Pantoprazole 20mg and 40mg Gastro-resistant Tablets
PL 30306/0298-9

UKPAR

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Pantoprazole 20mg and 40mg Gastro-resistant Tablets
PL 30306/0298-9

LAY SUMMARY

On 8th February 2010, the MHRA granted Caduceus Pharma Limited Marketing Authorisations (licences) for the medicinal products Pantoprazole 20 and 40mg Gastro-resistant tablets (PL 24668/0052-3). These are prescription-only medicines (POM) used to treat acid reflux (a type of heart-burn) and help prevent it from returning.

Pantoprazole Gastro-resistant Tablets may also be given to patients who need to take non-selective non-steroidal anti-inflammatory drugs (NSAIDS) for a continuous period. These patients are at a greater risk of developing an ulcer and associated symptoms. Pantoprazole Gastro-resistant tablets help reduce the risk by preventing an ulcer from developing.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Pantoprazole 20 and 40mg Gastro-resistant Tablets outweigh the risks; hence Marketing Authorisations have been granted.

A subsequent Change of Ownership (CoA) was granted for these products on 29 April 2010, to change the Marketing Authorisation Holder to Actavis Group PTC ehf (PL 30306/0298-9).

Pantoprazole 20mg and 40mg Gastro-resistant Tablets
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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Pantoprazole 20 and 40mg Gastro-resistant Tablets (PL 24668/0052-3, 58-9) on the 8th February 2010.

The products are for the treatment of mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing), for long-term management and prevention of relapse in reflux oesophagitis and prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment.

The applications are according to Article 10(1) of 2001/83/EC, generic applications, as amended. The applications are for the generic products Pantoprazole Gastro-resistant Tablets 20mg and 40mg in duplicate. The reference product is Pantoloc 40mg magensaftresistente Tabletten first authorised for Byk Gulden Lomberg (HIST) Chemische Fabrik GmbH on 23rd August 1994 in Germany. The UK reference product is Protium 20mg & 40mg gastro-resistant tablets registered in the UK since 17th March 2003 (Altana Pharma AG, PL 20141/0001-2). Bioequivalence has been established with the 40mg Pantozol magensaftresistente Tabletten, (Altana Pharma AG) from the German market.

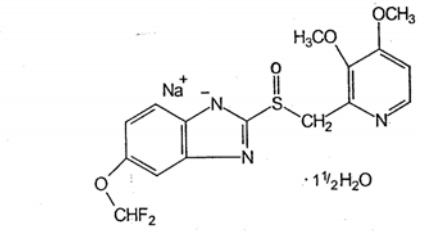
Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific action on the proton pumps of the parietal cells.

A subsequent Change of Ownership (CoA) was granted for these products on 29 April 2010, to change the Marketing Authorisation Holder to Actavis Group PTC ehf (PL 30306/0298-9).

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE – PANTOPRAZOLE

INN: Pantoprazole sodium sesquihydrate
Chemical Name: 5-(difluoromethoxy)-2-(((3,4-dimethoxy-2-pyridinyl)methyl) sulfinyl)-1H-benzimidazole sodium salt sesquihydrate
Molecular Formula: $C_{16}H_{14}F_2N_3NaO_4S.1½\ H_2O$
Chemical Structure:



Molecular Weight: 432.0
Appearance: White to off-white powder
Properties: Freely soluble in water.

The drug substance is the subject of a European Drug Master File (EDMF). A letter of access has been provided by the drug substance manufacturer.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificate of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients mannitol, sodium carbonate anhydrous, sodium starch glycolate, methacrylic acid copolymer, calcium stearate, Opadry white OY-D-7233 (hypromellose, titanium dioxide, talc, macrogol, sodium lauryl sulphate) and Kollicoat MAE 30 DP yellow (methacrylic acid-ethyl acrylate copolymer dispersion 30%, propylene glycol, yellow iron oxide, titanium dioxide, talc)

All excipients comply with their respective European Pharmacopoeia monograph with the exception of Opadry white OY-D-7233 which complies with in-house specification. A TSE statement from the suppliers of the calcium stearate, the Kollicoat MAE 30DP light yellow and dark yellow and the Opadry White OY-D-7233 has been provided.

Satisfactory Certificates of Analysis have been provided for all excipients.

Pharmaceutical development

Suitable pharmaceutical development data have been provided for these applications. Comparable dissolution and impurity profile are provided for these products versus the originator product.

Manufacture

A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results appear satisfactory.

Finished product specification

The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System

The finished product is supplied in aluminium/aluminium blisters in pack sizes of 2 (40 mg strength only), 7, 14, 15, 28, 30, 50, 56, 60, 84, 90, 100, 112, 140, 280, 500, or 700 tablets.

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with current guidelines concerning materials in contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years has been set.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling

The SPC, PIL and labelling are pharmaceutically satisfactory.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form

The MAA form is pharmaceutically satisfactory.

Expert Report

The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion

It is recommended that Marketing Authorisations are granted for these applications.

PRECLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of the product are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A preclinical expert report has been provided, written by an appropriately qualified person. This is satisfactory.

A suitable justification has been provided for non-submission of an environmental risk assessment.

CLINICAL ASSESSMENT

TOXICOLOGY

No new toxicological data have been submitted or are required for these applications.

CLINICAL PHARMACOLOGY

The applicant has submitted two bioequivalence studies – one under fasted and another under fed conditions.

Study No. 1 (Report AA 26974)

This was an open-label, randomised, single-dose, 2-way crossover, 2-sequence comparative bioavailability study of Actavis Group hf and Altana Pharma (Pantozol®) 40 mg Pantoprazole Sodium Delayed-Release Tablets in Healthy Adult Male Volunteers under Fasting conditions. The study was conducted by MDS Pharma Sevices, Montreal, Canada and was performed on 50 healthy non-smoking or moderate smoking (less that 10 cigarettes a day) adult male volunteers. A total of 48 subjects completed the clinical phase of the study. In each period, subjects were housed from at least 12 hours before dosing until after the 12-hour blood draw. Single oral doses of 40mg pantoprazole sodium were separated by a washout period of 14 days.

Table 1 Summary of the main Pharmacokinetic Parameters of 40mg Pantoprazole - Fasted State (N = 48)

	AUC 0-t* (ng.h/mL)	AUC inf* (ng.h/mL)	Cmax* (ng/mL)	Tmax (h)	Half-life(h)
Actavis Group hf (A)					
Mean	4759.50	4908.88	3200.625	2.4666	1.3285
CV	56.5	63.6	27.3	38.0	89.2
n	48	48	48	48	48
Altana Pharma (B)					
Mean	4521.58	4672.35	2794.750	2.5293	1.3884
CV	60.2	66.8	35.8	38.5	89.8
n	48	48	48	48	48
Ratio of Least-Square Means (A/B)	1.05	1.05	1.14		
90% Confidence Intervals (A/B)					
lower limit:	0.99	0.99	1.04		
upper limit:	1.12	1.11	1.246		

* For in-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.

The Test formulation (40mg pantoprazole by Activis Group hf) was shown to be bioequivalent to the Reference formulation (Altana Pharma Pantozol® 40mg) under fasting conditions following a single oral dose administration.

The essentially linear pharmacokinetics of pantoprazole, particularly at this relatively low dose range, makes it likely that the lower-doses of pantoprazole formulations also are bioequivalent to the corresponding marketed brand formulations although bioequivalence has not been assessed explicitly.

No subject experienced any adverse events attributable to the Test formulation and only one subject experienced minor adverse event attributed to the Reference product. No significant or serious adverse events were reported during the study.

Study Report 1742/08

This was an open-label, randomised, single-dose, 2-way crossover, 2-sequence comparative bioavailability study of pantoprazole 40mg enter coated tablets of Actavis Group PTC ehf and Pantozol®) 40 mg Pantoprazole 40 mg enterocoated tablets of Nycomed, Germany. A total of 80 subjects were recruited and 76 completed the study and 75 were evaluated. Three subjects were withdrawn due to protocol violation, one subject dropped out of the study. Another subject was excluded from statistical analysis due to several unquantifiable concentrations in period II Blood samples were collected frequently up to 24 post-dosing. There was a washout period of 7 days between dosing.

Summary of the main Pharmacokinetic Parameters of 40mg Pantoprazole - Fed State

	AUC 0-t (µg.h/mL)	**AUC inf. (µg.h/mL)**	**Cmax (µg/mL)**	**Tmax (h)**
Test Product				
Mean	6.665	7.037	2.674	8.867
CV (%)	95.95	104.45	37.71	42.25
n	75	74	75	75
Ref. Product				
Mean	7.193	7.684	2.804	8.953
CV(%)	90.66	111.27	34.25	49.91
n	75	74	75	75
Ratio	0.93	0.92	0.95	
90% CI	0.87 – 0.99	0.86 – 0.97	0.87 – 1.05	

The Test formulation (40mg pantoprazole by Activis Group hf) appears to have been shown to be bioequivalent to the Reference formulation (Nycomed Pantozol® 40mg)under fed conditions following a single oral dose administration.

The essentially linear pharmacokinetics of pantoprazole, particularly at this relatively low dose range, makes it likely that the lower-doses of pantoprazole formulations also are bioequivalent to the corresponding marketed brand formulations although bioequivalence has not been assessed explicitly.

There were nine adverse events reported during the study and all were assessed as mild. No serious adverse events were reported during the study.

The results of the fasted and fed study demonstrate bioequivalence. The 90% confidence intervals (CI) for the AUC and C_{max} ratios fall within the conventional 80-125% bioequivalence range.

EFFICACY
No new efficacy data have been submitted or are required for this submission.

SAFETY
No new data are submitted or needed.

EXPERT REPORT
The Clinical Expert Report has been written by an appropriately qualified person and is a suitable summary of the clinical aspects of the dossier.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
These are consistent with the SPC for the reference products and are satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
The PIL is an accurate reflection of the SPC and complies with the appropriate guidelines.

LABELLING
These are satisfactory.

MAA FORMS
These are satisfactory.

CONCLUSIONS
The proposed products are qualitatively and quantitatively equivalent to the reference product. The German reference product is considered to be equivalent to the UK reference product, Protium. Therefore, grant of Marketing Authorisations are recommended.

OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Pantoprazole 20mg and 40mg Gastro-resistant Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

The preclinical data submitted have not revealed any evidence of potential risks to human health from treatment with Pantoprazole 20mg and 40mg Gastro-resistant Tablets beyond those already described.

EFFICACY

No new data have been submitted and none are required for an application of this type.

Pantoprazole 20mg and 40mg Gastro-resistant Tablets is the generic version of Protium 20 and 40 mg Tablets (Altana Pharma AG, PL 20141/0001-2). The use of the reference product is well-established in the UK. Both products contain the same quantitative and qualitative composition of the active ingredients, pantoprazole.

The 90% confidence intervals for the test/reference lie within the acceptance criteria specified in the CPMP/EWP/QWP/1401/98 *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence*. Bioequivalence of the test product to the reference formulation has been satisfactorily demonstrated in accordance with CHMP criteria.

No new safety data are supplied or required for this generic application. Pantoprazole have well-established side-effect profiles and are generally well-tolerated.

The SPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with pantoprazole is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is, therefore, considered to be positive.

Pantoprazole 20mg and 40mg Gastro-resistant Tablets
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STEPS TAKEN FOR ASSESMENT

1	The MHRA received Marketing Authorisation applications (PL 24668/0052-3) on 30th April 2007
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 16th July 2007
3	Following assessment of the applications the MHRA requested further information on 23rd October 2007 for the quality part and on 8th February, 29th December 2008 and 22nd June 2009 for the clinical parts of the dossier
4	The applicant responded to the MHRA's requests, providing further information on 23rd November 2007 for the quality sections, and 8th February 2008, 3rd June 2008, 22nd April 2009 and 29th July 2009 for the clinical sections.
5	The applications were determined on 8th February 2010

Pantoprazole 20mg and 40mg Gastro-resistant Tablets
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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

The following table lists non-safety updates to Marketing Authorisations for these products that have been approved by the MHRA since the products were first licensed. The table includes updates that have been incorporated into the text of this Public Assessment Report (PAR) or added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

Date submitted	Application type	Scope	Outcome
04 March 2011	Type IB	To update Sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the Summary of Product Characteristics (SmPC) in line with the Article 30 referral for Protium (pantoprazole). Consequently, the Patient Information Leaflet has also been updated.	Approved 20 October 2011

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pantoprazole 20 mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 20 mg pantoprazole
(as pantoprazole sodium sesquihydrate 22.58 mg)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet

Elliptical, biconvex, light yellow gastro-resistant tablet

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the treatment of mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing).

For long-term management and prevention of relapse in reflux oesophagitis.

Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment (see section 4.4).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing)

The recommended oral dosage is one pantoprazole 20mg gastro-resistant tablet per day. Symptom relief is generally accomplished within 2-4 weeks, and a 4-week treatment period is usually required for healing of associated oesophagitis. If this is not sufficient, healing will normally be achieved within a further 4 weeks. When symptom relief has been achieved, reoccurring symptoms can be controlled using an on-demand regimen of 20 mg once daily, when required. A switch to continuous therapy may be considered in case satisfactory symptom control cannot be maintained with on-demand treatment.

Long-term management and prevention of relapse in reflux oesophagitis

For long-term management, a maintenance dose of one pantoprazole 20mg gastro-resistant tablet per day is recommended, increasing to 40 mg pantoprazole per day if a relapse occurs. Pantoprazole 40 mg gastro-resistant tablets are available for this case. After healing of the relapse the dosage can be reduced again to 20 mg pantoprazole.

Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment

The recommended oral dosage is one pantoprazole 20mg gastro-resistant tablet per day.

Note:
A daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver impairment.

No dose adjustment is necessary in elderly patients or in those with impaired renal function. There is no experience in children.

General instructions:
Pantoprazole 20 mg gastro-resistant tablets should not be chewed or crushed, and should be swallowed whole with liquid before a meal.

4.3 CONTRAINDICATIONS

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

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 Pantoprazole 20mg gastro-resistant tablets should be discontinued.

The use of Pantoprazole 20mg gastro-resistant tablets as a preventive of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued NSAID treatment and have an increased risk to develop gastrointestinal complications.
The increased risk should be assessed according to individual risk factors, e.g. high age >65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.
Pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

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

Note:
Prior to treatment a malignant disease of the oesophagus or stomach should be excluded as the treatment with pantoprazole may alleviate the symptoms of malignant diseases and can thus delay diagnosis.

Patients who do not respond after 4 weeks should be investigated.

There is no experience in children.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Pantoprazole 20mg gastro-resistant tablets may reduce or increase the absorption of drugs whose bioavailability is pH-dependent (e.g. ketoconazole).

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

Pantoprazole 20mg gastro-resistant tablets have no influence on the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequency Organ system	Common (>1/100, <1/10)	Uncommon (>1/1000, <1/100)	Rare (>1/10,000, <1/1000)	Very rare (<1/10,000, incl. isolated reports)
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, γ-GT); Elevated triglycerides; Increased body temperature
Musculoskeletal, connective tissue disorders			Arthralgia	Myalgia
Nervous system disorders	Headache	Dizziness; Disturbances in vision (blurred vision)		
Psychiatric disorders				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 over-dosage in man. Doses up to 240 mg i.v. were administered over 2 minutes and were well tolerated.

In the case of over-dosage with clinical signs of intoxication, the usual rules of intoxication therapy apply

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 under 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 20 mg oral dose. On average at about 2.0 h - 2.5 h p.a. the maximum serum concentrations of about 1-1.5 µg/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 (incl. 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 two-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

Mannitol
Sodium carbonate anhydrous
Sodium starch glycolate, Type A
Methacrylic acid copolymer
Calcium stearate
Opadry white OY-D-7233 (hypromellose, titanium dioxide, talc, macrogol, sodium lauryl sulphate)
Kollicoat MAE 30 DP yellow (methacrylic acid-ethyl acrylate copolymer dispersion 30%, propylene glycol, yellow iron oxide, titanium dioxide, talc)

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE
24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions.

6.5 NATURE AND CONTENTS OF CONTAINER
Pantoprazole 20mg gastro-resistant tablets are provided in aluminium/aluminium blister packs of 7, 14, 15, 28, 30, 50, 56, 60, 84, 90, 100, 112, 140, 280, 500, or 700 tablets.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements

7 MARKETING AUTHORISATION HOLDER
Actavis Group PTC ehf
Reykjavikurvegur 76-78
220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER(S)
PL 30306/0298

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
08/02/2010

10 DATE OF REVISION OF THE TEXT
08/02/2010

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

1 NAME OF THE MEDICINAL PRODUCT

Pantoprazole 40 mg gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet

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

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

The recommended dosage in duodenal ulcer, gastric ulcer and gastro-oesophageal reflux is one enteric-coated tablet per day. Pantoprazole 40mg gastro-resistant tablets should not be chewed or crushed, and should be swallowed whole with water either before or during breakfast.

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. Except for patients with Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions, the treatment with pantoprazole 40mg gastro-resistant tablets should not exceed 8 weeks, as experience with long-term administration in man is insufficient.

In most patients, freedom from symptoms is achieved rapidly. Except for patients with pathological hypersecretory conditions including Zollinger-Ellison syndrome, the treatment with pantoprazole 40mg gastro-resistant tablets should not exceed 8 weeks, as experience in man is insufficient. 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 management of Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions:
For the long-term management of Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions patients should start their treatment with a daily dose of 80 mg (2 pantoprazole 40 mg gastro-resistant tablets). Thereafter, the dosage can be titrated up or down as needed using measurements 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.

Elderly:
No dose adjustment is necessary in the elderly. However, 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:
No dose adjustment is necessary in patients with impaired renal function. However, the daily dose of 40mg pantoprazole should not be exceeded. For this reason, *H. pylori* triple therapy is not appropriate in these patients.

Patients with hepatic cirrhosis:
Due to an increased AUC and a modified metabolism of pantoprazole in patients with hepatic cirrhosis, the dose regimen should be reduced to one tablet every other day. 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In patients with severe liver impairment, particularly those on long-term use, liver enzymes should be monitored regularly during treatment with pantoprazole. In the case of a rise in liver enzymes, pantoprazole 40mg gastro-resistant tablets should be discontinued.

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

Note:
Prior to treatment of gastric ulcer, the possibility of malignancy should be excluded as treatment with pantoprazole 40mg gastro-resistant tablets may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

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.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

As with other acid secretion inhibitors, changes in absorption may be observed when drugs whose absorption is pH-dependent, e.g. ketoconazole, are taken concomitantly.

Pantoprazole is metabolised in the liver via the cytochrome P450 enzyme system. Although studies have shown that pantoprazole has no significant effect on cytochrome P450, an interaction of pantoprazole with other drugs or compounds, which are metabolised using the same enzyme system, cannot be excluded.

However, no clinically significant interactions were observed in specific tests with a number of such drugs/compounds, namely antipyrine, carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline and an oral contraceptive. There were also no interactions with concomitantly administered antacids.

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.

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.

During pregnancy and breastfeeding, pantoprazole 40mg gastro-resistant tablets should only be used when the benefit exceeds the potential risk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Pantoprazole 40mg gastro-resistant tablets have no influence on the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequency Organ system	Common (>1/100, <1/10)	Uncommon (>1/1000, <1/100)	Rare (>1/10,000, <1/1000)	Very rare (<1/10,000, incl. isolated reports)
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, γ-GT); Elevated triglycerides; Increased body temperature
Musculoskeletal, connective tissue disorders			Arthralgia	Myalgia
Nervous system disorders	Headache	Dizziness; Disturbances in vision (blurred vision)		
Psychiatric disorders				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 over dosage in man. However, pantoprazole is very specific in action and no particular problems are anticipated. Doses up to 240 mg i.v. were administered without obvious adverse effects. As pantoprazole is extensively protein bound, it is not readily dialysable.
Apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: proton pump inhibitors, ATC code: A02BC02

Pantoprazole is a proton pump inhibitor, i.e. it inhibits specifically and dose-proportionally the gastric H^+/K^+-ATPase enzyme, which is responsible for 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 sulphenamide, 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 distally to the receptor level, it can inhibit gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

Pantoprazole's selectivity is due to the fact that it can only exert 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.

Pantoprazole has the same effect whether administered orally or intravenously.
Following intravenous or oral administration, pantoprazole inhibits the pentagastrin-stimulated gastric acid secretion. In volunteers, acid secretion was inhibited by 56% following the first i.v. administration of 30 mg and by 99% after 5 days. With an oral dose of 40 mg, inhibition was 51% on day 1 and 85% on day 7. Basal 24-hour acidity was reduced by 37% and 98%, respectively.

The fasting gastrin values increased under pantoprazole but in most cases they did not exceed the normal upper limit. Following completion of a course of oral treatment, the median gastrin levels clearly declined again.

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, the maximum serum concentrations are approximately 2-3 µg/ml about 2.5 hours post-administration and these values remain constant after multiple administration. Terminal half-life is about 1 hour. Volume of distribution is about 0.15 l/kg and clearance is about 0.1 l/h/kg. There were a few cases of subjects with delayed elimination. Because of the specific activation within the parietal cell, the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

Pharmacokinetics does not vary after single or repeated administration. The plasma kinetics of pantoprazole are linear after both oral and intravenous administration.

Studies with pantoprazole in humans reveal no interaction with the cytochrome P450-system of the liver. There was no induction of the P450-system seen as tested after chronic administration with antipyrine as a marker. Also, no inhibition of metabolism was observed after concomitant administration of pantoprazole with either antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenprocoumon, phenytoin, piroxicam, theophylline and oral contraceptives. Concomitant administration of pantoprazole with warfarin has no influence on warfarin's effect on the coagulation factors.

The absolute bioavailability of the tablet is about 77%. Concomitant intake of food or antacids had no influence on AUC, maximum serum concentrations and thus bioavailability.

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

Characteristics in patients/special groups of subjects
Although for patients with hepatic cirrhosis (classes A and B according to *Child*) the half-time values increased to between 7 and 9 hours and the AUC values increased by a factor of 5 to 7, the maximum plasma concentration only increased slightly by a factor of 1.5 compared with healthy subjects. Therefore the dose regimen in patients with hepatic cirrhosis should be reduced to one tablet every other day.

No dose reduction is required when pantoprazole is administered to patients with impaired kidney function (including dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole are dialysed. Although the main metabolite has a moderately delayed half-life (2-3 hours), excretion is still rapid and thus accumulation does not occur.

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

5.3 PRECLINICAL SAFETY DATA

Acute toxicity
In acute toxicity studies in mice, the LD_{50} values were found to be 370 mg/kg bodyweight for i.v. administration and around 700 mg/kg bodyweight for oral administration.
In the rat, the corresponding values were around 240 mg/kg for i.v. administration and 900 mg/kg for oral administration.

Chronic toxicity
Hypergastrinaemia and morphologic changes of the mucosa were observed in studies investigating repeated administration for up to 12 months in the rat and dog. Most of the effects were reversible and attributable solely to the drug action, i.e. suppression of acid secretion.

In long-term studies in the rat and dog, there was an increase in stomach and liver weights; the increase being reversible after the substance was discontinued. The increase in liver weight following highly toxic doses was seen as a result of the induction of drug-metabolising enzymes.

Thyroid activation in two rat experiments is due to the rapid metabolism of thyroid hormones in the liver and has also been described in a similar form for other drugs. Changes in the thyroid and associated reduced degradation of cholesterol have been observed in one-year

studies in the rat and dog. Hypertrophy of the thyroid and increases in cholesterol levels are reversible.

In studies in the dog, a species-species specific pulmonary oedema was observed. The animal-specific metabolite, which was responsible for the oedema, could not be identified in man.

Carcinogenicity
In a 2-year carcinogenicity study in rats - which corresponds to lifetime treatment for rats - ECL cell carcinoids were found. 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 treatment. In addition, rats have more ECL cells in the mucosa of the glandular stomach than man, so that a larger number of responder cells for the increased gastrin values can become active.

ECL cell neoplasms were not observed in either the study in mice (24 months) or in long-term studies in the dog. In clinical studies (40 - 80 mg for 1 year), ECL cell density slightly increased.

In the two-year studies, an increased number of neoplastic changes of the liver was observed in rats and female mice and was interpreted as being due to pantoprazole's high rate of metabolism in the liver.

A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose. The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. In man, no changes in the thyroid hormones T3, T4 and TSH were observed. This high dose phenomenon in the rat is therefore not relevant for man.

Mutagenicity
In mutagenicity studies, there were no indications of a mutagenic action *in vivo* or *in vitro.*

Reproduction toxicology
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, the concentration of pantoprazole in the foetus is increased shortly before birth, regardless of the route of administration.

In humans, there is no experience of the use of the drug during pregnancy.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol
Sodium carbonate anhydrous
Sodium starch glycolate, Type A
Methacrylic acid copolymer
Calcium stearate
Opadry white OY-D-7233 (hypromellose, titanium dioxide, talc, macrogol, sodium lauryl sulphate)
Kollicoat MAE 30 DP yellow (methacrylic acid-ethyl acrylate copolymer dispersion 30%, propylene glycol, yellow iron oxide, titanium dioxide, talc)

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

This medicinal product does not require any special storage conditions.

6.5 NATURE AND CONTENTS OF CONTAINER

Pantoprazole 40mg gastro-resistant tablets are provided in aluminium/aluminium blister packs of 2, 7, 14, 15, 28, 30, 50, 56, 60, 84, 90, 100, 112, 140, 280, 500, or 700 tablets.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegur 76-78
220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER(S)

PL 30306/0299

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/02/2010

10 DATE OF REVISION OF THE TEXT

08/02/2010

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

The below text was approved for this product at the end of the Change of Ownership (CoA) procedure. The Marketing Authorisation Holder is required to submit the mock-up of the leaflets to the regulatory authorities before marketing any pack size.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Pantoprazole 20 mg Gastro-resistant Tablets

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT PANTOPRAZOLE 20 mg GASTRO-RESISTANT TABLETS ARE AND WHAT THEY ARE USED FOR

Pantoprazole 20 mg Gastro-resistant Tablets are used to treat acid reflux (a type of heart-burn) and help prevent it from returning.
Pantoprazole 20 mg Gastro-resistant Tablets may also be given to patients who need to take non-selective non-steroidal anti-inflammatory drugs (NSAIDs) for a continuous period. These patients are at a greater risk of developing an ulcer and associated symptoms. Pantoprazole 20 mg Gastro-resistant Tablets help reduce the risk by preventing an ulcer from developing.

2. BEFORE YOU TAKE PANTOPRAZOLE 20 mg GASTRO-RESISTANT TABLETS

Do not take Pantoprazole 20 mg Gastro-resistant Tablets
- if you are allergic (hypersensitive) to pantoprazole or any of the other ingredients of Pantoprazole 20mg Gastro-resistant Tablets.

Take special care with Pantoprazole 20 mg Gastro-resistant Tablets
- if you have a liver disease

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

This applies particularly for:
- ketoconazole (to treat fungal infections of the skin and nails)

Inform your doctor if you are taking medicines to thin your blood, such as warfarin, phenprocoumon or acenocoumarol.

Taking vitamin supplements

Please tell your doctor or pharmacist if you are taking Vitamin B supplements as Pantoprazole 20 mg Gastro-resistant Tablets may affect how well Vitamin B is absorbed.

Taking Pantoprazole 20 mg Gastro-resistant Tablets with food and drink
Pantoprazole 20 mg Gastro-resistant Tablets should be taken before a meal with water. Do not crush, break or chew the tablet.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Pantoprazole 20 mg Gastro-resistant Tablets must only be used during pregnancy and lactation if clearly advised by your doctor.

Driving and using machines
Pantoprazole 20 mg Gastro-resistant Tablets do not affect the ability to drive and use machines.

3. HOW TO TAKE PANTOPRAZOLE 20 mg GASTRO-RESISTANT TABLETS

Always take Pantoprazole 20 mg Gastro-resistant Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is:

Mild reflux disease and associated symptoms (e.g. heartburn, acid regurgitation, pain on swallowing)

The recommended oral dosage is one Pantoprazole 20 mg Gastro-resistant Tablet per day. Symptom relief is generally accomplished within 2-4 weeks, and a 4-week treatment period is usually required for healing of associated oesophagitis. If this is not sufficient, healing will normally be achieved within a further 4 weeks. When symptom relief has been achieved, reoccurring symptoms can be controlled using an on-demand regimen of 20 mg once daily, when required. A switch to continuous therapy may be considered in case satisfactory symptom control cannot be maintained with on-demand treatment.

Long-term management and prevention of relapse in reflux oesophagitis

For long-term management, a maintenance dose of one Pantoprazole 20 mg Gastro-resistant Tablet per day is recommended, increasing to 40 mg pantoprazole per day if a relapse occurs. Pantoprazole 40 mg Gastro-resistant Tablets are available for this case. After healing of the relapse the dosage can be reduced again to 20 mg pantoprazole.

Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment

The recommended oral dosage is one Pantoprazole 20 mg Gastro-resistant Tablet per day.

Elderly:
No dose adjustment is necessary. Follow your doctor's instructions.

Children:
Pantoprazole 20 mg Gastro-resistant Tablets are not recommended for children.

Reduced kidney function:
No dose adjustment is necessary. Follow your doctor's instructions

Reduced liver function:
A daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver impairment.

General instructions:

Pantoprazole 20 mg Gastro-resistant Tablets should not be chewed or crushed, and should be swallowed whole with liquid before a meal.

If you take more Pantoprazole 20 mg Gastro-resistant Tablets than you should
Contact your doctor, emergency room or pharmacist if you have taken more Pantoprazole 20 mg Gastro-resistant Tablets than stated in this leaflet or more than your doctor has prescribed.

If you forget to take Pantoprazole 20 mg Gastro-resistant Tablets
Do not take a double dose to make up for a forgotten tablet.

If you stop taking Pantoprazole 20 mg Gastro-resistant Tablets
Keep taking the tablets until you have finished the course of treatment or until your doctor tells you to stop. Do not stop just because you feel better. If you stop taking your tablets too soon, your symptoms may return.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Pantoprazole 20 mg Gastro-resistant Tablets can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Common (they occur in between one and ten per 100 patients who receive treatment)
Stomach pain, diarrhoea, constipation, wind, headache.

Uncommon (they occur in between one and ten per 1000 patients who receive treatment)
Nausea, vomiting, dizziness, blurred vision, allergic reactions.

Rare (they occur in between one and ten per 10,000 patients who receive treatment)
Dry mouth, joint pain

Very rare (they occur in less than one per 10,000 patients who receive treatment)
Reduction in some cells in your blood, swollen ankles, liver damage leading to jaundice with or without liver failure, anaphylactic reactions, fever, muscle pain, mental depression, inflammation of the kidneys, nettle rash, severe skin reactions with blistering of the skin.

5. HOW TO STORE PANTOPRAZOLE 20 mg GASTRO-RESISTANT TABLETS

Keep out of the reach and sight of children.
This medicinal product requires no special storage conditions.

Do not take Pantoprazole 20 mg Gastro-resistant Tablets after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Pantoprazole 20 mg Gastro-resistant Tablets contain

- The active substance is pantoprazole (as pantoprazole sodium sesquihydrate).
  Each tablet contains 20 mg pantoprazole
- The other ingredients are:
  Mannitol
  Sodium carbonate anhydrous
  Sodium starch glycolate
  Methacrylic acid copolymer
  Calcium stearate
  Opadry white OY-D-7233 (hypromellose 3cP, titanium dioxide, talc, macrogol, sodium lauryl sulphate)
  Kollicoat MAE 30 DP yellow (methacrylic acid-ethyl acrylate copolymer dispersion 30%, propylene glycol, yellow iron oxide, titanium dioxide, talc)

What Pantoprazole 20 mg Gastro-resistant Tablets look like and contents of the pack

Pantoprazole 20mg Gastro-resistant Tablets are elliptical, biconvex, light yellow gastro-resistant tablets.

Pack sizes:

(only the actual marketed pack sizes will be stated on the leaflet)

Pantoprazole 20 mg Gastro-resistant Tablets are supplied in blister packs of 7, 14, 15, 28, 30, 50, 56, 60, 84, 90, 100, 112, 140, 280, 500, or 700 tablets.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Actavis Group PTC ehf
Reykjavikurvegur 76-78
220 Hafnarfjordur
Iceland

Manufacturer:*

Actavis hf
Reykjavikurvegur 78
IS-220 Hafnarfjordur
Iceland

Actavis Ltd
BLB016 Bulebel Industrial Estate
Zejtun ZTN 3000
Malta

*(the actual leaflet will only refer to the batch release site that is utilised)

This leaflet was last approved in {MM/YYYY}.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Pantoprazole 40 mg Gastro-resistant Tablets

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT PANTOPRAZOLE 40 mg GASTRO-RESISTANT TABLETS ARE AND WHAT THEY ARE USED FOR

Pantoprazole 40 mg Gastro-resistant Tablets are used to treat acid reflux (a type of heartburn) and ulcers in the stomach (gastric ulcer) or in the upper part of the intestine (duodenal ulcer). Pantoprazole 40 mg Gastro-resistant Tablets are also used for the long-term treatment of people who secrete too much acid in conditions such as Zollinger-Ellison syndrome.

2. BEFORE YOU TAKE PANTOPRAZOLE 40 mg GASTRO-RESISTANT TABLETS

Do not take Pantoprazole 40 mg Gastro-resistant Tablets
- if you are allergic (hypersensitive) to pantoprazole or any of the other ingredients of Pantoprazole 40 mg Gastro-resistant Tablets.

Take special care with Pantoprazole 40 mg Gastro-resistant Tablets
- if you have a liver disease

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

This applies particularly for:
- ketoconazole (to treat fungal infections of the skin and nails)

Inform your doctor if you are taking medicines to thin your blood, such as warfarin, phenprocoumon or acenocoumarol.

Taking vitamin supplements
Please tell your doctor or pharmacist if you are taking Vitamin B supplements as Pantoprazole 40 mg Gastro-resistant Tablets may affect how well Vitamin B is absorbed.

Taking Pantoprazole 40 mg Gastro-resistant Tablets with food and drink
Pantoprazole 40 mg Gastro-resistant Tablets should be taken before a meal with water. Do not crush, break or chew the tablet.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

Pantoprazole 40 mg Gastro-resistant Tablets must only be used during pregnancy and lactation if clearly advised by your doctor.

Driving and using machines
Pantoprazole 40 mg Gastro-resistant Tablets do not affect the ability to drive and use machines

3. HOW TO TAKE PANTOPRAZOLE 40 mg GASTRO-RESISTANT TABLETS

Always take Pantoprazole 40 mg Gastro-resistant Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose is:

• The usual dose for the treatment of acid reflux, a gastric and duodenal ulcer is one tablet taken in the morning, with or without food.

• The usual starting dose for the treatment of Zollinger-Ellison syndrome is one tablet taken twice a day. You should take the first tablet in the morning and the second tablet just before your evening meal. Your doctor may then adjust the dosage, depending on how much medicine is required for your treatment.

Ask your doctor or pharmacist if you are unsure about anything.

Elderly:

No dose adjustment is necessary. However, 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.

Children:

Pantoprazole 40mg Gastro-resistant Tablets are not recommended for use in children below 12 years.

Patients with impaired kidney function:

No dose adjustment is necessary. However, the daily dose of 40mg pantoprazole should not be exceeded. For this reason, *H. pylori* triple therapy is not appropriate in these patients.

Patients with liver cirrhosis:

The dose should be reduced to one tablet every other day. For this reason, *H. pylori* triple therapy is not appropriate in these patients.

General instructions:

Pantoprazole 40 mg Gastro-resistant Tablets should not be chewed or crushed, and should be swallowed whole with liquid.

If you take more Pantoprazole 40 mg Gastro-resistant Tablets than you should

- The other ingredients are:
  Mannitol
  Sodium carbonate anhydrous
  Sodium starch glycolate
  Methacrylic acid copolymer
  Calcium stearate
  Opadry white OY-D-7233 (hypromellose, titanium dioxide, talc, macrogol, sodium lauryl sulphate)
  Kollicoat MAE 30 DP yellow (methacrylic acid-ethyl acrylate copolymer dispersion 30%, propylene glycol, yellow iron oxide, titanium dioxide, talc)

What Pantoprazole 40 mg Gastro-resistant Tablets look like and contents of the pack

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(only the actual marketed pack sizes will be stated on the leaflet)

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220 Hafnarfjordur
Iceland

Manufacturer:*

Actavis hf
Reykjavikurvegur 78
IS-220 Hafnarfjordur
Iceland

Actavis Ltd
BLB016 Bulebel Industrial Estate
Zejtun ZTN 3000
Malta

*(the actual leaflet will only refer to the batch release site that is utilised)

This leaflet was last approved in {MM/YYYY}.

The below text was approved for this product at the end of the Change of Ownership (CoA) procedure The Marketing Authorisation Holder is required to submit the mock-up of the labelling to the regulatory authorities before marketing any pack size.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Outer Cartons

1. NAME OF THE MEDICINAL PRODUCT

Pantoprazole 20 mg Gastro-resistant Tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant tablet contains 22.58 mg pantoprazole sodium sesquihydrate equivalent to 20 mg pantoprazole

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

7 gastro-resistant tablets
14 gastro-resistant tablets
15 gastro-resistant tablets
28 gastro-resistant tablets
30 gastro-resistant tablets
50 gastro-resistant tablets
56 gastro-resistant tablets
60 gastro-resistant tablets
84 gastro-resistant tablets
90 gastro-resistant tablets
100 gastro-resistant tablets
112 gastro-resistant tablets
140 gastro-resistant tablets
280 gastro-resistant tablets
500 gastro-resistant tablets
700 gastro-resistant tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use only.
To be taken as directed by your doctor.
Read the package leaflet before use.
Swallow whole, do not chew.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Expiry Date:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Actavis Group PTC ehf
Reykjavikurvegur 76-78
220 Hafnarfjordur
Iceland

12. MARKETING AUTHORISATION NUMBER(S)

PL 30306/0298

13. BATCH NUMBER

Batch Number:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pantoprazole 20 mg gastro-resistant tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Strips

1. NAME OF THE MEDICINAL PRODUCT

Pantoprazole 20 mg Gastro-resistant Tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

BN:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Outer Cartons

1. NAME OF THE MEDICINAL PRODUCT

Pantoprazole 40 mg Gastro-resistant Tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant tablet contains 45.16 mg pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

2 gastro-resistant tablets
7 gastro-resistant tablets
14 gastro-resistant tablets
15 gastro-resistant tablets
28 gastro-resistant tablets
30 gastro-resistant tablets
50 gastro-resistant tablets
56 gastro-resistant tablets
60 gastro-resistant tablets
84 gastro-resistant tablets
90 gastro-resistant tablets
100 gastro-resistant tablets
112 gastro-resistant tablets
140 gastro-resistant tablets
280 gastro-resistant tablets
500 gastro-resistant tablets
700 gastro-resistant tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use only.
To be taken as directed by your doctor.
Read the package leaflet before use.
Swallow whole, do not chew.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Expiry Date:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Actavis Group PTC ehf
Reykjavikurvegur 76-78
220 Hafnarfjordur
Iceland

12. MARKETING AUTHORISATION NUMBER(S)

PL 30306/0299

13. BATCH NUMBER

Batch Number:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

pantoprazole 40 mg gastro-resistant tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Strips

1. NAME OF THE MEDICINAL PRODUCT

Pantoprazole 40 mg Gastro-resistant Tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

BN:

5. OTHER

Annex 1

Reference:	PL 30306/0298-0005 and PL 30306/0299-0005
Product(s):	Pantoprazole 20 mg and 40 mg Gastro-resistant Tablets
Marketing Authorisation Holder:	Activis Group PTC ehf
Active Ingredient(s):	Pantoprazole sodium sesquihydrate

Reason:
To update Sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the Summary of Product Characteristics (SmPC) in line with the Article 30 referral for Protium (pantoprazole). Consequently, the Patient Information Leaflet (PIL) has also been updated.

Supporting Evidence
Revised SmPC and PILs have been provided. The currently approved labelling is acceptable and needs no further revision.

Evaluation
The amended sections of the SmPC and the amended PIL are satisfactory. These are provided below:

Amended sections for the SmPC for Pantoprazole 20 mg Gastro-resistant Tablets (PL 30606/0298):

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Adults and adolescents 12 years of age and above
Symptomatic gastro-oesophageal reflux disease.

For long-term management and prevention of relapse in reflux oesophagitis.

Adults
Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment (see section 4.4).

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

General instructions:
Tablets should not be chewed or crushed, and should be swallowed whole 1 hour before a meal with some water.

Recommended dose
Adults and adolescents 12 years of age and above

Symptomatic gastro-oesophageal reflux disease
The recommended oral dose is one pantoprazole 20 mg gastro-resistant tablet per day. Symptom relief is generally accomplished within 2-4 weeks. If this is not sufficient, symptom relief will normally be achieved within a further 4 weeks. When symptom relief has been achieved, reoccurring symptoms can be controlled using an on-demand regimen of 20 mg once daily, when required. A switch to continuous therapy may be considered in case satisfactory symptom control cannot be maintained with on-demand treatment.

Long-term management and prevention of relapse in reflux oesophagitis
For long-term management, a maintenance dose of one pantoprazole 20 mg gastro-resistant tablet per day is recommended, increasing to 40 mg pantoprazole per day if a relapse occurs.

Pantoprazole 40 mg is available for this case. After healing of the relapse the dose can be reduced again to 20 mg pantoprazole.

Adults
Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment
The recommended oral dose is one pantoprazole 20 mg gastro-resistant tablet per day.

Special populations

Children below 12 years of age
Pantoprazole is not recommended for use in children below 12 years of age due to limited data on safety and efficacy in this age group.

Hepatic Impairment
A daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver impairment (see section 4.4).

Renal Impairment
No dose adjustment is necessary in patients with impaired renal function.

Elderly
No dose adjustment is necessary in elderly patients.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance, substituted benzimidazoles or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hepatic Impairment
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 Pantoprazole 20mg gastro-resistant tablets should be discontinued.

Co-administration with NSAIDs
The use of Pantoprazole 20mg gastro-resistant tablets as a preventive of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) should be restricted to patients who require continued NSAID treatment and have an increased risk to develop gastrointestinal complications.

The increased risk should be assessed according to individual risk factors, e.g. high age >65 years), history of gastric or duodenal ulcer or upper gastrointestinal bleeding.

In presence of alarm symptoms
In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis.

Further investigation is to be considered if symptoms persist despite adequate treatment.

<u>Co-administration with atazanavir</u>
Co-administration of atazanavir with proton pump inhibitors is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g virus load) is recommended in combination with an increase in the dose of atazanavir to 400mg with 100mg of ritonavir. A pantoprazole dose of 20mg per day should not be exceeded.

Influence on vitamin B12 absorption
Pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy or if respective clinical symptoms are observed.

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

Gastrointestinal infections caused by bacteria
Pantoprazole, like all proton pump inhibitors (PPIs), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with Pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter*.

Note:
Prior to treatment a malignant disease of the oesophagus or stomach should be excluded as the treatment with pantoprazole may alleviate the symptoms of malignant diseases and can thus delay diagnosis.

Patients who do not respond after 4 weeks should be investigated.

There is no experience in children.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Effect of pantoprazole on the absorption of other medicinal products
Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may reduce the absorption of drugs with a gastric pH dependent bioavailability, e.g some azole antifungals as ketoconazole, itraconazole, posaconazole and other medicine as erlotinib.

HIV medications (atazanavir)
Co-administration of atazanavir and other HIV medications whose absorption is pH-dependent with proton-pump inhibitors might result in a substantial reduction in the bioavailability of these HIV medications and might impact the efficacy of these medicines. Therefore, the co-administration of proton pump inhibitors with atazanavir is not recommended (see section 4.4).

Coumarin anticoagulants (phenprocoumon or warfarin)
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.

Other interactions studies
Pantoprazole is extensively metabolized in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4.

Interaction studies with drugs also metabolized with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, and an oral contraceptive containing levonorgestrel and ethinyl oestradiol did not reveal clinically significant interactions.

Results from a range of interaction studies demonstrate that pantoprazole does not effect the metabolism of active substances metabolised by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol) or does not interfere with p-glycoprotein related absorption of digoxin.

There were also no interactions with concomitantly administered antacids.

Interaction studies have also been performed administering pantoprazole concomitantly with the respective antibiotics (clarithromycin, metronidazole, amoxicillin) No clinically relevant interactions were found.

4.6 PREGNANCY AND LACTATION

Pregnancy

There are no adequate data from the use of pantoprazole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Pantoprazole should not be used during pregnancy unless clearly necessary.

Lactation

Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported. Therefore a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with pantoprazole should be made taking into account the benefit of breastfeeding to the child and the benefit of pantoprazole therapy to women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machines.

4.8 UNDESIRABLE EFFECTS

Approximately 5 % of patients can be expected to experience adverse drug reactions (ADRs). The most commonly reported ADRs are diarrhoea and headache, both occurring in approximately 1 % of patients.

The table below lists adverse reactions reported with pantoprazole, ranked under the following frequency classification:
very common (≥1/10);
common (≥1/100 to <1/10);
uncommon (≥1/1,000 to <1/100);
rare (≥1/10,000 to <1/1,000);
very rare (<1/10,000),
not known (cannot be estimated from the available data).

For all adverse reactions reported from post-marketing experience, it is not possible to apply any Adverse Reaction frequency and therefore they are mentioned with a “not known” frequency.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. Adverse reactions with pantoprazole in clinical trials and post-marketing experience

Frequency Organ system	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system			Thrombocytopenia Leukopenia;	
Immune system disorders		Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutritional disorders		Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes		Hyponatraemia
Psychiatric disorders	Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggravations)	Hallucination; Confusion (especially in pre-disposed patients, as

Frequency Organ system	**Uncommon**	**Rare**	**Very rare**	**Not known**
				well as the aggravation of these symptoms in case of pre-existence)
Nervous system disorders	Headache; Dizziness			
Eye disorders		Disturbances in vison/ blurred vision		
Gastrointestinal Disorders	Diarrhoea; Nausea/vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort Flatulence			
Hepatobiliary disorders	Liver enzymes increased (transaminases, γ-GT)	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and sub-cutaneous tissue disorders	Rash/exanthema eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity
Musculoskeletal, connective tissue disorders		Arthralgia; Myalgia		
Renal and urinary disorders				Interstitial nephritis
Reproductive system and breast disorders		Gynaecomastia		
General disorders and administration site conditions	Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		

4.9 OVERDOSE

There are no known symptoms of overdose in man.

Systemic exposure with up to 240mg administered intravenously over 2 minutes were well tolerated.

As pantoprazole is extensively protein bound, it is not readily dialysable.
In the case of overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

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 under 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) have not been observed in humans.

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

Absorption

Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 20 mg oral dose. On average at about 2.0 h - 2.5 h p.a. the maximum serum concentrations of about 1-1.5 µg/ml are achieved, and these values remain constant after multiple administration. 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.

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.

Distribution

Pantoprazole's serum protein binding is about 98 %. Volume of distribution is about 0.15 l/kg

Elimination

The substance is almost exclusively metabolized in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, other metabolic pathway include oxidation by CYP3A4. Terminal half-life is about 1 hour and clearance is about 0.1 l/h/kg. 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).

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 hours) is not much longer than that of pantoprazole.

Characteristics in patients/special groups of subjects

Approximately 3 % of the European population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of pantoprazole is probably mainly catalysed by CYP3A4. After a single-dose administration of 40 mg pantoprazole, the mean area under the plasma concentration-time curve was approximately 6 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60 %. These findings have no implications for the posology of pantoprazole.

No dose reduction is recommended when pantoprazole is administered to patients with impaired renal function (including dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole are dialyzed. Although the main

metabolite has a moderately delayed halflife (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.

Children

Following administration of single oral doses of 20 or 40 mg pantoprazole to children aged 5 - 16 years AUC and Cmax were in the range of corresponding values in adults.

Following administration of single i.v. doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2 – 16 years there was no significant association between pantoprazole clearance and age or weight. AUC and volume of distribution were in accordance with data from adults.

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 two-year carcinogenicity studies in rats neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats. 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 two-year rodent studies an increased number of liver tumors was observed in rats 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). 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 harmful effects on the thyroid glands are expected.

In animal reproduction studies, signs of slight fetotoxicity were observed at doses above 5 mg/kg. 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.

Amended sections for the SmPC for Pantoprazole 40 mg Gastro-resistant Tablets (PL 30606/0299):

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Adults and adolescents 12 years of age and above

- Reflux oesophagitis.

Adults

- Eradication of *Helicobacter pylori* (*H. pylori*) in combination with appropriate antibiotic therapy in patients with *H. pylori* associated ulcers.
- Gastric and duodenal ulcer.
- Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Tablets should not be chewed or crushed, and should be swallowed whole 1 hour before a meal with some water.

Recommended dose

Adults and adolescents 12 years of age and above

Reflux oesophagitis

One tablet of Pantoprazole tablets per day. In individual cases the dose may be doubled (increase to 2 tablets Pantoprazole tablets daily) especially when there has been no response to other treatment. A 4-week period is usually required for the treatment of reflux oesophagitis. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

Adults

Eradication of *H. pylori* in combination with two appropriate antibiotics in *H. pylori* positive patients with gastric and duodenal ulcers, eradication of the germ by a combination therapy should be achieved. Considerations should be given to official local guidance (e.g. national recommendations) regarding bacterial resistance and the appropriate use and prescription of antibacterial agents. Depending upon the resistance pattern, the following combinations can be recommended for the eradication of *H. pylori*:

a) twice daily one tablet Pantoprazole tablets
   + twice daily 1000 mg amoxicillin
   + twice daily 500 mg clarithromycin
b) twice daily one tablet Pantoprazole tablets
   + twice daily 400 - 500 mg metronidazole (or 500 mg tinidazole)
   + twice daily 250 - 500 mg clarithromycin
c) twice daily one tablet Pantoprazole tablets
   + twice daily 1000 mg amoxicillin
   + twice daily 400 - 500 mg metronidazole (or 500 mg tinidazole)

In combination therapy for eradication of *H. pylori* infection, the second Pantoprazole tablets tablet should be taken 1 hour before the evening meal. The combination therapy is implemented for 7 days in general and can be prolonged for a further 7 days to a total duration of up to two weeks. If, to ensure healing of the ulcers, further treatment with pantoprazole is indicated, the dose recommendations for duodenal and gastric ulcers should be considered.

If combination therapy is not an option, e.g. if the patient has tested negative for *H. pylori*, the following dose guidelines apply for Pantoprazole tablets monotherapy:

Treatment of gastric ulcer

One tablet of Pantoprazole tablets per day. In individual cases the dose may be doubled (increase to 2 tablets Pantoprazole tablets daily) especially when there has been no response to other treatment. 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.

Treatment of duodenal ulcer

One tablet of Pantoprazole tablets per day. In individual cases the dose may be doubled (increase to 2 tablets Pantoprazole tablets daily) especially when there has been no response to other treatment. A duodenal ulcer generally heals 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.

Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions
For the long-term management of Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions patients should start their treatment with a daily dose of 80 mg (2 tablets of Pantoprazole tablets 40 mg). Thereafter, the dose can be titrated up or down as needed using measurements 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 dose 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.

Special populations
Children below 12 years of age
Pantoprazole tablets is not recommended for use in children below 12 years of age due to limited data on safety and efficacy in this age group.

Hepatic Impairment
A daily dose of 20 mg pantoprazole (1 tablet of 20 mg pantoprazole) should not be exceeded in patients with severe liver impairment. Pantoprazole tablets must not be used in combination treatment for eradication of *H. pylori* in patients with moderate to severe hepatic dysfunction since currently no data are available on the efficacy and safety of Pantoprazole tablets in combination treatment of these patients (see section 4.4).

Renal Impairment
No dose adjustment is necessary in patients with impaired renal function. Pantoprazole tablets must not be used in combination treatment for eradication of *H. pylori* in patients with impaired renal function since currently no data are available on the efficacy and safety of Pantoprazole tablets in combination treatment for these patients.

Elderly
No dose adjustment is necessary in elderly patients.

4.3 CONTRA-INDICATIONS
Hypersensitivity to the active substance, substituted benzimidazoles or to any of the excipients

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Hepatic Impairment
In patients with severe liver impairment, particularly those on long-term use, liver enzymes should be monitored regularly during treatment with pantoprazole. In the case of a rise in liver enzymes, pantoprazole 40mg gastro-resistant tablets should be discontinued.

Combination therapy
In the case of combination therapy, the summaries of product characteristics of the respective medicinal products should be observed.

In presence of alarm symptoms
In the presence of any alarm symptom (e. g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis.

Further investigation is to be considered if symptoms persist despite adequate treatment.

Co-administration with atazanavir
Co-administration of atazanavir with proton pump inhibitors is not recommended (see section 4.5). If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g virus load) is recommended in combination with an increase in the dose of atazanavir to 400mg with 100mg of ritonavir. A pantoprazole dose of 20mg per day should not be exceeded.

Influence on vitamin B12 absorption
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 in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy or if respective clinical symptoms are observed.

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

Gastrointestinal infections caused by bacteria
Pantoprazole, like all proton pump inhibitors (PPIs), might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with Pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella and Campylobacter*.

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

Note:
Prior to treatment of gastric ulcer, the possibility of malignancy should be excluded as treatment with pantoprazole 40mg gastro-resistant tablets may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Effect of pantoprazole on the absorption of other medicinal products
Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may reduce the absorption of drugs with a gastric pH dependent bioavailability, e.g some azole antifungals as ketoconazole, itraconazole, posaconazole and other medicine as erlotinib.

HIV medications (atazanavir)
Co-administration of atazanavir and other HIV medications whose absorption is pH-dependent with proton-pump inhibitors might result in a substantial reduction in the bioavailability of these HIV medications and might impact the efficacy of these medicines. Therefore, the co-administration of proton pump inhibitors with atazanavir is not recommended (see section 4.4).

Coumarin anticoagulants (phenprocoumon or warfarin)
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.

Other interactions studies
Pantoprazole is extensively metabolized in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4. Interaction studies with drugs also metabolized with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, and an oral contraceptive containing levonorgestrel and ethinyl oestradiol did not reveal clinically significant interactions.

Results from a range of interaction studies demonstrate that pantoprazole does not effect the metabolism of active substances metabolised by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol) or does not interfere with p-glycoprotein related absorption of digoxin.

There were no interactions with concomitantly administered antacids.

Interaction studies have also been performed administering pantoprazole concomitantly with the respective antibiotics (clarithromycin, metronidazole, amoxicillin) No clinically relevant interactions were found.

4.6 PREGNANCY AND LACTATION

Pregnancy

There are no adequate data from the use of pantoprazole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Pantoprazole should not be used during pregnancy unless clearly necessary.

Lactation

Animal studies have shown excretion of pantoprazole in breast milk. Excretion into human milk has been reported. Therefore a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with pantoprazole should be made taking into account the benefit of breastfeeding to the child and the benefit of pantoprazole therapy to women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Adverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machines.

4.8 UNDESIRABLE EFFECTS

Approximately 5 % of patients can be expected to experience adverse drug reactions (ADRs). The most commonly reported ADRs are diarrhoea and headache, both occurring in approximately 1 % of patients.

The table below lists adverse reactions reported with pantoprazole, ranked under the following frequency classification:
very common (≥1/10);
common (≥1/100 to <1/10);
uncommon (≥1/1,000 to <1/100);
rare (≥1/10,000 to <1/1,000);
very rare (<1/10,000),
not known (cannot be estimated from the available data).
For all adverse reactions reported from post-marketing experience, it is not possible to apply any Adverse Reaction frequency and therefore they are mentioned with a “not known” frequency.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions with pantoprazole in clinical trials and post-marketing experience

Frequency Organ system	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system			Thrombocytopenia Leukopenia;	
Immune system disorders		Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutritional disorders		Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes		Hyponatraemia
Psychiatric disorders	Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggravations)	Hallucination; Confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence)
Nervous system disorders	Headache; Dizziness			
Eye disorders		Disturbances in vison/ blurred vision		
Gastrointestinal Disorders	Diarrhoea; Nausea/vomiting; Abdominal distension and bloating; Constipation; Dry mouth; Abdominal pain and discomfort Flatulence			
Hepatobiliary disorders	Liver enzymes increased (transaminases, γ-GT)	Bilirubin increased		Hepatocellular injury; Jaundice; Hepatocellular failure
Skin and sub-cutaneous tissue disorders	Rash/exanthema eruption; Pruritus	Urticaria; Angioedema		Stevens-Johnson syndrome; Lyell syndrome; Erythema multiforme; Photosensitivity
Musculoskeletal, connective tissue disorders		Arthralgia; Myalgia		
Renal and urinary disorders				Interstitial nephritis
Reproductive system and breast disorders		Gynaecomastia		
General disorders and administration site conditions	Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		

4.9 OVERDOSE

There are no known symptoms of overdose in man.
Systemic exposure with up to 240mg administered intravenously over 2 minutes were well tolerated.
As pantoprazole is extensively protein bound, it is not readily dialysable.
In the case of overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: proton pump inhibitors, ATC code: A02BC02
Mechanism of action
Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific blockade of the proton pumps of the parietal cells.

Pantoprazole is converted to its active form in the acidic environment in 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 within 2 weeks. As with other proton pump inhibitors and H_2 receptor inhibitors, treatment with pantoprazole reduces acidity in the stomach and thereby increases 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, it can inhibit 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 under pantoprazole. On short-term use, in most cases they do not exceed the upper limit of normal. 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 longterm 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) have not been observed in humans.

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

5.2 PHARMACOKINETIC PROPERTIES

General pharmacokinetics
Absorption
Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 40mg oral dose. On average at about 2.5 h p.a. the maximum serum concentrations of about 2 - 3 µg/ml are achieved, and these values remain constant after multiple administration.

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

Distribution
Pantoprazole's serum protein binding is about 98 %. Volume of distribution is about 0.15 l/kg

Elimination
The substance is almost exclusively metabolized in the liver. The main metabolic pathway is demethylation by CYP2C19 with subsequent sulphate conjugation, other metabolic pathway include oxidation by CYP3A4. Terminal half-life is about 1 hour and clearance is about 0.1 l/h/kg. 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).

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 hours) is not much longer than that of pantoprazole.

Characteristics in patients/special groups of subjects
Approximately 3 % of the European population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of pantoprazole is probably mainly catalysed by CYP3A4. After a single-dose administration of 40 mg pantoprazole, the mean area under the plasma concentration-time curve was approximately 6 times higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were increased by about 60 %. These findings have no implications for the posology of pantoprazole.

No dose reduction is recommended when pantoprazole is administered to patients with impaired renal function (including dialysis patients). As with healthy subjects, pantoprazole's half-life is short. Only very small amounts of pantoprazole are dialyzed. Although the main metabolite has a moderately delayed halflife (2 - 3 h), 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 7 and 9 h and the AUC values increased by a factor of 5 - 7, the maximum serum concentration only increased slightly by a factor of 1.5 compared with healthy subjects.

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

Children
Following administration of single oral doses of 20 or 40 mg pantoprazole to children aged 5 - 16 years AUC and Cmax were in the range of corresponding values in adults.

Following administration of single i.v. doses of 0.8 or 1.6 mg/kg pantoprazole to children aged 2 - 16 years there was no significant association between pantoprazole clearance and age or weight. AUC and volume of distribution were in accordance with data from adults.

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 two-year carcinogenicity studies in rats neuroendocrine neoplasms were found. In addition, squamous cell papillomas were found in the forestomach of rats. 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 two-year rodent studies an increased number of liver tumors was observed in rats 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). 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 harmful effects on the thyroid glands are expected.

In animal reproduction studies, signs of slight fetotoxicity were observed at doses above 5 mg/kg. 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.

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Pantoprazole 20mg Gastro-resistant Tablets

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- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
- The full name of this medicine is Pantoprazole 20mg Gastro-resistant Tablets but within the leaflet it will be referred to as Pantoprazole tablets.

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Adults and adolescents 12 years of age and above:
- Treating symptoms (e.g. heartburn, acid regurgitation, pain on swallowing) associated to gastro-oesophageal reflux disease caused by reflux of acid from the stomach.
- Long-term management of reflux oesophagitis (inflammation of the oesophagus accompanied by the regurgitation of stomach acid) and preventing its return.

Adults:
- Preventing duodenal and stomach ulcers caused by non-steroidal anti-inflammatory drugs (NSAIDs, for example, ibuprofen) in patients at risk who need to take NSAIDs continuously.

2 Before you take

Do not take Pantoprazole tablets if you
- are **allergic** (hypersensitive) **to pantoprazole**, or any of the other ingredients of Pantoprazole tablets.
- are **allergic to** medicines containing other **proton pump inhibitors**.

Take special care with Pantoprazole tablets if you
- have severe **liver problems**. Please tell your doctor if you have ever had problems with your liver. He will check your liver enzymes more frequently, especially when you are taking Pantoprazole tablets as a long-term treatment. In the case of a rise of liver enzymes the treatment should be stopped.

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- need to take medicines called **NSAIDs** continuously and receive Pantoprazole tablets because you have an increased risk of developing stomach and intestinal complications. Any increased risk will be assessed according to your own personal risk factors such as your age (65 years old or more), a history of stomach or duodenal ulcers or of stomach or intestinal bleeding.
- have reduced body stores or risk factors for reduced **vitamin B12** and receive pantoprazole long-term treatment. As with all acid reducing agents, pantoprazole may lead to a reduced absorption of vitamin B12.
- are taking a medicine containing **atazanavir** (for the treatment of HIV-infection) at the same time as pantoprazole, ask your doctor for specific advise.

Tell your doctor immediately if you notice any of the following symptoms:
- an unintentional loss of weight
- repeated vomiting
- difficulty in swallowing
- vomiting blood
- you look pale and feel weak (anaemia)
- you notice blood in your stools
- severe and/or persistent diarrhoea as pantoprazole has been associated with a small increase in infectious diarrhoea.

Your doctor may decide that you need some tests to rule out malignant disease because pantoprazole also alleviates the symptoms of cancer and could cause a delay in diagnosing it. If your symptoms continue in spite of your treatment, further investigations will be considered.

If you take Pantoprazole tablets on a long-term basis (longer than 1 year) your doctor will probably keep you under regular surveillance. You should report any new and exceptional symptoms and circumstances whenever you see you doctor.

Taking other medicines
Pantoprazole tablets may influence the effectiveness of other medicines, so tell your doctor if you are taking

- Medicines such as **ketoconazole**, **itraconazole** and **posaconazole** (used to treat fungal infections) or **erlotinib** (used for certain types of cancer) because Pantoprazole tablets may stop these and other medicines from working properly.
- **Warfarin** and **phenprocoumon**, which affect the thickening, or thinning of the blood. You may need further checks.
- **Atazanavir** (used to treat HIV-infection).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
There are no adequate data from the use of pantoprazole in pregnant women. Excretion into human milk has been reported. If you are pregnant, or think you may be pregnant, or if you are breast-feeding, you should use this medicine only if your doctor considers the benefit for you greater than the potential risk for your unborn child or baby.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
If you experience side effects like dizziness or disturbed vision, you should not drive or operate machines.

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3 How to take

Always take Pantoprazole tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

When and how should you take Pantoprazole tablets

Take the tablets 1 hour before a meal without chewing or breaking them and swallow them whole with some water.

Unless told otherwise by your doctor, the usual dose is:

Adults and adolescents 12 years of age and above:
To treat symptoms (e.g. heartburn, acid regurgitation, pain on swallowing) associated to gastro-oesophageal reflux disease
The usual dose is one tablet a day. This dose usually brings relief within 2 - 4 weeks – at most after another 4 weeks. Your doctor will tell you how long to continue taking the medicine. After this any recurring symptoms can be controlled by **taking one tablet daily**, when required.

For long-term management and for preventing the return of reflux oesophagitis
The usual dose is one tablet a day. If the illness returns, your doctor can double the dose, in which case you can use Pantoprazole 40mg tablets instead, one a day. After healing, you can reduce the dose back again to one tablet 20mg a day.

Adults:
To prevent duodenal and stomach ulcers in patients who need to take NSAIDs continuously
The usual dose is one tablet a day.

Special patient groups
- If you suffer from **severe liver problems**, you should not take more than one 20mg tablet a day.
- **Children below 12 years**. These tablets are not recommended for use in children below 12 years.

If you take more Pantoprazole tablets than you should

Tell your doctor or pharmacist. There are no known symptoms of overdose.

If you forget to take Pantoprazole tablets

Do not take a double dose to make up for a forgotten tablet. Take your next normal dose at the usual time.

If you stop taking Pantoprazole tablets

Do not stop taking these tablets without first talking to your doctor or pharmacist. If you have any further questions about the use of this product, ask your doctor or pharmacist.

4 Possible side effects

Like all medicines, Pantoprazole tablets can cause side effects, although not everybody gets them.

If you get any of the following side effects, stop taking these tablets and tell your doctor immediately, or contact the casualty department at your nearest hospital:
- **Serious allergic reactions (frequency rare):** swelling of the tongue and/or throat, difficulty in swallowing, hives (nettle rash), difficulties in breathing, allergic facial swelling (Quincke's oedema / angioedema), severe dizziness with very fast heartbeat and heavy sweating.
- **Serious skin conditions (frequency not known):** blistering of the skin and rapid deterioration of your general condition, erosion (including slight bleeding) of eyes, nose, mouth/lips or genitals (Stevens-Johnson-Syndrome, Lyell-Syndrome, Erythema multiforme) and sensitivity to light.
- **Other serious conditions (frequency not known):** yellowing of the skin or whites of the eyes (severe damage to liver cells, jaundice) or fever, rash, and enlarged kidneys sometimes with painful urination and lower back pain (serious inflammation of the kidneys).

Other side effects are:
Uncommon (affects 1 to 10 users in 1,000)**:** headache; dizziness; diarrhoea; feeling sick, vomiting; bloating and flatulence (wind); constipation; dry mouth; abdominal pain and discomfort; skin rash, exanthema, eruption; itching; feeling weak, exhausted or generally unwell; sleep disorders.
Rare (affects 1 to 10 users in 10,000)**:** disturbances in vision such as blurred vision; hives; pain in the joints; muscle pains; weight changes; raised body temperature; swelling of the extremities (peripheral oedema); allergic reactions; depression; breast enlargement in males.
Very Rare (affects less than 1 user in 10,000)**:** disorientation.
Not known (frequency cannot be estimated from the available data)**:** hallucination, confusion (especially in patients with a history of these symptoms); decreased sodium level in blood.

Side effects identified through blood tests:
Uncommon (affects 1 to 10 users in 1,000); an increase in liver enzymes.
Rare (affects 1 to 10 users in 10,000); an increase in bilirubin; increased fats in the blood.
Very Rare (affects less than 1 user in 10,000); a reduction in the number of blood platelets, which may cause you to bleed or bruise more than normal; a reduction in the number of white blood cells, which may lead to more frequent infections.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5 How to store

Keep out of the reach and sight of children.
Do not take Pantoprazole tablets after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.
This medicine does not require any special storage conditions.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 Further information

What Pantoprazole tablets contain

- The active substance is pantoprazole. Each gastro-resistant tablet contains 20mg of pantoprazole (as sodium sesquihydrate).
- The other ingredients are:
  Mannitol, Sodium carbonate anhydrous, Sodium starch glycolate, Methacrylic acid copolymer, Calcium stearate, Opadry white OY-D-7233 (hypromellose 3cP, titanium dioxide, talc, macrogol, sodium lauryl sulphate), Kollicoat MAE 30 DP yellow (methacrylic acid-ethyl acrylate copolymer dispersion 30%, propylene glycol, yellow iron oxide, titanium dioxide, talc)

What Pantoprazole tablets look like and contents of the pack

Pantoprazole 20mg Gastro-resistant Tablets are elliptical, biconvex, light yellow gastro-resistant tablets.

Pack sizes: 28

Marketing Authorisation Holder:
Actavis Group PTC ehf
Reykjavikurvegur 76-78
220 Hafnarfjordur
Iceland

Manufacturer:
Balkanpharma – Dupnitsa AD
3 Samokovsko Schosse Str.,
Dupnitsa 2600
Bulgaria

This leaflet was last revised in June 2011

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Actavis, Barnstaple, EX32 8NS, UK

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- The other ingredients are:
  Mannitol, Sodium carbonate anhydrous, Sodium starch glycolate, Methacrylic acid copolymer, Calcium stearate, Opadry white OY-D-7233 (hypromellose 3cP, titanium dioxide, talc, macrogol, sodium lauryl sulphate), Kollicoat MAE 30 DP yellow (methacrylic acid-ethyl acrylate copolymer dispersion 30%, propylene glycol, yellow iron oxide, titanium dioxide, talc)

What Pantoprazole tablets look like and contents of the pack

Pantoprazole 20mg Gastro-resistant Tablets are elliptical, biconvex, light yellow gastro-resistant tablets.

Pack sizes: 28

Marketing Authorisation Holder:
Actavis Group PTC ehf
Reykjavikurvegur 76-78
220 Hafnarfjordur
Iceland

Manufacturer:
Actavis Ltd
BLB016 Bulebel Industrial Estate
Zejtun ZTN 3000
Malta

This leaflet was last revised in June 2011

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L20164ACT-30

Actavis, Barnstaple, EX32 8NS, UK

Pantoprazole 40mg Gastro-resistant Tablets

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
- The full name of this medicine is Pantoprazole 40mg Gastro-resistant Tablets but within the leaflet it will be referred to as Pantoprazole tablets.

In this leaflet:

1 What Pantoprazole tablets are and what they are used for

Pantoprazole is a selective "proton pump inhibitor", a medicine which reduces the amount of acid produced in your stomach. It is used for treating acid-related diseases of the stomach and intestine.

Pantoprazole tablets are used for treating:
Adults and adolescents 12 years of age and above:
- Reflux oesophagitis. An inflammation of your oesophagus (the tube which connects your throat to your stomach) accompanied by the regurgitation of stomach acid.

Adults:
- Stomach and duodenal ulcers.
- Zollinger-Ellison-Syndrome and other conditions producing too much acid in the stomach.

2 Before you take

Do not take Pantoprazole tablets if you
- are **allergic** (hypersensitive) **to pantoprazole** or any of the other ingredients of Pantoprazole tablets.
- are **allergic to** medicines containing **other proton pump inhibitors**.

Take special care with Pantoprazole tablets if you
- have severe **liver problems**. Please tell your doctor if you ever had problems with your liver in the past. He will check your liver enzymes more frequently, especially when you are taking Pantoprazole tablets as a long-term treatment. In the case of a rise of liver enzymes the treatment should be stopped.
- have reduced body stores or risk factors for reduced **vitamin B12** and receive pantoprazole long-term treatment. As with all acid reducing agents, pantoprazole may lead to a reduced absorption of vitamin B12.
- are taking a medicine containing **atazanavir** (for the treatment of HIV-infection) at the same time as pantoprazole, ask your doctor for specific advise.

Tell your doctor immediately if you notice any of the following symptoms:
- an unintentional loss of weight
- repeated vomiting
- difficulty swallowing
- vomiting blood
- you look pale and feel weak (anaemia)
- you notice blood in your stools
- severe and/or persistent diarrhoea, as pantoprazole has been associated with a small increase in infectious diarrhoea.

Your doctor may decide that you need some tests to rule out malignant disease because pantoprazole also alleviates the symptoms of cancer and could cause delay in diagnosing it. If your symptoms continue in spite of your treatment, further investigations will be considered.

If you take Pantoprazole tablets on a long-term basis (longer than 1 year) your doctor will probably keep you under regular surveillance. You should report any new and exceptional symptoms and circumstances whenever you see your doctor.

Taking other medicines
Pantoprazole tablets may influence the effectiveness of other medicines, so tell you doctor if you are taking
- Medicines such as **ketoconazole**, **itraconazole** and **posaconazole** (used to treat fungal infections) or **erlotinib** (used for certain types of cancer) because Pantoprazole tablets may stop these and other medicines from working properly.
- **Warfarin** and **phenprocoumon** which affect the thickening, or thinning of the blood. You may need further checks.
- **Atazanavir** (used to treat HIV-infection).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
There are no adequate data from the use of pantoprazole in pregnant women. Excretion into human milk has been reported. If you are pregnant, or think you may be pregnant, or if you are breast-feeding, you should use this medicine only if your doctor considers the benefit for you greater than the potential risk for your unborn child or baby.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
If you experience side effects like dizziness or disturbed vision, you should not drive or operate machines.

3 How to take

Always take Pantoprazole tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

When and how should you take Pantoprazole tablets
Take the tablets 1 hour before a meal without chewing or breaking them and swallow them whole with some water.

Unless told otherwise by your doctor, the usual dose is:
Adults and adolescents 12 years of age and above:
To treat reflux oesophagitis
The usual dose is one tablet a day. Your doctor may tell you to increase to 2 tablets daily. The treatment period for reflux oesophagitis is usually between 4 and 8 weeks. Your doctor will tell you how long to take your medicine.

Adults:
For the treatment of stomach and duodenal ulcers.
The usual dose is one tablet a day. After consultation with your doctor, the dose may be doubled.
Your doctor will tell you how long to take your medicine. The treatment period for stomach ulcers is usually between 4 and 8 weeks. The treatment period for duodenal ulcers is usually between 2 and 4 weeks.

For the long-term treatment of Zollinger-Ellison-Syndrome and of other conditions in which too much stomach acid is produced.
The recommended starting dose is usually two tablets a day.
Take the two tablets 1 hour before a meal. Your doctor may later adjust the dose, depending on the amount of stomach acid you produce. If prescribed more than two tablets a day, the tablets should be taken twice daily.
If your doctor prescribes a daily dose of more than four tablets a day, you will be told exactly when to stop taking the medicine.

Special patient groups:
- If you have **kidney problems**, moderate or severe **liver problems**, you should not take Pantoprazole tablets for eradication of *Helicobacter pylori*.
- If you suffer from **severe liver problems**, you should not take more than one tablet 20mg pantoprazole a day (for this purpose tablets containing 20mg pantoprazole are available).
- **Children below 12 years.** These tablets are not recommended for use in children below 12 years.

If you take more Pantoprazole tablets than you should
Contact your doctor or pharmacist. There are no known symptoms of overdose.

If you forget to take Pantoprazole tablets
Do not take a double dose to make up for the forgotten dose. Take your next, normal dose at the usual time.

If you stop taking Pantoprazole tablets
Do not stop taking these tablets without first talking to your doctor or pharmacist.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4 Possible side effects
Like all medicines, Pantoprazole tablets can cause side effects, although not everybody gets them.

If you get any of the following side effects, stop taking these tablets and tell your doctor immediately, or contact the casualty department at your nearest hospital:
- **Serious allergic reactions (frequency rare):** swelling of the tongue and/or throat, difficulty in swallowing, hives (nettle rash), difficulties in breathing, allergic facial swelling (Quincke's oedema / angioedema), severe dizziness with very fast heartbeat and heavy sweating.
- **Serious skin conditions (frequency not known):** blistering of the skin and rapid deterioration of your general condition, erosion (including slight bleeding) of eyes, nose, mouth/lips or genitals (Stevens-Johnson-Syndrome, Lyell-Syndrome, Erythema multiforme) and sensitivity to light.
- **Other serious conditions (frequency not known):** yellowing of the skin or whites of the eyes (severe damage to liver cells, jaundice) or fever, rash, and enlarged kidneys sometimes with painful urination and lower back pain (serious inflammation of the kidneys).

Other side effects are:
Uncommon (affects 1 to 10 users in 1,000): headache; dizziness; diarrhoea; feeling sick, vomiting; bloating and flatulence (wind); constipation; dry mouth; abdominal pain and discomfort; skin rash, exanthema, eruption; itching; feeling weak, exhausted or generally unwell; sleep disorders.
Rare (affects 1 to 10 users in 10,000): disturbances in vision such as blurred vision; hives; pain in the joints; muscle pains; weight changes; raised body temperature; swelling of the extremities (peripheral oedema); allergic reactions; depression; breast enlargement in males.
Very Rare (affects less than 1 user in 10,000): disorientation.
Not known (frequency cannot be estimated from the available data): hallucination, confusion (especially in patients with a history of these symptoms); decreased sodium level in blood.

Side effects identified through blood tests:
Uncommon (affects 1 to 10 users in 1,000): an increase in liver enzymes.
Rare (affects 1 to 10 users in 10,000): an increase in bilirubin; increased fats in the blood.
Very Rare (affects less than 1 user in 10,000): a reduction in the number of blood platelets, which may cause you to bleed or bruise more than normal; a reduction in the number of white blood cells, which may lead to more frequent infections.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5 How to store
Keep out of the reach and sight of children.
Do not use Pantoprazole tablets after the expiry date, which is stated on the carton and the container after EXP. The expiry date refers to the last day of that month.
This medicine does not require any special storage conditions.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 Further information
What Pantoprazole tablets contain
- The active substance is pantoprazole. Each gastro-resistant tablet contains 40mg of pantoprazole (as sodium sesquihydrate).
- The other ingredients are:
  Mannitol, Sodium carbonate anhydrous, Sodium starch glycolate, Methacrylic acid copolymer Calcium stearate, Opadry white OY-D-7233 (hypromellose, titanium dioxide, talc, macrogol, sodium lauryl sulphate), Kollicoat MAE 30 DP yellow (methacrylic acid-ethyl acrylate copolymer dispersion 30%, propylene glycol, yellow iron oxide, titanium dioxide, talc).

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Pantoprazole 40mg Gastro-resistant Tablets are elliptical, biconvex, dark yellow gastro-resistant tablets.

Pack sizes: 28

Marketing Authorisation Holder:
Actavis Group PTC ehf
Reykjavikurvegur 76-78
220 Hafnarfjordur
Iceland

Manufacturer:
Balkanpharma – Dupnitsa AD
3 Samokovsko Schosse Str.,
Dupnitsa 2600
Bulgaria

This leaflet was last revised in June 2011

Pantoprazole 40mg Gastro-resistant Tablets

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Pack sizes:28

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Actavis Group PTC ehf
Reykjavikurvegur 76-78
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Manufacturer:
Actavis Ltd
BLB016 Bulebel Industrial Estate
Zejtun ZTN 3000
Malta

This leaflet was last revised in June 2011

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L20166ACT-30

Actavis, Barnstaple, EX32 8NS, UK

Conclusion

The proposed SmPC and PIL amendments are in-line with the Article 30 harmonised documents and there are no objections to approval.

Decision – Approved 20 October 2011