rare ( $\geq 1/1000$ , $< 1/10,000$ )	Very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data)
Organ system				
Blood and lymphatic system				Leukopenia; Thrombocytopenia
Gastrointestinal Disorders	Upper abdominal pain; Diarrhoea; Constipation; Flatulence	Nausea/Vomiting	Dry mouth	
General disorders and administration site conditions				Peripheral oedema
Hepatobiliary disorders				Severe hepatocellular damage leading to jaundice with or without hepatic failure
Immune system disorders				Anaphylactic reactions including

				anaphylactic shock
Investigations				Increased liver enzymes (transaminases, $\gamma$ -GT); Elevated triglycerides; Increased body temperature
Musculoskeletal, connective tissue disorders			Arthralgia	Myalgia
Nervous system disorders	Headache	Dizziness; Disturbances in vision (blurred vision)		
Psychiatric disorders			Depression, hallucinations, disorientation and confusion, especially in predisposed patients as well as the aggravation of these symptoms in case of pre-existence	Mental depression
Renal and urinary disorders				Interstitial nephritis
Skin and sub-cutaneous tissue disorders		Allergic reactions such as pruritus and skin rash		Urticaria; Angioedema; Severe skin reactions such as Stevens Johnson Syndrome, Erythema Multi-forme, Lyell-Syndrome; Photosensitivity

#### 4.9 Overdose

There are no known symptoms of overdosage in man. Doses up to 240 mg i.v. were administered over 2 minutes and were well tolerated.

In the case of overdosage with clinical signs of intoxication, the usual rules of intoxication therapy apply. As pantoprazole is extensively protein bound, it is not readily dialyzable

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: proton pump inhibitors, ATC code: A02BC02

Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific action on the proton pumps of the parietal cells.

Pantoprazole is converted to its active form in the acidic canaliculi of the parietal cells where it inhibits the  $H^+$ ,  $K^+$ -ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved in 2 weeks. As with other proton pump inhibitors and  $H_2$  receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, the substance can affect hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is given orally or intravenously.

The fasting gastrin values increase when undergoing treatment with pantoprazole. On short-term use, in most cases they do not exceed the normal upper limit. During long-term treatment, gastrin levels double in most cases. An excessive increase, however, occurs only in isolated cases. As a result, a mild to moderate increase in the number of specific endocrine (ECL) cells in the stomach is observed in a minority of cases during long-term treatment (simple to adenomatoid hyperplasia). However, according to the studies conducted so far, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids as were found in animal experiments (see Section 5.3) can be ruled out for humans for a 1-year treatment period.

An influence of a long term treatment with pantoprazole exceeding one year cannot be completely ruled out on endocrine parameters of the thyroid and liver enzymes according to results in animal studies.

### 5.2 Pharmacokinetic properties

#### General pharmacokinetics

Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 40 mg oral dose. On average at about 2.0 h - 2.5 h p.a. the maximum serum concentrations of about 2-3  $\mu\text{g/ml}$  are achieved and these values remain constant after multiple administration. Volume of distribution is about 0.15 l/kg and clearance is about 0.1 l/h/kg.

Terminal half-life is about 1 h. There were a few cases of subjects with delayed elimination. Because of the specific binding of pantoprazole to the proton pumps of the parietal cell, the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

Pharmacokinetics do not vary after single or repeated administration. In the dose range of 10 to 80 mg, the plasma kinetics of pantoprazole are linear after both oral and intravenous administration.

Pantoprazole's serum protein binding is about 98%. The substance is almost exclusively metabolized in the liver. Renal elimination represents the major route of excretion (about 80%) for the metabolites of pantoprazole, the rest is excreted with the faeces. The main metabolite in both the serum and urine is desmethylpantoprazole which is conjugated with sulphate. The half-life of the main metabolite (about 1.5 h) is not much longer than that of pantoprazole.

#### Bioavailability

Pantoprazole is completely absorbed after oral administration. The absolute bioavailability from the tablet was found to be about 77%. Concomitant intake of food had no influence on AUC, maximum serum concentration and thus bioavailability. Only the variability of the lag-time will be increased by concomitant food intake.

#### Characteristics in patients/special groups of subjects

No dose reduction is requested when pantoprazole is administered to patients with restricted kidney function (including dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small

amounts of pantoprazole can be dialyzed. Although the main metabolite has a moderately delayed half-life (2 - 3h), excretion is still rapid and thus accumulation does not occur.

Although for patients with liver cirrhosis (classes A and B according to *Child*) the half-life values increased to between 3 and 6 h and the AUC values increased by a factor of 3 - 5, the maximum serum concentration only increased slightly by a factor of 1.3 compared with healthy subjects.

A slight increase in AUC and Cmax in elderly volunteers compared with younger counterparts is also not clinically relevant.

### **5.3 Preclinical safety data**

Preclinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

In the 2 year carcinogenicity studies (corresponding to lifetime treatment) in rats, neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats in one study. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and allows the conclusion that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during chronic high-dose treatment.

In the 2 year rodent studies, an increased number of liver tumors was observed in rats (in one rat study only) and in female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver.

A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose (200 mg/kg) in one 2 year study. The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no side effects on the thyroid glands are expected.

From mutagenicity studies, cell transformation tests and a DNA binding study it is concluded that pantoprazole has no genotoxic potential.

Investigations revealed no evidence of impaired fertility or teratogenic effects.

Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentration of pantoprazole in the foetus is increased shortly before birth.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Tablet core:

Mannitol

Sodium carbonate, anhydrous

Sodium starch glycolate (type A)

Methacrylic acid-ethylacrylate copolymer (Eudragit E PO)

Calcium stearate

Opadry white OY-D-7233 (hypromellose, titanium dioxide E71, Macrogol 400, sodium lauryl sulphate)

Film coating:

Kollicoat MAE 30 DP, light yellow consisting of:

Methacrylic acid-ethyl acrylate copolymer dispersion

Propyleneglycol

Yellow iron oxide (E172)

Titanium dioxide (E171)

Talc

Purified water

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

18 months.

### **6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

### **6.5 Nature and contents of container**

HDPE container with LDPE-cap and desiccant  
Aluminium/aluminium blister pack

Pack sizes:

Blister: 7, 14, 15, 20, 28, 30, 56, 60, 98, 100 tablets

HDPE bottle: 30, 100, 250 tablets

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

No special requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Actavis Group PTC ehf.  
Reykjavíkurvegi 76-78  
220 Hafnarfjörður  
Iceland

## **8. MARKETING AUTHORISATION NUMBER(S)**

MA628/00402

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

6<sup>th</sup> October 2008

## **10. DATE OF REVISION OF THE TEXT**