Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Pantodia 20mg and 40 mg Gastro-resistant Tablets

Dialoc 20mg and 40mg Gastro-resistant Tablets

Pantoprazole sodium sesquihydrate

UK/H/1802-3/01-02/DC

UK licence no: PL 32652/0001-4

Applicant: DiaMed GmbH

Medicines and Healthcare products Regulatory Agency

LAY SUMMARY

On the 24th May 2010 the MHRA granted DiaMed GmbH Marketing Authorisations (licences) for the medicinal products Pantodia/Dialoc 20mg and 40mg Gastro-resistant Tablets. These are prescription-only medicines (POM).

Pantoprazole belongs to a group of medicines called proton pump inhibitors which work by reducing the amount of acid your stomach makes.

Pantodia/Dialoc 20 mg is used:

- To treat mild oesophageal disease due to reflux of acid from the stomach (reflux disease) and associated symptoms such as heartburn, acid regurgitation and pain on swallowing.
- For the long-term treatment and the prevention of oesophageal inflammation (reflux oesophagitis) and its relapse.
- To prevent duodenal (small bowel) and stomach ulcers caused by non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk, who need long-term treatment with these medicines.

Pantodia/Dialoc 40 mg is used:

- in the treatment of moderate to severe forms of reflux oesophagitis (an inflammation of your oesophagus, or gullet, caused by the regurgitation of stomach acid).
- in treating an infection with a bacterium called *Helicobacter pylori* in patients with duodenal ulcers and stomach ulcers in combination with two antibiotics (Eradication therapy). The aim is to get rid of the bacteria and so reduce the likelihood of these ulcers returning.
- in the treatment of duodenal (small bowel) and stomach ulcers
- to treat Zollinger-Ellison syndrome and other conditions producing too much acid in the stomach.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Pantodia/Dialoc outweigh the risks; hence Marketing Authorisations have been granted.

TABLE OF CONTENTS

Module 1

Product Name	Pantodia/Dialoc 20mg and 40mg Gastro-resistant Tablets
Type of Application	Generic, Article 10.1
Active Substance	Pantoprazole sodium sesquihydrate
Form	Gastro-resistant Tablets
Strength	20mg and 40mg
MA Holder	DiaMed GmbH, Kaiser-Wilhelm-ring 4-6, 48145 Munster Germany
RMS	UK
CMS	UK/H/1802/01-02/DC: Poland, Romania, and Slovenia UK/H/1803/01-02/DC: Austria, Belgium, Denmark, Finland, The Netherlands, Norway, Poland and Sweden
Procedure Number	UK/H/1802-3/01-02/DC
Timetable	Day 210 – 21st April 2010

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pantodia 20 mg Gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 20 mg pantoprazole (as pantoprazole sodium sesquihydrate 22.55 mg)

Excipient: Lactose 18.1 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet
Yellow to ochre, elongated coated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- For the treatment of mild reflux disease and related symptoms (e.g. heartburn, acid regurgitation and pain on swallowing).
- For the long-term treatment and prevention of relapse in reflux oesophagitis.
- To prevent peptic ulcers caused 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

Method of administration
Pantodia 20 mg should be swallowed whole with water before a meal. The tablets should not be chewed or crushed.

Adults and adolescents 12 years of age and above:

Mild reflux disease and related symptoms (e.g. heartburn, acid regurgitation and pain on swallowing):
The recommended dose is one Pantodia 20 mg gastro-resistant tablet per day. Symptom relief is generally achieved within 2 - 4 weeks, and a 4-week treatment period is usually required for healing of associated oesophagitis. If still symptomatic, healing will normally be achieved with a further 4-weeks' treatment.

Recurrent symptoms can be controlled by taking 20 mg once a day as required (on-demand therapy). A switch to continuous therapy may need to be considered if satisfactory symptom control cannot be maintained with on-demand treatment.

Long-term therapy and preventing relapses of reflux oesophagitis.
For long-term therapy, a maintenance dose of 20 mg pantoprazole daily (one Pantodia 20 mg tablet per day is recommended). If relapse occurs, the dosage can be increased to 40 mg pantoprazole per day. If required, Pantodia 40 mg is available. After the oesophageal inflammation has been cured the dose can be reduced to 20 mg pantoprazole again.

Adults

Prevention of peptic ulcers caused by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk who require continuous NSAID therapy.
The recommended dose is one Pantodia 20 mg gastro-resistant tablet per day.

Patients with hepatic impairment:
Patients with severe hepatic impairment should not take more than 20 mg pantoprazole a day (see section 4.4). In these patients, liver function tests should be monitored during treatment. If a rise in liver enzymes is observed, treatment with pantoprazole should be discontinued.

Patients with reduced kidney function:
A daily dose of 40mg pantoprazole should not be exceeded.

Elderly patients:
A daily dose of 40mg pantoprazole should not be exceeded.

Children below 12 years of age:
There is no experience in the use of pantoprazole in children. Pantoprazole should therefore not be used in children.

4.3 Contraindications

Pantodia 20 mg should not be taken under the following circumstances:
Hypersensitivity to pantoprazole or to any of the excipients (see section 6.1)

Pantoprazole, like other proton pump inhibitors, should not be administered with atazanavir (see section 4.5).

4.4 Special warnings and precautions for use

Pantoprazole is not intended for the treatment of the gastrointestinal symptoms accompanying functional dyspepsia.

Patients with severe liver damage should have their liver function tested regularly when being treated with pantoprazole, especially if it is a long-term course of treatment. If their liver enzyme levels rise they should stop taking Pantodia 20 mg.

Pantodia 20 mg should only be used to prevent peptic ulcers caused by non-selective, non-steroidal anti-inflammatory drugs (NSAIDs) if the patient needs continuous treatment with these medicines and has an increased risk of gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. old age (> 65), previous peptic ulcers or bleeding in the upper gastrointestinal tract.

As with all drugs which inhibit gastric acid production, (cyanocobalamin) malabsorption due to hypochlorhydria or achlorhydria may occur. This should be considered in patients on long-term therapy who have reduced vitamin B12 body stores or risk factors for reduced B12 absorption or in those who exhibit signs or symptoms of B12 deficiency.

Patients should be regularly monitored if they take this medication for a long period of time, especially if their course of treatment lasts more than a year.

If the patient exhibits worrying signs or symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or blood in their stool and/or melena) or if a stomach ulcer is suspected or has been confirmed, malignant disease of the oesophagus or stomach should be excluded since treatment with pantoprazole can mask the symptoms of malignancy and 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*.

If the symptoms persist after 4 weeks despite adequate treatment, further tests should be considered.

Pantoprazole is not intended for the treatment of the gastrointestinal symptoms accompanying functional dyspepsia.

There is no experience in children.

Patients with rare hereditary galactose intolerance, lactase deficiency or glucose galactose malabsorption should not take Pantodia 20 mg.

This medicinal product contains 1.34 mg sodium per dose. This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Studies with other proton pump inhibitors have shown that the bioavailability of atazanavir is significantly reduced when it is used concomitantly with proton pump inhibitors. Therefore the use of pantoprazole is contraindicated during atazanavir treatment.

Pantodia 20 mg can reduce the absorption of medicines, whose bioavailability is dependent on pH level (e.g. ketoconazole and itraconazole).

Pantoprazole is metabolised in the liver by the cytochrome P450 enzyme system. Interaction with other medicines such as substances, which are broken down by the same enzyme system, cannot be ruled out. However, no clinically significant interactions were found in targeted studies with a range of such medicines or compounds, such as carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline and oral contraceptives.

Although no interactions were found in clinical pharmacokinetic studies when phenprocoumon or warfarin were taken concomitantly, a few isolated post-marketing reports of changes in prothrombin time / INR have been reported. It is therefore recommended that prothrombin time / INR are monitored in patients being treated with concomitant coumarin anticoagulants 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 with pregnant women is limited. In animal experimental reproduction studies mild fetotoxicity was observed with doses above 5 mg/kg. There is no information on the transfer of pantoprazole into breast milk in humans. If a patient is pregnant or breast-feeding a child, she should only take pantoprazole if the benefit of the treatment for her is higher than the potential risk for her unborn child or baby.

4.7 Effects on ability to drive and use machines

There are no known effects on the ability to drive or use machines. However uncommon side-effects such as dizziness or blurred vision have been reported (see section 4.8) if affected the patient should refrain from driving or using machines.

4.8 Undesirable effects

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, including isolated reports

Frequency	**common**	**uncommon**	**rare**	**very rare**
Organ system				
Blood and the lymphatic system disorders				Leucopenia, thrombocytopenia
Immune system disorders		Hypersensitivity manifesting as pruritus and skin rash		Anaphylactic reactions including anaphylactic shock
Psychiatric			Depression,	

disorders			hallucination, disorientation and confusion especially in predisposed patients, as well as the aggravation of such symptoms	
Nervous system disorders	Headache	Dizziness, visual disturbance (blurred vision)		
Gastrointestinal disorders	Upper abdominal pain, diarrhoea, constipation, flatulence	Nausea, vomiting,	Dry mouth	
Hepatobiliary disorders				Severe hepatocellular damage leading to jaundice with or without hepatic failure
Skin and sub-cutaneous tissue disorders		Hypersensitivity reactions such as pruritus and skin rash		Urticaria, angioedema, severe skin reactions such as Stevens-Johnson syndrome, erythema multiforme, Lyell's syndrome, photosensitivity
Musculoskeletal, connective tissue disorders			Arthralgia	Myalgia
Renal and urinary disorders				Interstitial nephritis
General disorders and administration site conditions				Peripheral edema subsiding after termination of therapy

4.9 Overdose

There are no recognised symptoms of overdose and doses up to 240 mg i.v., administered over 2 minutes, have been well tolerated.

If overdose is accompanied by clinical signs or symptoms indicative of toxicity, standard supportive therapy should be initiated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors
ATC Code: A02BC02

Pantoprazole is a substituted benzimidazole, which inhibits gastric juice secretion through specific reactions with proton pumps in the parietal cells.

Pantoprazole is converted to its active form in the acidic channel 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 acts on both basal and stimulated gastric juice secretion. Most patients are symptom-free within 2 weeks. Like with other proton pump inhibitors and H_2 receptor blockers, treatment with pantoprazole reduces levels of gastric juice, which causes a rise in gastrin in relation to the acid reduction. The rise in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the receptor level, it can affect

acid secretion independently of stimulation by other substances (acetylcholine, histamine and gastrin). Pantoprazole has the same effect when administered orally and intravenously.

Fasting gastrin levels rise with pantoprazole. If pantoprazole is only used for a short term therapy, it doesn't usually exceed the upper limit of normal. If pantoprazole is taken over a long period of time, gastrin levels can double. An excessive increase, however, occurs only in isolated cases. With long-term treatment a mild to moderate increase of specific endocrine (ECL = enterochromaffin-like) cells in the stomach occurs in a minority of patients (simple to adenomatoid hyperplasia). However, to date, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids, such as were reported in animal trials (see section 5.3), have not been observed in studies in humans.

5.2 Pharmacokinetic properties

General pharmacokinetics

Pantoprazole is rapidly absorbed and the maximum serum concentration of around 1 - 1.5 µg/ml is reached after an average of 2.0 – 2.5 hours and remains constant on multiple dosing. The volume of distribution is around 0.15 l/kg, and clearance is around 0.1 l/h/kg.

The terminal elimination half-life is about 1 hour though a small number of subjects show slower elimination. Because of the mechanism of binding of pantoprazole to the proton pumps of parietal cells, the elimination half-life does not correlate with the much longer duration of therapeutic action (inhibition of acid secretion).

For both oral and intravenous administration, the pharmacokinetics remain constant after single and multiple dosing and are linear over the dose range 10 – 80 mg.

Serum protein binding of pantoprazole is around 98%. Pantoprazole is virtually entirely metabolised by the liver. Most metabolites (around 80 %) are eliminated in the kidneys, and the rest are excreted in faeces. The main metabolite in serum and urine is desmethyl-pantoprazole conjugated with sulphate. The half-life of this main metabolite (about 1.5 h) is not much longer than that of pantoprazole.

Bioavailability

Pantoprazole is completely absorbed after oral administration. The bioavailability of the tablet being around 77 %. AUC, maximum serum concentration and oral bioavailability are unaffected by food, though lag-time may be increased.

Special patient groups

No dose reduction is required when pantoprazole is given to patients with reduced kidney function (including dialysis patients) although a daily dose of 40 mg should not be exceeded (see section 4.2). The half-life is not prolonged. Pantoprazole is only dialysed to a very small extent. Although the main metabolite shows a moderately increased half-life (2 – 3 hours), there is no accumulation with this rapid elimination.

In patients with liver cirrhosis (Child A and Child B classification) the half-life increases to 3 - 6 hours and the AUC increases by a factor of 3 – 5. However, the maximum serum concentration only increased by a factor of 1.3 compared to in those with normal hepatic function.

A relative slight increase of AUC and C_{max} in elderly patients is of no clinical relevance.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

In a 2-year carcinogenicity study on rats, neuroendocrine tumours were found. Squamous cell papilloma also appeared in the rats' gastroesophageal vestibule. The mechanism, which is based on stomach carcinoids forming due to substituted benzimidazole, was studied

immediately and the conclusion was that it is an indirect mechanism due to the significantly increased serum gastrin level in rats when it is administered chronically and in high doses.

A higher rate of liver tumours was observed in rats (only in one study) and female mice in the 2-year studies, which can be interpreted as a consequence of pantoprazole's high metabolic rate in the liver. In one 2-year study a smaller rise in neoplasms in the rats' thyroid gland was observed in the highest dose group (200 mg/kg). The appearance of these neoplasms is related to thyroxin being broken down differently in the rats' liver due to pantoprazole. On the basis of the low therapeutic dose in humans, 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.

Tests have revealed no evidence of impaired fertility or teratogenic effects. The placental transfer of pantoprazole was examined in the rats. It increases with progressive pregnancy. Therefore the concentration is elevated in the fetus just before it is born.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
microcrystalline cellulose (E460i)
lactose monohydrate
croscarmellose sodium
colloidal anhydrous silica
magnesium stearate

Colour coating:
polyvinyl alcohol
macrogol 3350
titanium dioxide (E171)
talc (E553b)
iron oxide yellow (E172)
quinoline yellow aluminium lake (E104)

Gastro-resistant coating:
methacryl acid-ethyl acrylate copolymer
sodium lauryl sulphate
polysorbate 80
triethyl citrate (E1505)
talc (E553b)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Blister: 2 years.
Tablet container: 3 years. Shelf life after first opening: 28 days.

6.4 Special precautions for storage

Blister: Do not store above 30 °C.
Tablet container: Do not store above 25 °C.

6.5 Nature and contents of container

Blister: Aluminium-Aluminium foil blister
Original packages of 7, 14, 28 or 56 gastro-resistant tablets.

Tablet container: HDPE bottles with HDPE or PP screw cap closure with desiccant.
Original packages of 7, 14, 28 or 50 gastro-resistant tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
DiaMed GmbH
Kaiser-Wilhelm-Ring 4-6
48145 Münster
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 32652/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/05/2010

10 DATE OF REVISION OF THE TEXT
24/05/2010

1 NAME OF THE MEDICINAL PRODUCT

Pantodia 40 mg Gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 40 mg pantoprazole (as pantoprazole sodium sesquihydrate 45.1 mg)

Excipients: Lactose 36.2 mg, tartrazine

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet
Pale yellow to ochre, elongated coated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For relieving the symptoms of, and for the short-term treatment of, gastrointestinal diseases which require a reduction in gastric acid secretion.

- Moderate and severe reflux oesophagitis
- Duodenal ulcer
- Gastric ulcer
- Eradication of *Helicobacter pylori*, in combination with antibiotic therapy, in patients with peptic ulceration
- Zollinger-Ellison syndrome and other diseases associated with a pathological hypersecretion of gastric acid.

4.2 Posology and method of administration

Method of administration
Pantodia 40 mg should be swallowed whole with water before a meal. The tablets should not be chewed or crushed.

Adults and adolescents 12 years of age and above
Moderate and severe reflux oesophagitis:
The recommended dosage is 40 mg pantoprazole daily. In some cases this may be doubled, especially when there has been no response to other treatment. A four-week period is usually required for the treatment of reflux oesophagitis. If this is not sufficient, healing will usually be achieved within a further four weeks.

Adults
Gastric and duodenal ulcer:
The recommended dosage is 40 mg pantoprazole daily. In some cases this may be doubled, especially when there has been no response to other treatment.
Duodenal ulcers generally heal within two weeks. If a two-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further two weeks.

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

Eradication of *Helicobacter pylori* (*H. pylori*):
The recommended dose is 40 mg pantoprazole twice daily, in combination with one of the following three antibiotic regimens:

a) Amoxicillin 1000 mg twice daily + clarithromycin 500 mg twice daily.
b) Clarithromycin 500 mg twice daily + metronidazole 500 mg twice daily

c) Amoxicillin 1000 mg twice daily + metronidazole 500 mg twice daily

The second pantoprazole tablet should be taken before the evening meal. Combination therapy should be continued for seven days in most cases but may sometimes be required for up to 14 days.

Zollinger-Ellison Syndrome and other hypersecretory conditions:
For long-term therapy of Zollinger-Ellison syndrome and other diseases associated with a pathological hypersecretion of gastric acid, the recommended initial dose is 80 mg (2 tablets Pantodia 40 mg) per day. The dosage can subsequently be adjusted individually according to the determination of gastric acid secretion. For doses of more than 80 mg per day, the dose should be divided and given twice daily. A temporary increase in dose to more than 160 mg pantoprazole per day is possible. However, the increase should only last as long as required to sufficiently control acid secretion. With Zollinger-Ellison syndrome and other diseases associated with a pathological hypersecretion of gastric acid, the period of treatment is not restricted and should continue as long as clinically required.

Elderly
A daily dose of 40 mg pantoprazole should not be exceeded unless for the eradication treatment of *H. pylori* in which case a regimen including pantoprazole 40 mg twice daily should be used (see above).

Patients with renal impairment
A daily dose of 40 mg pantoprazole should not be exceeded. For this reason the *H.pylori* eradication regimen is not recommended in these patients (see section 4.3).

Patients with hepatic impairment
The dose should be reduced to 40 mg pantoprazole every other day in patients with severe liver insufficiency and for this reason the *H. pylori* eradication regimen is not recommended in these patients (see section 4.3).

In addition, liver function tests should be monitored in these patients during therapy with Pantodia 40 mg and treatment discontinued if an increase in liver enzymes is observed.

Children below 12 years of age
There is no experience in the use of pantoprazole in children. Therefore pantoprazole tablets should not be used in children.

4.3 Contraindications

Pantodia 40 mg should not be taken under the following circumstances:

- Hypersensitivity to pantoprazole or to any of the excipients (see section 6.1)
- in combination therapy for eradication of Helicobacter pylori in patients with moderate to severe hepatic or renal dysfunction, since currently no data is available on the efficacy and safety of pantoprazole in combination treatment of these patients.
- Pantoprazole, like other proton pump inhibitors, should not be administered with atazanavir (see section 4.5).
- Pantoprazole should not be used in combination therapy for the eradication of *H. pylori* in patients with moderate to severe hepatic or renal dysfunction since there are currently no relevant efficacy and safety data in relation to this.

4.4 Special warnings and precautions for use

Pantoprazole is not intended for the treatment of gastrointestinal symptoms accompanying functional dyspepsia.

The Summaries of Product Characteristics for each medication should be observed for combination therapy.

For patients with Zollinger-Ellison syndrome and other diseases associated with abnormal overproduction of gastric acid requiring long-term treatment, pantoprazole, as with other acid-blocking drugs, may reduce the absorption of Vitamin B12 (cyanocobalamin) due to hypochlorhydria or achlorhydria. This should be considered in patients on long-term therapy who have reduced B12 body stores or risk factors for reduced vitamin B12 absorption or in those who exhibit signs or symptoms of B12 deficiency.

If the patient exhibits worrying signs or symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or blood in the stool/melena) or if a stomach ulcer is suspected or has been confirmed, malignant disease of the oesophagus or stomach should be excluded. This is because treatment with pantoprazole may mask the symptoms of malignancy and thus delay diagnosis.

Diagnoses of peptic oesophagitis should be performed endoscopically.

There are no data currently available on the use of pantoprazole in children.

Patients with rare hereditary galactose intolerance, lactase deficiency or glucose galactose malabsorption should not take Pantodia 40 mg.

This product contains tartrazine, which may cause allergic reactions.

This medicinal product contains 2.68 mg sodium per dose. This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Studies with other proton pump inhibitors have shown that the bioavailability of atazanavir is significantly reduced when it is used concomitantly with proton pump inhibitors. Therefore the use of pantoprazole is contraindicated during atazanavir treatment.

Pantodia 40 mg can reduce the absorption of medicines, whose bioavailability is dependent on pH level (e.g. ketoconazole and itraconazole).

Pantoprazole is metabolised in the liver by the cytochrome P450 enzyme system. Interaction with other medicines such as substances, which are broken down by the same enzyme system, cannot be ruled out. However, no clinically significant interactions were found in targeted studies with a range of such medicines or compounds, such as carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline and oral contraceptives.

No clinically relevant interactions have been observed in human pharmacokinetic studies with clarithromycin, metronidazole or amoxicillin.

Although no interactions were found in clinical pharmacokinetic studies when phenprocoumon or warfarin were taken concomitantly, a few isolated post-marketing reports of changes in prothrombin time / INR have been reported. It is therefore recommended that prothrombin time / INR are monitored in patients being treated with concomitant coumarin anticoagulants 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 with pregnant women is limited. In animal experimental reproduction studies mild fetotoxicity was observed with doses above 5 mg/kg. There is no information on the transfer of pantoprazole into breast milk in humans. If a patient is pregnant or breast-feeding a child, she should only take pantoprazole if the benefit of the treatment for her is higher than the potential risk for her unborn child or baby.

4.7 Effects on ability to drive and use machines

There are no known effects on the ability to drive or use machines. However, uncommon side-effects such as dizziness or blurred vision have been reported (see section 4.8) if affected the patient should refrain from driving or using machines.

4.8 Undesirable effects

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, including isolated reports

Frequency	**common**	**uncommon**	**rare**	**very rare**
Organ system				
Blood and the lymphatic system disorders				Leucopenia, thrombocytopenia
Immune system disorders		Hypersensitivity manifesting as pruritus and skin rash		Anaphylactic reactions including anaphylactic shock
Psychiatric disorders			Depression, hallucination, disorientation and confusion especially in predisposed patients, as well as the aggravation of such symptoms	
Nervous system disorders	Headache	Dizziness, visual disturbance (blurred vision)		
Gastrointestinal disorders	Upper abdominal pain, diarrhoea, constipation, flatulence	Nausea, vomiting,	Dry mouth	
Hepatobiliary disorders				Severe hepatocellular damage leading to jaundice with or without hepatic failure
Skin and sub-cutaneous tissue disorders		Hypersensitivity reactions such as pruritus and skin rash		Urticaria, angioedema, severe skin reactions such as Stevens-Johnson syndrome, erythema multiforme, Lyell's syndrome, photosensitivity
Musculoskeletal, connective tissue disorders			Arthralgia	Myalgia
Renal and urinary disorders				Interstitial nephritis
General disorders and administration site conditions				Peripheral edema subsiding after termination of therapy

4.9 Overdose

There are no recognised symptoms of overdose and doses up to 240 mg i.v., administered over 2 minutes, have been well tolerated.

If overdose is accompanied by clinical signs or symptoms indicative of toxicity, standard supportive therapy should be initiated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors
ATC Code: A02BC02

Pantoprazole is a substituted benzimidazole, which inhibits gastric juice secretion through specific reactions with proton pumps in the parietal cells.

Pantoprazole is converted to its active form in the acidic channel 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 acts on both basal and stimulated gastric juice secretion. Most patients are symptom-free within 2 weeks. Like with other proton pump inhibitors and H_2 receptor blockers, treatment with pantoprazole reduces levels of gastric juice, which causes a rise in gastrin in relation to the acid reduction. The rise in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the receptor level, it can affect acid secretion independently of stimulation by other substances (acetylcholine, histamine and gastrin). Pantoprazole has the same effect when administered orally and intravenously.

Fasting gastrin levels rise with pantoprazole. If pantoprazole is only used for a short term therapy, it usually doesn't exceed the upper limit of normal. If pantoprazole is taken over a long period of time, gastrin levels can double. An excessive increase, however, occurs only in isolated cases. With long-term treatment a mild to moderate increase of specific endocrine (ECL = enterochromaffin-like) cells in the stomach occurs in a minority of patients (simple to adenomatoid hyperplasia). However, to date, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids, such as were reported in animal trials (see section 5.3), have not been observed in studies in humans.

5.2 Pharmacokinetic properties

General pharmacokinetics
Pantoprazole is rapidly absorbed and the maximum serum concentration of around 2 - 3 µg/ml is reached after an average of 2.0 – 2.5 hours. The volume of distribution is around 0.15 l/kg, and clearance is around 0.1 l/h/kg.

The terminal elimination half-life is about 1 hour though a small number of subjects show slower elimination. Because of the mechanism of binding of pantoprazole to the proton pumps of parietal cells, the elimination half-life does not correlate with the much longer duration of therapeutic action (inhibition of acid secretion).

For both oral and intravenous administration, the pharmacokinetics remain constant after single and multiple dosing and are linear over the dose range 10 – 80 mg.

Serum protein binding of pantoprazole is around 98 %. Pantoprazole is virtually entirely metabolised by the liver. Most metabolites (around 80 %) are eliminated in the kidneys, and the rest are excreted in faeces. The main metabolite in serum and urine is desmethyl-pantoprazole conjugated with sulphate. The half-life of this main metabolite (about 1.5 h) is not much longer than that of pantoprazole.

Bioavailability
Pantoprazole is completely absorbed after oral administration. The bioavailability of the tablet being around 77 %. AUC, maximum serum concentration and oral bioavailability are unaffected by food, though lag-time may be increased.

Special patient groups

No dose reduction is required when pantoprazole is given to patients with reduced kidney function (including dialysis patients) although a daily dose of 40 mg should not be exceeded (see section 4.2). The half-life is not prolonged. Pantoprazole is only dialysed to a very small extent. Although the main metabolite shows a moderately increased half-life (2 – 3 hours), there is no accumulation with this rapid elimination.

In patients with liver cirrhosis (Child A and Child B classification) the half-life increases to 3 - 6 hours and the AUC increases by a factor of 3 – 5. However, the maximum serum concentration only increased by a factor of 1.3 compared to in those with normal hepatic function.

A relative slight increase of AUC and C_{max} in elderly patients is of no clinical relevance.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

In a 2-year carcinogenicity study on rats, neuroendocrine tumours were found. Squamous cell papilloma also appeared in the rats' gastroesophageal vestibule. The mechanism, which is based on stomach carcinoids forming due to substituted benzimidazole, was studied immediately and the conclusion was that it is an indirect mechanism due to the significantly increased serum gastrin level in rats when it is administered chronically and in high doses.

A higher rate of liver tumours was observed in rats (only in one study) and female mice in the 2-year studies, which can be interpreted as a consequence of pantoprazole's high metabolic rate in the liver. In one 2-year study a smaller rise in neoplasms in the rats' thyroid gland was observed in the highest dose group (200 mg/kg). The appearance of these neoplasms is related to thyroxin being broken down differently in the rats' liver due to pantoprazole. On the basis of the low therapeutic dose in humans, 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.

Tests have revealed no evidence of impaired fertility or teratogenic effects. The placental transfer of pantoprazole was examined in the rats. It increases with progressive pregnancy. Therefore the concentration is elevated in the fetus just before it is born.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
microcrystalline cellulose (E460i)
lactose monohydrate
croscarmellose sodium
colloidal anhydrous silica
magnesium stearate

Colour coating:
polyvinyl alcohol
macrogol 3350
titanium dioxide (E171)
talc (E553b)
iron oxide yellow (E172)
tartrazine aluminium lake (E102)

Gastro-resistant coating:
methacryl acid-ethyl acrylate copolymer
sodium lauryl sulphate
polysorbate 80
triethyl citrate (E1505)

talc (E553b)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Blister: 2 years.
Tablet container: 3 years. Shelf life after first opening: 28 days.

6.4 Special precautions for storage
Blister: Do not store above 30 °C.
Tablet container: Do not store above 25 °C.

6.5 Nature and contents of container
Blister: Aluminium-Aluminium foil blister
Original packages of 7, 14, 28 or 56 gastro-resistant tablets.

Tablet container: HDPE bottles with HDPE or PP screw cap closure with desiccant.
Original packages of 7, 14, 28 or 50 gastro-resistant tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
DiaMed GmbH
Kaiser-Wilhelm-Ring 4-6
48145 Münster
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 32652/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/05/2010

10 DATE OF REVISION OF THE TEXT
24/05/2010

1 NAME OF THE MEDICINAL PRODUCT

Dialoc 20 mg Gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 20 mg pantoprazole (as pantoprazole sodium sesquihydrate 22.55 mg)

Excipient: Lactose 18.1 mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet
Yellow to ochre, elongated coated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- For the treatment of mild reflux disease and related symptoms (e.g. heartburn, acid regurgitation and pain on swallowing).
- For the long-term treatment and prevention of relapse in reflux oesophagitis.
- To prevent peptic ulcers caused 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

Method of administration
Dialoc 20 mg should be swallowed whole with water before a meal. The tablets should not be chewed or crushed.

Adults and adolescents 12 years of age and above:

Mild reflux disease and related symptoms (e.g. heartburn, acid regurgitation and pain on swallowing):
The recommended dose is one Dialoc 20 mg gastro-resistant tablet per day. Symptom relief is generally achieved within 2 - 4 weeks, and a 4-week treatment period is usually required for healing of associated oesophagitis. If still symptomatic, healing will normally be achieved with a further 4-weeks' treatment.

Recurrent symptoms can be controlled by taking 20 mg once a day as required (on-demand therapy). A switch to continuous therapy may need to be considered if satisfactory symptom control cannot be maintained with on-demand treatment.

Long-term therapy and preventing relapses of reflux oesophagitis.
For long-term therapy, a maintenance dose of 20 mg pantoprazole daily (one Dialoc 20 mg tablet per day is recommended). If relapse occurs, the dosage can be increased to 40 mg pantoprazole per day. If required, Dialoc 40 mg is available. After the oesophageal inflammation has been cured the dose can be reduced to 20 mg pantoprazole again.

Adults

Prevention of peptic ulcers caused by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk who require continuous NSAID therapy.
The recommended dose is one Dialoc 20 mg gastro-resistant tablet per day.

Patients with hepatic impairment:

Patients with severe hepatic impairment should not take more than 20 mg pantoprazole a day (see section 4.4). In these patients, liver function tests should be monitored during treatment. If a rise in liver enzymes is observed, treatment with pantoprazole should be discontinued.

Patients with reduced kidney function:
A daily dose of 40mg pantoprazole should not be exceeded.

Elderly patients:
A daily dose of 40mg pantoprazole should not be exceeded.

Children below 12 years of age:
There is no experience in the use of pantoprazole in children. Pantoprazole should therefore not be used in children.

4.3 Contraindications

Dialoc 20 mg should not be taken under the following circumstances:

– Hypersensitivity to pantoprazole or to any of the excipients (see section 6.1)

– Pantoprazole, like other proton pump inhibitors, should not be administered with atazanavir (see section 4.5).

4.4 Special warnings and precautions for use

Pantoprazole is not intended for the treatment of the gastrointestinal symptoms accompanying functional dyspepsia.

Patients with severe liver damage should have their liver function tested regularly when being treated with pantoprazole, especially if it is a long-term course of treatment. If their liver enzyme levels rise they should stop taking Dialoc 20 mg.

Dialoc 20 mg should only be used to prevent peptic ulcers caused by non-selective, non-steroidal anti-inflammatory drugs (NSAIDs) if the patient needs continuous treatment with these medicines and has an increased risk of gastrointestinal complications. The increased risk should be assessed according to individual risk factors, e.g. old age (> 65), previous peptic ulcers or bleeding in the upper gastrointestinal tract.

As with all drugs which inhibit gastric acid production, (cyanocobalamin) malabsorption due to hypochlorhydria or achlorhydria may occur. This should be considered in patients on long-term therapy who have reduced vitamin B12 body stores or risk factors for reduced B12 absorption or in those who exhibit signs or symptoms of B12 deficiency.

Patients should be regularly monitored if they take this medication for a long period of time, especially if their course of treatment lasts more than a year.

If the patient exhibits worrying signs or symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or blood in their stool and/or melena) or if a stomach ulcer is suspected or has been confirmed, malignant disease of the oesophagus or stomach should be excluded since treatment with pantoprazole can mask the symptoms of malignancy and 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*.

If the symptoms persist after 4 weeks despite adequate treatment, further tests should be considered.

Pantoprazole is not intended for the treatment of the gastrointestinal symptoms accompanying functional dyspepsia.

There is no experience in children.

Patients with rare hereditary galactose intolerance, lactase deficiency or glucose galactose malabsorption should not take Dialoc 20 mg.

This medicinal product contains 1.34 mg sodium per dose. This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Studies with other proton pump inhibitors have shown that the bioavailability of atazanavir is significantly reduced when it is used concomitantly with proton pump inhibitors. Therefore the use of pantoprazole is contraindicated during atazanavir treatment.

Dialoc 20 mg can reduce the absorption of medicines, whose bioavailability is dependent on pH level (e.g. ketoconazole and itraconazole).

Pantoprazole is metabolised in the liver by the cytochrome P450 enzyme system. Interaction with other medicines such as substances, which are broken down by the same enzyme system, cannot be ruled out. However, no clinically significant interactions were found in targeted studies with a range of such medicines or compounds, such as carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline and oral contraceptives.

Although no interactions were found in clinical pharmacokinetic studies when phenprocoumon or warfarin were taken concomitantly, a few isolated post-marketing reports of changes in prothrombin time / INR have been reported. It is therefore recommended that prothrombin time / INR are monitored in patients being treated with concomitant coumarin anticoagulants 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 with pregnant women is limited. In animal experimental reproduction studies mild fetotoxicity was observed with doses above 5 mg/kg. There is no information on the transfer of pantoprazole into breast milk in humans. If a patient is pregnant or breast-feeding a child, she should only take pantoprazole if the benefit of the treatment for her is higher than the potential risk for her unborn child or baby.

4.7 Effects on ability to drive and use machines

There are no known effects on the ability to drive or use machines. However uncommon side-effects such as dizziness or blurred vision have been reported (see section 4.8) if affected the patient should refrain from driving or using machines.

4.8 Undesirable effects

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, including isolated reports

Frequency	**common**	**uncommon**	**rare**	**very rare**
Organ system				
Blood and the lymphatic system disorders				Leucopenia, thrombocytopenia
Immune system disorders		Hypersensitivity manifesting as pruritus and skin rash		Anaphylactic reactions including anaphylactic shock
Psychiatric disorders			Depression, hallucination, disorientation and	

			confusion especially in predisposed patients, as well as the aggravation of such symptoms	
Nervous system disorders	Headache	Dizziness, visual disturbance (blurred vision)		
Gastrointestinal disorders	Upper abdominal pain, diarrhoea, constipation, flatulence	Nausea, vomiting,	Dry mouth	
Hepatobiliary disorders				Severe hepatocellular damage leading to jaundice with or without hepatic failure
Skin and sub-cutaneous tissue disorders		Hypersensitivity reactions such as pruritus and skin rash		Urticaria, angioedema, severe skin reactions such as Stevens-Johnson syndrome, erythema multiforme, Lyell's syndrome, photosensitivity
Musculoskeletal, connective tissue disorders			Arthralgia	Myalgia
Renal and urinary disorders				Interstitial nephritis
General disorders and administration site conditions				Peripheral edema subsiding after termination of therapy

4.9 Overdose

There are no recognised symptoms of overdose and doses up to 240 mg i.v., administered over 2 minutes, have been well tolerated.

If overdose is accompanied by clinical signs or symptoms indicative of toxicity, standard supportive therapy should be initiated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors
ATC Code: A02BC02

Pantoprazole is a substituted benzimidazole, which inhibits gastric juice secretion through specific reactions with proton pumps in the parietal cells.

Pantoprazole is converted to its active form in the acidic channel 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 acts on both basal and stimulated gastric juice secretion. Most patients are symptom-free within 2 weeks. Like with other proton pump inhibitors and H_2 receptor blockers, treatment with pantoprazole reduces levels of gastric juice, which causes a rise in gastrin in relation to the acid reduction. The rise in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the receptor level, it can affect acid secretion independently of stimulation by other substances (acetylcholine, histamine and gastrin). Pantoprazole has the same effect when administered orally and intravenously.

Fasting gastrin levels rise with pantoprazole. If pantoprazole is only used for a short term therapy, it doesn't usually exceed the upper limit of normal. If pantoprazole is taken over a long period of time, gastrin levels can double. An excessive increase, however, occurs only in isolated cases. With long-term treatment a mild to moderate increase of specific endocrine (ECL = enterochromaffin-like) cells in the stomach occurs in a minority of patients (simple to adenomatoid hyperplasia). However, to date, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids, such as were reported in animal trials (see section 5.3), have not been observed in studies in humans.

5.2 Pharmacokinetic properties

General pharmacokinetics

Pantoprazole is rapidly absorbed and the maximum serum concentration of around 1 - 1.5 µg/ml is reached after an average of 2.0 – 2.5 hours and remains constant on multiple dosing. The volume of distribution is around 0.15 l/kg, and clearance is around 0.1 l/h/kg.

The terminal elimination half-life is about 1 hour though a small number of subjects show slower elimination. Because of the mechanism of binding of pantoprazole to the proton pumps of parietal cells, the elimination half-life does not correlate with the much longer duration of therapeutic action (inhibition of acid secretion).

For both oral and intravenous administration, the pharmacokinetics remain constant after single and multiple dosing and are linear over the dose range 10 – 80 mg.

Serum protein binding of pantoprazole is around 98%. Pantoprazole is virtually entirely metabolised by the liver. Most metabolites (around 80 %) are eliminated in the kidneys, and the rest are excreted in faeces. The main metabolite in serum and urine is desmethyl-pantoprazole conjugated with sulphate. The half-life of this main metabolite (about 1.5 h) is not much longer than that of pantoprazole.

Bioavailability

Pantoprazole is completely absorbed after oral administration. The bioavailability of the tablet being around 77 %. AUC, maximum serum concentration and oral bioavailability are unaffected by food, though lag-time may be increased.

Special patient groups

No dose reduction is required when pantoprazole is given to patients with reduced kidney function (including dialysis patients) although a daily dose of 40 mg should not be exceeded (see section 4.2). The half-life is not prolonged. Pantoprazole is only dialysed to a very small extent. Although the main metabolite shows a moderately increased half-life (2 – 3 hours), there is no accumulation with this rapid elimination.

In patients with liver cirrhosis (Child A and Child B classification) the half-life increases to 3 - 6 hours and the AUC increases by a factor of 3 – 5. However, the maximum serum concentration only increased by a factor of 1.3 compared to in those with normal hepatic function.

A relative slight increase of AUC and C_{max} in elderly patients is of no clinical relevance.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

In a 2-year carcinogenicity study on rats, neuroendocrine tumours were found. Squamous cell papilloma also appeared in the rats' gastroesophageal vestibule. The mechanism, which is based on stomach carcinoids forming due to substituted benzimidazole, was studied immediately and the conclusion was that it is an indirect mechanism due to the significantly increased serum gastrin level in rats when it is administered chronically and in high doses.

A higher rate of liver tumours was observed in rats (only in one study) and female mice in the 2-year studies, which can be interpreted as a consequence of pantoprazole's high metabolic rate in the liver. In one 2-year study a smaller rise in neoplasms in the rats' thyroid gland was observed in the highest dose group (200 mg/kg). The appearance of these neoplasms is related to thyroxin being broken down differently in the rats' liver due to pantoprazole. On the basis of the low therapeutic dose in humans, 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.

Tests have revealed no evidence of impaired fertility or teratogenic effects. The placental transfer of pantoprazole was examined in the rats. It increases with progressive pregnancy. Therefore the concentration is elevated in the fetus just before it is born.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
microcrystalline cellulose (E460i)
lactose monohydrate
croscarmellose sodium
colloidal anhydrous silica
magnesium stearate

Colour coating:
polyvinyl alcohol
macrogol 3350
titanium dioxide (E171)
talc (E553b)
iron oxide yellow (E172)
quinoline yellow aluminium lake (E104)

Gastro-resistant coating:
methacryl acid-ethyl acrylate copolymer
sodium lauryl sulphate
polysorbate 80
triethyl citrate (E1505)
talc (E553b)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Blister: 2 years.
Tablet container: 3 years. Shelf life after first opening: 28 days.

6.4 Special precautions for storage

Blister: Do not store above 30 °C.
Tablet container: Do not store above 25 °C.

6.5 Nature and contents of container

Blister: Aluminium-Aluminium foil blister
Original packages of 7, 14, 28 or 56 gastro-resistant tablets.

Tablet container: HDPE bottles with HDPE or PP screw cap closure with desiccant.
Original packages of 7, 14, 28 or 50 gastro-resistant tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

DiaMed GmbH
Kaiser-Wilhelm-Ring 4-6
48145 Münster
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 32652/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/05/2010

10 DATE OF REVISION OF THE TEXT

24/05/2010

1 NAME OF THE MEDICINAL PRODUCT

Dialoc 40 mg Gastro-resistant tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 40 mg pantoprazole (as pantoprazole sodium sesquihydrate 45.1 mg)

Excipients: Lactose 36.2 mg, tartrazine

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet
Pale yellow to ochre, elongated coated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For relieving the symptoms of, and for the short-term treatment of, gastrointestinal diseases which require a reduction in gastric acid secretion.

- Moderate and severe reflux oesophagitis
- Duodenal ulcer
- Gastric ulcer
- Eradication of *Helicobacter pylori*, in combination with antibiotic therapy, in patients with peptic ulceration
- Zollinger-Ellison syndrome and other diseases associated with a pathological hypersecretion of gastric acid.

4.2 Posology and method of administration

Method of administration
Dialoc 40 mg should be swallowed whole with water before a meal. The tablets should not be chewed or crushed.

Adults and adolescents 12 years of age and above
Moderate and severe reflux oesophagitis:
The recommended dosage is 40 mg pantoprazole daily. In some cases this may be doubled, especially when there has been no response to other treatment. A four-week period is usually required for the treatment of reflux oesophagitis. If this is not sufficient, healing will usually be achieved within a further four weeks.

Adults
Gastric and duodenal ulcer:
The recommended dosage is 40 mg pantoprazole daily. In some cases this may be doubled, especially when there has been no response to other treatment.
Duodenal ulcers generally heal within two weeks. If a two-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further two weeks.

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

Eradication of *Helicobacter pylori* (*H. pylori*):
The recommended dose is 40 mg pantoprazole twice daily, in combination with one of the following three antibiotic regimens:

a) Amoxicillin 1000 mg twice daily + clarithromycin 500 mg twice daily.
b) Clarithromycin 500 mg twice daily + metronidazole 500 mg twice daily

c) Amoxicillin 1000 mg twice daily + metronidazole 500 mg twice daily

The second pantoprazole tablet should be taken before the evening meal. Combination therapy should be continued for seven days in most cases but may sometimes be required for up to 14 days.

Zollinger-Ellison Syndrome and other hypersecretory conditions:
For long-term therapy of Zollinger-Ellison syndrome and other diseases associated with a pathological hypersecretion of gastric acid, the recommended initial dose is 80 mg (2 tablets Dialoc 40 mg) per day. The dosage can subsequently be adjusted individually according to the determination of gastric acid secretion. For doses of more than 80 mg per day, the dose should be divided and given twice daily. A temporary increase in dose to more than 160 mg pantoprazole per day is possible. However, the increase should only last as long as required to sufficiently control acid secretion. With Zollinger-Ellison syndrome and other diseases associated with a pathological hypersecretion of gastric acid, the period of treatment is not restricted and should continue as long as clinically required.

Elderly
A daily dose of 40 mg pantoprazole should not be exceeded unless for the eradication treatment of *H. pylori* in which case a regimen including pantoprazole 40 mg twice daily should be used (see above).

Patients with renal impairment
A daily dose of 40 mg pantoprazole should not be exceeded. For this reason the *H.pylori* eradication regimen is not recommended in these patients (see section 4.3).

Patients with hepatic impairment
The dose should be reduced to 40 mg pantoprazole every other day in patients with severe liver insufficiency and for this reason the *H. pylori* eradication regimen is not recommended in these patients (see section 4.3).

In addition, liver function tests should be monitored in these patients during therapy with Dialoc 40 mg and treatment discontinued if an increase in liver enzymes is observed.

Children below 12 years of age
There is no experience in the use of pantoprazole in children. Therefore pantoprazole tablets should not be used in children.

4.3 Contraindications

Dialoc 40 mg should not be taken under the following circumstances:

- Hypersensitivity to pantoprazole or to any of the excipients (see section 6.1)
- in combination therapy for eradication of Helicobacter pylori in patients with moderate to severe hepatic or renal dysfunction, since currently no data is available on the efficacy and safety of pantoprazole in combination treatment of these patients.
- Pantoprazole, like other proton pump inhibitors, should not be administered with atazanavir (see section 4.5).
- Pantoprazole should not be used in combination therapy for the eradication of *H.pylori* in patients with moderate to severe hepatic or renal dysfunction since there are currently no relevant efficacy and safety data in relation to this.

4.4 Special warnings and precautions for use

Pantoprazole is not intended for the treatment of gastrointestinal symptoms accompanying functional dyspepsia.

The Summaries of Product Characteristics for each medication should be observed for combination therapy.

For patients with Zollinger-Ellison syndrome and other diseases associated with abnormal overproduction of gastric acid requiring long-term treatment, pantoprazole, as with other acid-blocking drugs, may reduce the absorption of Vitamin B12 (cyanocobalamin) due to hypochlorhydria or achlorhydria. This should be considered in patients on long-term therapy who have reduced B12 body stores or risk factors for reduced vitamin B12 absorption or in those who exhibit signs or symptoms of B12 deficiency.

If the patient exhibits worrying signs or symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or blood in the stool/melena) or if a stomach ulcer is suspected or has been confirmed, malignant disease of the oesophagus or stomach should be excluded. This is because treatment with pantoprazole may mask the symptoms of malignancy and thus delay diagnosis.

Diagnoses of peptic oesophagitis should be performed endoscopically.

There are no data currently available on the use of pantoprazole in children.

Patients with rare hereditary galactose intolerance, lactase deficiency or glucose galactose malabsorption should not take Dialoc 40 mg.

This product contains tartrazine, which may cause allergic reactions.

This medicinal product contains 2.68 mg sodium per dose. This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Studies with other proton pump inhibitors have shown that the bioavailability of atazanavir is significantly reduced when it is used concomitantly with proton pump inhibitors. Therefore the use of pantoprazole is contraindicated during atazanavir treatment.

Dialoc 40 mg can reduce the absorption of medicines, whose bioavailability is dependent on pH level (e.g. ketoconazole and itraconazole).

Pantoprazole is metabolised in the liver by the cytochrome P450 enzyme system. Interaction with other medicines such as substances, which are broken down by the same enzyme system, cannot be ruled out. However, no clinically significant interactions were found in targeted studies with a range of such medicines or compounds, such as carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline and oral contraceptives.

No clinically relevant interactions have been observed in human pharmacokinetic studies with clarithromycin, metronidazole or amoxicillin.

Although no interactions were found in clinical pharmacokinetic studies when phenprocoumon or warfarin were taken concomitantly, a few isolated post-marketing reports of changes in prothrombin time / INR have been reported. It is therefore recommended that prothrombin time / INR are monitored in patients being treated with concomitant coumarin anticoagulants 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 with pregnant women is limited. In animal experimental reproduction studies mild fetotoxicity was observed with doses above 5 mg/kg. There is no information on the transfer of pantoprazole into breast milk in humans. If a patient is pregnant or breast-feeding a child, she should only take pantoprazole if the benefit of the treatment for her is higher than the potential risk for her unborn child or baby.

4.7 Effects on ability to drive and use machines

There are no known effects on the ability to drive or use machines. However, uncommon side-effects such as dizziness or blurred vision have been reported (see section 4.8) if affected the patient should refrain from driving or using machines.

4.8 Undesirable effects

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, including isolated reports

Frequency	**common**	**uncommon**	**rare**	**very rare**
Organ system				
Blood and the lymphatic system disorders				Leucopenia, thrombocytopenia
Immune system disorders		Hypersensitivity manifesting as pruritus and skin rash		Anaphylactic reactions including anaphylactic shock
Psychiatric disorders			Depression, hallucination, disorientation and confusion especially in predisposed patients, as well as the aggravation of such symptoms	
Nervous system disorders	Headache	Dizziness, visual disturbance (blurred vision)		
Gastrointestinal disorders	Upper abdominal pain, diarrhoea, constipation, flatulence	Nausea, vomiting,	Dry mouth	
Hepatobiliary disorders				Severe hepatocellular damage leading to jaundice with or without hepatic failure
Skin and sub-cutaneous tissue disorders		Hypersensitivity reactions such as pruritus and skin rash		Urticaria, angioedema, severe skin reactions such as Stevens-Johnson syndrome, erythema multiforme, Lyell's syndrome, photosensitivity
Musculoskeletal, connective tissue disorders			Arthralgia	Myalgia
Renal and urinary disorders				Interstitial nephritis
General disorders and administration site conditions				Peripheral edema subsiding after termination of therapy

4.9 Overdose

There are no recognised symptoms of overdose and doses up to 240 mg i.v., administered over 2 minutes, have been well tolerated.

If overdose is accompanied by clinical signs or symptoms indicative of toxicity, standard supportive therapy should be initiated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors
ATC Code: A02BC02

Pantoprazole is a substituted benzimidazole, which inhibits gastric juice secretion through specific reactions with proton pumps in the parietal cells.

Pantoprazole is converted to its active form in the acidic channel 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 acts on both basal and stimulated gastric juice secretion. Most patients are symptom-free within 2 weeks. Like with other proton pump inhibitors and H_2 receptor blockers, treatment with pantoprazole reduces levels of gastric juice, which causes a rise in gastrin in relation to the acid reduction. The rise in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the receptor level, it can affect acid secretion independently of stimulation by other substances (acetylcholine, histamine and gastrin). Pantoprazole has the same effect when administered orally and intravenously.

Fasting gastrin levels rise with pantoprazole. If pantoprazole is only used for a short term therapy, it usually doesn't exceed the upper limit of normal. If pantoprazole is taken over a long period of time, gastrin levels can double. An excessive increase, however, occurs only in isolated cases. With long-term treatment a mild to moderate increase of specific endocrine (ECL = enterochromaffin-like) cells in the stomach occurs in a minority of patients (simple to adenomatoid hyperplasia). However, to date, the formation of carcinoid precursors (atypical hyperplasia) or gastric carcinoids, such as were reported in animal trials (see section 5.3), have not been observed in studies in humans.

5.2 Pharmacokinetic properties

General pharmacokinetics
Pantoprazole is rapidly absorbed and the maximum serum concentration of around 2-3 µg/ml is reached after an average of 2.0 – 2.5 hours. The volume of distribution is around 0.15 l/kg, and clearance is around 0.1 l/h/kg.

The terminal elimination half-life is about 1 hour though a small number of subjects show slower elimination. Because of the mechanism of binding of pantoprazole to the proton pumps of parietal cells, the elimination half-life does not correlate with the much longer duration of therapeutic action (inhibition of acid secretion).

For both oral and intravenous administration, the pharmacokinetics remain constant after single and multiple dosing and are linear over the dose range 10 – 80 mg.

Serum protein binding of pantoprazole is around 98 %. Pantoprazole is virtually entirely metabolised by the liver. Most metabolites (around 80 %) are eliminated in the kidneys, and the rest are excreted in faeces. The main metabolite in serum and urine is desmethyl-pantoprazole conjugated with sulphate. The half-life of this main metabolite (about 1.5 h) is not much longer than that of pantoprazole.

Bioavailability
Pantoprazole is completely absorbed after oral administration. The bioavailability of the tablet being around 77 %. AUC, maximum serum concentration and oral bioavailability are unaffected by food, though lag-time may be increased.

Special patient groups

No dose reduction is required when pantoprazole is given to patients with reduced kidney function (including dialysis patients) although a daily dose of 40 mg should not be exceeded (see section 4.2). The half-life is not prolonged. Pantoprazole is only dialysed to a very small extent. Although the main metabolite shows a moderately increased half-life (2 – 3 hours), there is no accumulation with this rapid elimination.

In patients with liver cirrhosis (Child A and Child B classification) the half-life increases to 3 - 6 hours and the AUC increases by a factor of 3 – 5. However, the maximum serum concentration only increased by a factor of 1.3 compared to in those with normal hepatic function.

A relative slight increase of AUC and C_{max} in elderly patients is of no clinical relevance.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

In a 2-year carcinogenicity study on rats, neuroendocrine tumours were found. Squamous cell papilloma also appeared in the rats' gastroesophageal vestibule. The mechanism, which is based on stomach carcinoids forming due to substituted benzimidazole, was studied immediately and the conclusion was that it is an indirect mechanism due to the significantly increased serum gastrin level in rats when it is administered chronically and in high doses.

A higher rate of liver tumours was observed in rats (only in one study) and female mice in the 2-year studies, which can be interpreted as a consequence of pantoprazole's high metabolic rate in the liver. In one 2-year study a smaller rise in neoplasms in the rats' thyroid gland was observed in the highest dose group (200 mg/kg). The appearance of these neoplasms is related to thyroxin being broken down differently in the rats' liver due to pantoprazole. On the basis of the low therapeutic dose in humans, 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.

Tests have revealed no evidence of impaired fertility or teratogenic effects. The placental transfer of pantoprazole was examined in the rats. It increases with progressive pregnancy. Therefore the concentration is elevated in the fetus just before it is born.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
microcrystalline cellulose (E460i)
lactose monohydrate
croscarmellose sodium
colloidal anhydrous silica
magnesium stearate

Colour coating:
polyvinyl alcohol
macrogol 3350
titanium dioxide (E171)
talc (E553b)
iron oxide yellow (E172)
tartrazine aluminium lake (E102)

Gastro-resistant coating:
methacryl acid-ethyl acrylate copolymer
sodium lauryl sulphate
polysorbate 80
triethyl citrate (E1505)

talc (E553b)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Blister: 2 years.
Tablet container: 3 years. Shelf life after first opening: 28 days.

6.4 Special precautions for storage
Blister: Do not store above 30 °C.
Tablet container: Do not store above 25 °C.

6.5 Nature and contents of container
Blister: Aluminium-Aluminium foil blister
Original packages of 7, 14, 28 or 56 gastro-resistant tablets.

Tablet container: HDPE bottles with HDPE or PP screw cap closure with desiccant.
Original packages of 7, 14, 28 or 50 gastro-resistant tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
DiaMed GmbH
Kaiser-Wilhelm-Ring 4-6
48145 Münster
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 32652/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/05/2010

10 DATE OF REVISION OF THE TEXT
24/05/2010

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

Pantodia 20 mg
Gastro-resistant tablets
Pantoprazole

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.

1. WHAT IS PANTODIA 20 MG AND WHAT IS IT USED FOR

Pantoprazole belongs to a group of medicines called proton pump inhibitors which work by reducing the amount of acid your stomach makes.

Pantodia 20 mg is used:
- To treat mild oesophageal disease due to reflux of acid from the stomach (reflux disease) and associated symptoms such as heartburn, acid regurgitation and pain on swallowing.
- For the long-term treatment and the prevention of oesophageal inflammation (reflux oesophagitis) and its relapse.
- To prevent duodenal (small bowel) and stomach ulcers caused by non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk, who need long-term treatment with these medicines.

2. BEFORE YOU TAKE PANTODIA 20 MG

Do not take Pantodia 20 mg:
- If you are hypersensitive (allergic) to pantoprazole or one of the other ingredients in Pantodia 20 mg.
- If you have to take a medicine which contains atazanavir (to treat an HIV infection) as well.

Take special care with Pantodia 20 mg:
- If you suffer from a severe liver disease, you should advise your doctor. If necessary, he/she will regularly check your liver enzymes.

- If you have unintentionally lost weight recently, have suffered from repeated vomiting, have vomited blood (this can look dark like “coffee grounds”), have difficulty swallowing,

or if you have noticed blood in your stool (faeces) or have passed tarry black stools, speak to your doctor. If necessary, he/she will do further tests (e.g. gastroscopy; a visual inspection of the gullet, stomach and upper intestine).

- If you are taking Pantodia 20 mg on a long-term basis (e.g. over a year) your doctor will examine you regularly. Consult your doctor about any new symptom that appears or any other unusual problems. Tell your doctor if you have had vitamin B12 (cyanocobalamin) deficiency in the past.

- Tell your doctor if you are also taking painkillers called non-steroidal anti-inflammatory medicines (NSAIDs). You should also carefully read the package leaflets for these medicines.

Please also tell your doctor if your symptoms continue after 4 weeks, despite regularly taking this medicine.

Taking Pantodia 20 mg with 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.

It is especially important to tell your doctor if you are taking or have taken the following medicines:
- Antifungals (e.g. ketokonazole or itraconazole) which are used to treat fungal infections of the skin and nails
- Anticoagulants to thin the blood (so-called coumarin derivatives such as phenprocoumon or warfarin). If necessary, your doctor should test your blood coagulation more frequently.
- Atazanavir to treat HIV infections. Atazanavir should not be taken with pantoprazole.

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

Clinical experience with pregnant women is limited. There is no information on the transfer of pantoprazole, the active agent in Pantodia 20 mg, into breast milk in humans.
If you are pregnant or are breast-feeding a child, you should only take Pantodia 20 mg tablets if your attending physician thinks that the benefit of the treatment for you is higher than the possible risk for your unborn child or baby.

Driving and using machines:
Taking pantoprazole normally has no impact on your ability to drive or use machines. However, dizziness and visual problems are possible side effects, which could affect your ability to drive or use machines. In this case you should not drive or use machines.

Important information about some of the ingredients of Pantodia 20 mg
This medicine contains lactose. Please only take Pantodia 20 mg after you have consulted your doctor, if you know that you suffer from tolerance problems with certain sugars.
This medicinal product contains 1.34 mg sodium per dose. This should be taken into consideration by patients on a controlled sodium diet.

3. HOW TO TAKE PANTODIA 20 MG

Always take Pantodia 20 mg exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- Pantodia 20 mg should be taken on an empty stomach (before meals).
- You should swallow the tablet(s) whole with water.
- Do not crush, break or chew the tablet(s) as this will prevent them from working properly.

Adults and adolescents 12 years of age and above

Unless your doctor prescribes otherwise, the usual dose is:

Mild oesophageal disease due to gastric acid reflux (reflux disease) and related symptoms (e.g. heartburn, acid regurgitation and pain on swallowing)
The recommended oral dose is one Pantodia 20 mg gastro-resistant tablet per day for 2 – 4 weeks (continuing for another 4 weeks if necessary). After this, any recurrent symptoms can be controlled taking one tablet daily, as needed.

If your symptoms cannot be controlled with on-demand therapy, your doctor should consider an alternative long-term treatment.

Long-term therapy and preventing relapses of oesophageal inflammation (reflux oesophagitis)
The recommended dose is one 20 mg tablet per day, which can be increased to 40 mg daily if symptoms return., in which case Pantodia 40 mg is available. After the oesophageal inflammation has been healed the dose can be reduced to 20 mg pantoprazole again.

Adults

Preventing stomach and duodenal ulcers caused by anti-inflammatory drugs (NSAIDs)
The recommended dose is one Pantodia 20 mg gastro-resistant tablet per day, for as long as prescribed by your doctor.

Elderly patients and patients with kidney disease
A daily dose of 40 mg should not be exceeded.

Patients with liver disease
A daily dose of 20 mg should not be exceeded.

Children under 12 years of age
Pantodia 20 mg should not be used in children.

Please consult your doctor if you think that the effect of Pantodia 20 mg is too strong or too weak.

If you take more Pantodia 20 mg than you should
If you take too much Pantodia 20 mg, contact your doctor immediately.

If you forget to take Pantodia 20 mg
If you forget to take a dose, take it as soon as you remember unless it is almost time for your next dose.

If you stop taking Pantodia 20 mg
Do not stop taking the medicine without first consulting your doctor Do not stop just because you feel better. If you stop taking the 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 tablets can cause side effects, although not everybody will experience them.

You should stop taking Pantoprazole and seek immediate medical advice if you experience any of the following symptoms as they could be due to a severe allergic reaction:

- a swollen face, mouth, tongue and/or throat
- difficulty swallowing
- an itchy rash (hives) and difficulty breathing

The list below includes side-effects which may occur with pantoprazole

Common (less than 1 in 10 but more than 1 in 100 people treated)

- stomach-ache, diarrhoea, constipation or wind
- headaches

Uncommon (less than 1 in 100 but more than 1 in 1,000 people treated)

- nausea (feeling sick)
- vomiting (being sick)
- dizziness
- blurred vision
- allergic reactions, such as itchy skin and rash.

Rare (Less than 1 in 1000 but more than 1 in 10,000 people treated)

- dry mouth
- joint pain
- depression, hallucination, disorientation, confusion.

Very rare (Less than 1 in 10,000 people treated)

- a fall in the number of white cells or platelets in the blood.
- swollen legs
- muscle pain
- liver damage and jaundice (yellowing of the skin) which can be serious
- allergic reactions (these may be accompanied by a skin rash and can be severe, causing swelling of the face or mouth). This can cause difficulty breathing (see warning at the beginning of this section)
- raised body temperature
- kidney inflammation (nephritis)
- severe skin reactions (Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis or Lyell's disease)
- increased sensitivity of the skin to sunlight (photosensitivity)
- raised blood triglycerides (a type of fat in the blood)

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

5. HOW TO STORE PANTODIA 20 MG

Keep out of the reach and sight of children.

Do not use Pantodia 20 mg after the expiry date which is stated on the carton.

Tablet container: Shelf life after first opening: 28 days.

Storage conditions:
Tablet container: Do not store above 25 °C.
Blister: Do not store above 30 °C.

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 Pantodia 20 mg contains:
The active substance is pantoprazole.
Each gastro-resistant tablet contains 20 mg pantoprazole (as pantoprazole sodium sesquihydrate 22.55 mg).

The other ingredients are:

Tablet Core:
microcrystalline cellulose (E460i), lactose monohydrate, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate

Colour coating:
polyvinyl alcohol, macrogol 3350, titanium dioxide (E171), talc (E553b), iron oxide yellow (E172), quinoline yellow aluminium lake (E104)

Gastro-resistant coating:
methacryl acid-ethyl acrylate copolymer, sodium lauryl sulphate, polysorbate 80, triethyl citrate (E1505), talc (E553b)

What Pantodia 20 mg looks like and contents of the pack:
Pantodia 20 mg are yellow to ochre, elongated coated tablets.
Pantodia 20 mg is available in:

Tablet containers (HDPE bottles with HDPE or PP screw cap closure with desiccant) in packages of 7, 14, 28 or 50 gastro-resistant tablets.

Blisters (Aluminium-Aluminium foil blisters) in packages of 7, 14, 28 or 56 gastro-resistant tablets.

Marketing Authorisation Holder:

DiaMed GmbH
Kaiser-Wilhelm-Ring 4 – 6
48145 Münster
Germany

Manufacturer:
Laboratorios Dr. Esteve S. A.
Sant Marti, s/n. Poligon Industrial
08107 Martorelles (Barcelona), Spain

This medicinal product is authorised in the Member States of the EEA under the following names:

Poland	Pantodia
Romania	Pantoprazol DiaMed 20 mg Comprimate gastrorezistente
Slovenia	Pantoprazol DiaMed 20 mg gastrorezistentne tablete
United Kingdom	Pantodia 20 mg gastro-resistant tablets

This user leaflet was last approved in >mm yyyy<**.**

Pantodia 40 mg
Gastro-resistant tablets
Pantoprazole

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.

1. WHAT IS PANTODIA 40 MG AND WHAT IS IT USED FOR

Pantoprazole belongs to a group of medicines called proton pump inhibitors which work by reducing the amount of acid your stomach makes.

Pantodia 40 mg is used:
- in the treatment of moderate to severe forms of reflux oesophagitis (an inflammation of your oesophagus, or gullet, caused by the regurgitation of stomach acid).
- in treating an infection with a bacterium called *Helicobacter pylori* in patients with duodenal ulcers and stomach ulcers in combination with two antibiotics (Eradication therapy). The aim is to get rid of the bacteria and so reduce the likelihood of these ulcers returning.
- in the treatment of duodenal (small bowel) and stomach ulcers
- to treat Zollinger-Ellison syndrome and other conditions producing too much acid in the stomach.

2. BEFORE YOU TAKE PANTODIA 40 MG

Do not take Pantodia 40 mg:
- If you are hypersensitive (allergic) to pantoprazole, tartrazine or one of the other ingredients in Pantodia 40 mg.
- If you suffer from a moderate to severe hepatic or renal dysfunction and shall receive a combination therapy for eradication of the bacterium Helicobacter pylori.
- If you have to take a medicine which contains atazanavir (to treat an HIV infection) as well.

Take special care with Pantodia 40 mg:

- If you have severe liver disease - your doctor may need to monitor your liver function while you are taking pantoprazole.

- If you have unintentionally lost weight recently, have suffered from repeated vomiting, have vomited blood (this can look dark like "coffee grounds"), have difficulty swallowing, or if you have noticed blood in your stool (faeces) or have passed tarry black stools, speak to your doctor. If necessary, he/she will do further tests (e.g. gastroscopy; a visual inspection of the gullet, stomach and upper intestine).

- If you are receiving a combination therapy (for the eradication of the bacterium Helicobacter pylori): Please observe the package inserts of the other medications.

- Tell your doctor if you are also taking painkillers called non-steroidal anti-inflammatory medicines (NSAIDs). You should also carefully read the package leaflets for these medicines.

Please also tell your doctor if your symptoms continue after 4 weeks, despite regularly taking this medicine.

Taking Pantodia 40 mg with 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.

It is especially important to tell your doctor if you are taking or have taken the following medicines:
- Antifungals (e.g. ketokonazole or itraconazole) which are used to treat fungal infections of the skin and nails.
- Anticoagulants to thin the blood (so-called coumarin derivatives such as phenprocoumon or warfarin). If necessary, your doctor should test your blood coagulation more frequently.
- Atazanavir to treat HIV infections. Atazanavir should not be taken with pantoprazole.

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

Clinical experience with pregnant women is limited. There is no information on the transfer of pantoprazole, the active agent in Pantodia 40 mg, into breast milk in humans.
If you are pregnant or are breast-feeding a child, you should only take Pantodia 40 mg tablets if your attending physician thinks that the benefit of the treatment for you is higher than the possible risk for your unborn child or baby.

Driving and using machines:
Taking pantoprazole normally has no impact on your ability to drive or use machines. However, dizziness and visual problems are possible side effects, which could affect your ability to drive or use machines. In this case you should not drive or use machines.

Important information about some of the ingredients of Pantodia 40 mg:
This medicine contains lactose. Please only take Pantodia 40 mg after you have consulted your doctor, if you know that you suffer from tolerance problems with certain sugars.
This medicinal product contains 2.68 mg sodium per dose. This should be taken into consideration by patients on a controlled sodium diet.

3. HOW TO TAKE PANTODIA 40 MG

Always take Pantodia 40 mg exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- Pantodia 40 mg should be taken on an empty stomach (before meals).
- You should swallow the tablet(s) whole with water.
- Do not crush, break or chew the tablet(s) as this will prevent them from working properly.

Adults and adolescents 12 years of age and above

Unless your doctor prescribes otherwise, the usual dose is:

Reflux oesophagitis
The usual dose is one 40 mg tablet per day for 4 - 8 weeks. Your doctor may then change your dose, depending on how you respond.

Stomach or duodenal ulcer
The usual dose is one 40 mg Pantodia 40 mg per day though your doctor may sometimes prescribe more.

A duodenal ulcer generally heals within 2 - 4 weeks. A stomach ulcer usually heals within 4 - 8 weeks.

In combination with antibiotics in patients whose ulcers are due to the bacteria *Helicobacter pylori*
Your doctor is likely to prescribe you one of the following combinations of twice daily Pantodia 40 mg tablets and antibiotics. The second Pantodia 40 mg dose should be taken before your evening meal.:

The usual combinations are:

a) twice daily one Pantodia 40 mg tablet
+ twice daily 1000 mg amoxicillin
+ twice daily 500 mg clarithromycin

b) twice daily one tablet Pantodia 40 mg tablet
+ twice daily 500 mg metronidazole
+ twice daily 500 mg clarithromycin

c) twice daily one Pantodia 40 mg tablet
+ twice daily 1000 mg amoxicillin
+ twice daily 500 mg metronidazole

The usual treatment period is 1-2 weeks.

If further treatment with pantoprazole is indicated to ensure healing of the ulcers, the dosage recommendations for duodenal and gastric ulcers should be considered.

Zollinger-Ellison syndrome and other diseases associated with too much acid in the stomach
The starting dose is usually 80 mg (2 tablets Pantodia 40 mg) per day. The dose can then be adjusted depending on how you respond. If prescribed more than two tablets a day, take the tablets in two equal doses.

The second dose should be taken one hour before your evening meal.

Elderly patients
A daily dose of 40 mg pantoprazole. should not be exceeded unless being used to treat *H. pylori*.

Patients with kidney disease
A daily dose of 40 mg should not be exceeded.

Patients with liver disease
In general, you should take one dose of 40 mg every other day.

Children under 12 years of age
Pantodia 40 mg should not be used in children.

Please consult your doctor if you think that the effect of Pantodia 40 mg is too strong or too weak.

If you take more Pantodia 40 mg than you should
If you take too much Pantodia 40 mg, contact your doctor immediately.

If you forget to take Pantodia 40 mg
If you forget to take a dose, take it as soon as you remember unless it is almost time for your next dose.

If you stop taking Pantodia 40 mg
Do not stop taking the medicine without first consulting your doctor. Do not stop just because you feel better. If you stop taking the 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 tablets can cause side effects, although not everybody will experience them.

You should stop taking Pantoprazole and seek immediate medical advice if you experience any of the following symptoms as they could be due to a severe allergic reaction:

- a swollen face, mouth, tongue and/or throat
- difficulty swallowing
- an itchy rash (hives) and difficulty breathing

The list below includes side-effects which may occur with pantoprazole

Common (less than 1 in 10 but more than 1 in 100 people treated)

- stomach-ache, diarrhoea, constipation or wind
- headaches

Uncommon (less than 1 in 100 but more than 1 in 1,000 people treated)

- nausea (feeling sick)
- vomiting (being sick)

- dizziness
- blurred vision
- allergic reactions, such as itchy skin and rash.

Rare (Less than 1 in 1000 but more than 1 in 10,000 people treated)

- dry mouth
- joint pain
- depression, hallucination, disorientation, confusion.

Very rare (Less than 1 in 10,000 people treated)

- a fall in the number of white cells or platelets in the blood.
- swollen legs
- muscle pain
- liver damage and jaundice (yellowing of the skin) which can be serious
- allergic reactions (these may be accompanied by a skin rash and can be severe, causing swelling of the face or mouth). This can cause difficulty breathing (see warning at the beginning of this section)
- raised body temperature
- kidney inflammation (nephritis)
- severe skin reactions (Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis or Lyell's disease)
- increased sensitivity of the skin to sunlight (photosensitivity)
- raised blood triglycerides (a type of fat in the blood)

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

This product contains tartrazine, which may cause allergic reactions.

5. HOW TO STORE PANTODIA 40 MG

Keep out of the reach and sight of children.

Do not use Pantodia 40 mg after the expiry date which is stated on the carton.

Tablet container: Shelf life after first opening: 28 days.

Storage conditions:
Tablet Container: Do not store above 25 °C.
Blister: Do not store above 30 °C.

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 Pantodia 40 mg contains:
The active substance is pantoprazole.
Each gastro-resistant tablet contains 40 mg pantoprazole (as pantoprazole sodium sesquihydrate 45.1 mg).

The other ingredients are:

Tablet Core:
microcrystalline cellulose (E460i), lactose monohydrate, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate

Colour coating:
polyvinyl alcohol, macrogol 3350, titanium dioxide (E171), talc (E553b), iron oxide yellow (E172), tartrazine aluminium lake (E102)

Gastro-resistant coating:
methacryl acid-ethyl acrylate copolymer, sodium lauryl sulphate, polysorbate 80, triethyl citrate (E1505), talcum (E553b)

What Pantodia 40 mg looks like and contents of the pack:
Pantodia 40 mg are pale yellow to ochre, elongated coated tablets.
Pantodia 40 mg is available in:

Tablet containers (HDPE bottles with HDPE or PP screw cap closure with desiccant) in packages of 7, 14, 28 or 50 gastro-resistant tablets.

Blisters (Aluminium-Aluminium foil blisters) in packages of 7, 14, 28 or 56 gastro-resistant tablets.

Marketing Authorisation Holder:

To be completed nationally

Manufacturer:
Laboratorios Dr. Esteve S. A.
Sant Marti, s/n. Poligon Industrial
08107 Martorelles (Barcelona), Spain

This medicinal product is authorised in the Member States of the EEA under the following names:

Poland	Pantodia
Romania	Pantoprazol DiaMed 40 mg Comprimate gastrorezistente
Slovenia	Pantoprazol DiaMed 40 mg gastrorezistentne tablete
United Kingdom	Pantodia 40 mg gastro-resistant tablets

This user leaflet was last approved in >mm yyyy<**.**

Dialoc 20 mg
Gastro-resistant tablets
Pantoprazole

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.

1. WHAT IS DIALOC 20 MG AND WHAT IS IT USED FOR

Pantoprazole belongs to a group of medicines called proton pump inhibitors which work by reducing the amount of acid your stomach makes.

Dialoc 20 mg is used:
- To treat mild oesophageal disease due to reflux of acid from the stomach (reflux disease) and associated symptoms such as heartburn, acid regurgitation and pain on swallowing.
- For the long-term treatment and the prevention of oesophageal inflammation (reflux oesophagitis) and its relapse.
- To prevent duodenal (small bowel) and stomach ulcers caused by non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk, who need long-term treatment with these medicines.

2. BEFORE YOU TAKE DIALOC 20 MG

Do not take Dialoc 20 mg:
- If you are hypersensitive (allergic) to pantoprazole or one of the other ingredients in Dialoc 20 mg.
- If you have to take a medicine which contains atazanavir (to treat an HIV infection) as well.

Take special care with Dialoc 20 mg:
- If you suffer from a severe liver disease, you should advise your doctor. If necessary, he/she will regularly check your liver enzymes.

- If you have unintentionally lost weight recently, have suffered from repeated vomiting, have vomited blood (this can look dark like "coffee grounds"), have difficulty swallowing,

or if you have noticed blood in your stool (faeces) or have passed tarry black stools, speak to your doctor. If necessary, he/she will do further tests (e.g. gastroscopy; a visual inspection of the gullet, stomach and upper intestine).

- If you are taking Dialoc 20 mg on a long-term basis (e.g. over a year) your doctor will examine you regularly. Consult your doctor about any new symptom that appears or any other unusual problems. Tell your doctor if you have had vitamin B12 (cyanocobalamin) deficiency in the past.

- Tell your doctor if you are also taking painkillers called non-steroidal anti-inflammatory medicines (NSAIDs). You should also carefully read the package leaflets for these medicines.

Please also tell your doctor if your symptoms continue after 4 weeks, despite regularly taking this medicine.

Taking Dialoc 20 mg with 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.

It is especially important to tell your doctor if you are taking or have taken the following medicines:
- Antifungals (e.g. ketokonazole or itraconazole) which are used to treat fungal infections of the skin and nails
- Anticoagulants to thin the blood (so-called coumarin derivatives such as phenprocoumon or warfarin). If necessary, your doctor should test your blood coagulation more frequently.
- Atazanavir to treat HIV infections. Atazanavir should not be taken with pantoprazole.

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

Clinical experience with pregnant women is limited. There is no information on the transfer of pantoprazole, the active agent in Dialoc 20 mg, into breast milk in humans.
If you are pregnant or are breast-feeding a child, you should only take Dialoc 20 mg tablets if your attending physician thinks that the benefit of the treatment for you is higher than the possible risk for your unborn child or baby.

Driving and using machines:
Taking pantoprazole normally has no impact on your ability to drive or use machines. However, dizziness and visual problems are possible side effects, which could affect your ability to drive or use machines. In this case you should not drive or use machines.

Important information about some of the ingredients of Dialoc 20 mg
This medicine contains lactose. Please only take Dialoc 20 mg after you have consulted your doctor, if you know that you suffer from tolerance problems with certain sugars.
This medicinal product contains 1.34 mg sodium per dose. This should be taken into consideration by patients on a controlled sodium diet.

3. HOW TO TAKE DIALOC 20 MG

Always take Dialoc 20 mg exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- Dialoc 20 mg should be taken on an empty stomach (before meals).
- You should swallow the tablet(s) whole with water.
- Do not crush, break or chew the tablet(s) as this will prevent them from working properly.

Adults and adolescents 12 years of age and above

Unless your doctor prescribes otherwise, the usual dose is:

Mild oesophageal disease due to gastric acid reflux (reflux disease) and related symptoms (e.g. heartburn, acid regurgitation and pain on swallowing)
The recommended oral dose is one Dialoc 20 mg gastro-resistant tablet per day for 2 – 4 weeks (continuing for another 4 weeks if necessary). After this, any recurrent symptoms can be controlled taking one tablet daily, as needed.

If your symptoms cannot be controlled with on-demand therapy, your doctor should consider an alternative long-term treatment.

Long-term therapy and preventing relapses of oesophageal inflammation (reflux oesophagitis)
The recommended dose is one 20 mg tablet per day, which can be increased to 40 mg daily if symptoms return., in which case Dialoc 40 mg is available. After the oesophageal inflammation has been healed the dose can be reduced to 20 mg pantoprazole again.

Adults

Preventing stomach and duodenal ulcers caused by anti-inflammatory drugs (NSAIDs)
The recommended dose is one Dialoc 20 mg gastro-resistant tablet per day, for as long as prescribed by your doctor.

Elderly patients and patients with kidney disease
A daily dose of 40 mg should not be exceeded.

Patients with liver disease
A daily dose of 20 mg should not be exceeded.

Children under 12 years of age
Dialoc 20 mg should not be used in children.

Please consult your doctor if you think that the effect of Dialoc 20 mg is too strong or too weak.

If you take more Dialoc 20 mg than you should
If you take too much Dialoc 20 mg, contact your doctor immediately.

If you forget to take Dialoc 20 mg
If you forget to take a dose, take it as soon as you remember unless it is almost time for your next dose.

If you stop taking Dialoc 20 mg
Do not stop taking the medicine without first consulting your doctor Do not stop just because you feel better. If you stop taking the 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 tablets can cause side effects, although not everybody will experience them.

You should stop taking Pantoprazole and seek immediate medical advice if you experience any of the following symptoms as they could be due to a severe allergic reaction:

- a swollen face, mouth, tongue and/or throat
- difficulty swallowing
- an itchy rash (hives) and difficulty breathing

The list below includes side-effects which may occur with pantoprazole

Common (less than 1 in 10 but more than 1 in 100 people treated)

- stomach-ache, diarrhoea, constipation or wind
- headaches

Uncommon (less than 1 in 100 but more than 1 in 1,000 people treated)

- nausea (feeling sick)
- vomiting (being sick)
- dizziness
- blurred vision
- allergic reactions, such as itchy skin and rash.

Rare (Less than 1 in 1000 but more than 1 in 10,000 people treated)

- dry mouth
- joint pain
- depression, hallucination, disorientation, confusion.

Very rare (Less than 1 in 10,000 people treated)

- a fall in the number of white cells or platelets in the blood.
- swollen legs
- muscle pain
- liver damage and jaundice (yellowing of the skin) which can be serious
- allergic reactions (these may be accompanied by a skin rash and can be severe, causing swelling of the face or mouth). This can cause difficulty breathing (see warning at the beginning of this section)
- raised body temperature
- kidney inflammation (nephritis)
- severe skin reactions (Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis or Lyell's disease)
- increased sensitivity of the skin to sunlight (photosensitivity)
- raised blood triglycerides (a type of fat in the blood)

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

5. HOW TO STORE DIALOC 20 MG

Keep out of the reach and sight of children.

Do not use Dialoc 20 mg after the expiry date which is stated on the carton.

Tablet container: Shelf life after first opening: 28 days.

Storage conditions:
Tablet container: Do not store above 25 °C.
Blister: Do not store above 30 °C.

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 Dialoc 20 mg contains:
The active substance is pantoprazole.
Each gastro-resistant tablet contains 20 mg pantoprazole (as pantoprazole sodium sesquihydrate 22.55 mg).

The other ingredients are:

Tablet Core:
microcrystalline cellulose (E460i), lactose monohydrate, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate

Colour coating:
polyvinyl alcohol, macrogol 3350, titanium dioxide (E171), talc (E553b), iron oxide yellow (E172), quinoline yellow aluminium lake (E104)

Gastro-resistant coating:
methacryl acid-ethyl acrylate copolymer, sodium lauryl sulphate, polysorbate 80, triethyl citrate (E1505), talc (E553b)

What Dialoc 20 mg looks like and contents of the pack:
Dialoc 20 mg are yellow to ochre, elongated coated tablets.
Dialoc 20 mg is available in:

Tablet containers (HDPE bottles with HDPE or PP screw cap closure with desiccant) in packages of 7, 14, 28 or 50 gastro-resistant tablets.

Blisters (Aluminium-Aluminium foil blisters) in packages of 7, 14, 28 or 56 gastro-resistant tablets.

Marketing Authorisation Holder:

DiaMed GmbH
Kaiser-Wilhelm-Ring 4 – 6
48145 Münster
Germany

Manufacturer:

Laboratorios Dr. Esteve S. A.
Sant Marti, s/n. Poligon Industrial
08107 Martorelles (Barcelona), Spain

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria	Pantoprazol DiaMed 20 mg magensaftresistente Tabletten
Belgium	Pantoprazol DiaMed 20 mg maagsapresistente tablet/Comprimé gastro-résistant/magensaftresistente Tablette
Denmark	Pantoprazol DiaMed S 20 mg Enterotablet
Finland	Pantoprazol Diamed 20 mg Enterotabletti
Norway	Pantoprazol DiaMed 20 mg Enterotablett
Poland	Dialoc
Sweden	Pantoprazol DiaMed 20 mg Enterotablett
The Netherlands	Pantoprazol DiaMed S 20 mg maagsapresistente tablet
United Kingdom	Dialoc S 20 mg gastro-resistant tablets

This user leaflet was last approved in >mm yyyy<**.**

Dialoc 40 mg
Gastro-resistant tablets
Pantoprazole

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.

1. WHAT IS DIALOC 40 MG AND WHAT IS IT USED FOR

Pantoprazole belongs to a group of medicines called proton pump inhibitors which work by reducing the amount of acid your stomach makes.

Dialoc 40 mg is used:
- in the treatment of moderate to severe forms of reflux oesophagitis (an inflammation of your oesophagus, or gullet, caused by the regurgitation of stomach acid).
- in treating an infection with a bacterium called *Helicobacter pylori* in patients with duodenal ulcers and stomach ulcers in combination with two antibiotics (Eradication therapy). The aim is to get rid of the bacteria and so reduce the likelihood of these ulcers returning.
- in the treatment of duodenal (small bowel) and stomach ulcers
- to treat Zollinger-Ellison syndrome and other conditions producing too much acid in the stomach.

2. BEFORE YOU TAKE DIALOC 40 MG

Do not take Dialoc 40 mg:
- If you are hypersensitive (allergic) to pantoprazole, tartrazine or one of the other ingredients in Dialoc 40 mg.
- If you suffer from a moderate to severe hepatic or renal dysfunction and shall receive a combination therapy for eradication of the bacterium Helicobacter pylori.
- If you have to take a medicine which contains atazanavir (to treat an HIV infection) as well.

Take special care with Dialoc 40 mg:

- If you have severe liver disease - your doctor may need to monitor your liver function while you are taking pantoprazole.

- If you have unintentionally lost weight recently, have suffered from repeated vomiting, have vomited blood (this can look dark like "coffee grounds"), have difficulty swallowing, or if you have noticed blood in your stool (faeces) or have passed tarry black stools, speak to your doctor. If necessary, he/she will do further tests (e.g. gastroscopy; a visual inspection of the gullet, stomach and upper intestine).

- If you are receiving a combination therapy (for the eradication of the bacterium Helicobacter pylori): Please observe the package inserts of the other medications.

- Tell your doctor if you are also taking painkillers called non-steroidal anti-inflammatory medicines (NSAIDs). You should also carefully read the package leaflets for these medicines.

Please also tell your doctor if your symptoms continue after 4 weeks, despite regularly taking this medicine.

Taking Dialoc 40 mg with 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.

It is especially important to tell your doctor if you are taking or have taken the following medicines:
- Antifungals (e.g. ketokonazole or itraconazole) which are used to treat fungal infections of the skin and nails.
- Anticoagulants to thin the blood (so-called coumarin derivatives such as phenprocoumon or warfarin). If necessary, your doctor should test your blood coagulation more frequently.
- Atazanavir to treat HIV infections. Atazanavir should not be taken with pantoprazole.

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

Clinical experience with pregnant women is limited. There is no information on the transfer of pantoprazole, the active agent in Dialoc 40 mg, into breast milk in humans.
If you are pregnant or are breast-feeding a child, you should only take Dialoc 40 mg tablets if your attending physician thinks that the benefit of the treatment for you is higher than the possible risk for your unborn child or baby.

Driving and using machines:
Taking pantoprazole normally has no impact on your ability to drive or use machines. However, dizziness and visual problems are possible side effects, which could affect your ability to drive or use machines. In this case you should not drive or use machines.

Important information about some of the ingredients of Dialoc 40 mg:
This medicine contains lactose. Please only take Dialoc 40 mg after you have consulted your doctor, if you know that you suffer from tolerance problems with certain sugars.
This medicinal product contains 2.68 mg sodium per dose. This should be taken into consideration by patients on a controlled sodium diet.

3. HOW TO TAKE DIALOC 40 MG

Always take Dialoc 40 mg exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- Dialoc 40 mg should be taken on an empty stomach (before meals).
- You should swallow the tablet(s) whole with water.
- Do not crush, break or chew the tablet(s) as this will prevent them from working properly.

Adults and adolescents 12 years of age and above

Unless your doctor prescribes otherwise, the usual dose is:

Reflux oesophagitis
The usual dose is one 40 mg tablet per day for 4 - 8 weeks. Your doctor may then change your dose, depending on how you respond.

Stomach or duodenal ulcer
The usual dose is one 40 mg Dialoc 40 mg per day though your doctor may sometimes prescribe more.

A duodenal ulcer generally heals within 2 - 4 weeks. A stomach ulcer usually heals within 4 - 8 weeks.

In combination with antibiotics in patients whose ulcers are due to the bacteria *Helicobacter pylori*
Your doctor is likely to prescribe you one of the following combinations of twice daily Dialoc 40 mg tablets and antibiotics. The second Dialoc 40 mg dose should be taken before your evening meal.:

The usual combinations are:

a) twice daily one Dialoc 40 mg tablet
+ twice daily 1000 mg amoxicillin
+ twice daily 500 mg clarithromycin

b) twice daily one tablet Dialoc 40 mg tablet
+ twice daily 500 mg metronidazole
+ twice daily 500 mg clarithromycin

c) twice daily one Dialoc 40 mg tablet
+ twice daily 1000 mg amoxicillin
+ twice daily 500 mg metronidazole

The usual treatment period is 1-2 weeks.

If further treatment with pantoprazole is indicated to ensure healing of the ulcers, the dosage recommendations for duodenal and gastric ulcers should be considered.

Zollinger-Ellison syndrome and other diseases associated with too much acid in the stomach
The starting dose is usually 80 mg (2 tablets Dialoc 40 mg) per day. The dose can then be adjusted depending on how you respond. If prescribed more than two tablets a day, take the tablets in two equal doses.

The second dose should be taken one hour before your evening meal.

Elderly patients
A daily dose of 40 mg pantoprazole. should not be exceeded unless being used to treat *H. pylori*.

Patients with kidney disease
A daily dose of 40 mg should not be exceeded.

Patients with liver disease
In general, you should take one dose of 40 mg every other day.

Children under 12 years of age
Dialoc 40 mg should not be used in children.

Please consult your doctor if you think that the effect of Dialoc 40 mg is too strong or too weak.

If you take more Dialoc 40 mg than you should
If you take too much Dialoc 40 mg, contact your doctor immediately.

If you forget to take Dialoc 40 mg
If you forget to take a dose, take it as soon as you remember unless it is almost time for your next dose.

If you stop taking Dialoc 40 mg
Do not stop taking the medicine without first consulting your doctor. Do not stop just because you feel better. If you stop taking the 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 tablets can cause side effects, although not everybody will experience them.

You should stop taking Pantoprazole and seek immediate medical advice if you experience any of the following symptoms as they could be due to a severe allergic reaction:

- a swollen face, mouth, tongue and/or throat
- difficulty swallowing
- an itchy rash (hives) and difficulty breathing

The list below includes side-effects which may occur with pantoprazole

Common (less than 1 in 10 but more than 1 in 100 people treated)

- stomach-ache, diarrhoea, constipation or wind
- headaches

Uncommon (less than 1 in 100 but more than 1 in 1,000 people treated)

- nausea (feeling sick)
- vomiting (being sick)
- dizziness

- blurred vision
- allergic reactions, such as itchy skin and rash.

Rare (Less than 1 in 1000 but more than 1 in 10,000 people treated)

- dry mouth
- joint pain
- depression, hallucination, disorientation, confusion.

Very rare (Less than 1 in 10,000 people treated)

- a fall in the number of white cells or platelets in the blood.
- swollen legs
- muscle pain
- liver damage and jaundice (yellowing of the skin) which can be serious
- allergic reactions (these may be accompanied by a skin rash and can be severe, causing swelling of the face or mouth). This can cause difficulty breathing (see warning at the beginning of this section)
- raised body temperature
- kidney inflammation (nephritis)
- severe skin reactions (Stevens-Johnson Syndrome, erythema multiforme and toxic epidermal necrolysis or Lyell's disease)
- increased sensitivity of the skin to sunlight (photosensitivity)
- raised blood triglycerides (a type of fat in the blood)

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

This product contains tartrazine, which may cause allergic reactions.

5. HOW TO STORE DIALOC 40 MG

Keep out of the reach and sight of children.

Do not use Dialoc 40 mg after the expiry date which is stated on the carton.

Tablet container: Shelf life after first opening: 28 days.

Storage conditions:
Tablet container: Do not store above 25 °C.
Blister: Do not store above 30 °C.

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 Dialoc 40 mg contains:
The active substance is pantoprazole.
Each gastro-resistant tablet contains 40 mg pantoprazole (as pantoprazole sodium sesquihydrate 45.1 mg).

The other ingredients are:

Tablet Core:
microcrystalline cellulose (E460i), lactose monohydrate, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate

Colour coating:
polyvinyl alcohol, macrogol 3350, titanium dioxide (E171), talc (E553b), iron oxide yellow (E172), tartrazine aluminium lake (E102)

Gastro-resistant coating:
methacryl acid-ethyl acrylate copolymer, sodium lauryl sulphate, polysorbate 80, triethyl citrate (E1505), talcum (E553b)

What Dialoc 40 mg looks like and contents of the pack:
Dialoc 40 mg are pale yellow to ochre, elongated coated tablets.
Dialoc 40 mg is available in:

Tablet containers (HDPE bottles with HDPE or PP screw cap closure with desiccant) in packages of 7, 14, 28 or 50 gastro-resistant tablets.

Blisters (Aluminium-Aluminium foil blisters) in packages of 7, 14, 28 or 56 gastro-resistant tablets.

Marketing Authorisation Holder:

DiaMed GmbH
Kaiser-Wilhelm-Ring 4 – 6
48145 Münster
Germany

Manufacturer:
Laboratorios Dr. Esteve S. A.
Sant Marti, s/n. Poligon Industrial
08107 Martorelles (Barcelona), Spain

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria	Pantoprazol DiaMed 40 mg magensaftresistente Tabletten
Belgium	Pantoprazol DiaMed 40 mg maagsapresistente tablet/Comprimé gastro-résistant/magensaftresistente Tablette
Denmark	Pantoprazol DiaMed S 40 mg Enterotablet
Finland	Pantoprazol Diamed 40 mg Enterotabletti
Norway	Pantoprazol DiaMed 40 mg Enterotablett
Poland	Dialoc
Sweden	Pantoprazol DiaMed 40 mg Enterotablett
The Netherlands	Pantoprazol DiaMed S 40 mg maagsapresistente tablet
United Kingdom	Dialoc 40 mg gastro-resistant tablets

This user leaflet was last approved in >mm yyyy<**.**

Module 4
Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton label

1. NAME OF THE MEDICINAL PRODUCT

Pantodia 20 mg
Gastro-resistant tablets
Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant tablet contains 20 mg pantoprazole (as pantoprazole sodium sesquihydrate 22.55 mg).

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 Gastro-resistant tablets
14 Gastro-resistant tablets
28 Gastro-resistant tablets
50 Gastro-resistant tablets
56 Gastro-resistant tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

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

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8. EXPIRY DATE

EXP:

Tablet container: Shelf life after first opening: 28 days.

9. SPECIAL STORAGE CONDITIONS

Tablet container: Do not store above 25 °C.
Blister: Do not store above 30 °C.

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

DiaMed GmbH
Kaiser-Wilhelm-Ring 4 – 6
48145 Münster
Germany

12. MARKETING AUTHORISATION NUMBER(S)

PL 32652/0001

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

---

16. INFORMATION IN BRAILLE

Pantodia 20 mg

PARTICULARS TO APPEAR ON THE INNER PACKAGING

Label tablet container

1. NAME OF THE MEDICINAL PRODUCT

Pantodia 20 mg
Gastro-resistant tablets
Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant tablet contains 20 mg pantoprazole (as pantoprazole sodium sesquihydrate 22.55 mg).

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 Gastro-resistant tablets
14 Gastro-resistant tablets
28 Gastro-resistant tablets
50 Gastro-resistant tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

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

EXP:

Shelf life after first opening: 28 days.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

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

---

11. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

DiaMed GmbH
Kaiser-Wilhelm-Ring 4 – 6
48145 Münster
Germany

12. MARKETING AUTHORISATION NUMBER(S)

PL 32652/0001

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

---

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE INNER PACKAGING

Label Blister

1. NAME OF THE MEDICINAL PRODUCT

Pantodia 20 mg
Gastro-resistant tablets
Pantoprazole

2. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

DiaMed GmbH

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton label

1. NAME OF THE MEDICINAL PRODUCT

Pantodia 40 mg
Gastro-resistant tablets
Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant tablet contains 40 mg pantoprazole (as pantoprazole sodium sesquihydrate 45.1 mg).

3. LIST OF EXCIPIENTS

Contains lactose and tartrazine. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 Gastro-resistant tablets
14 Gastro-resistant tablets
28 Gastro-resistant tablets
50 Gastro-resistant tablets
56 Gastro-resistant tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

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

EXP:

Tablet container: Shelf life after first opening: 28 days.

9. SPECIAL STORAGE CONDITIONS

Tablet container: Do not store above 25 °C.

Blister: Do not store above 30 °C.

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

DiaMed GmbH
Kaiser-Wilhelm-Ring 4 – 6
48145 Münster
Germany

12. MARKETING AUTHORISATION NUMBER(S)

PL 32652/0002

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

---

16. INFORMATION IN BRAILLE

Pantodia 40 mg

PARTICULARS TO APPEAR ON THE INNER PACKAGING

Label tablet container

1. NAME OF THE MEDICINAL PRODUCT

Pantodia 40 mg
Gastro-resistant tablets
Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant tablet contains 40 mg pantoprazole (as pantoprazole sodium sesquihydrate 45.1 mg).

3. LIST OF EXCIPIENTS

Contains lactose and tartrazine. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 Gastro-resistant tablets
14 Gastro-resistant tablets
28 Gastro-resistant tablets
50 Gastro-resistant tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

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

EXP:

Shelf life after first opening: 28 days.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

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

11. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

DiaMed GmbH
Kaiser-Wilhelm-Ring 4 – 6
48145 Münster
Germany

12. MARKETING AUTHORISATION NUMBER(S)

PL 32652/0002

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

---

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE INNER PACKAGING

Label Blister

1. NAME OF THE MEDICINAL PRODUCT

Pantodia 40 mg
Gastro-resistant tablets
Pantoprazole

2. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

DiaMed GmbH

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton label

1. NAME OF THE MEDICINAL PRODUCT

Dialoc 20 mg
Gastro-resistant tablets
Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant tablet contains 20 mg pantoprazole (as pantoprazole sodium sesquihydrate 22.55 mg).

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 Gastro-resistant tablets
14 Gastro-resistant tablets
28 Gastro-resistant tablets
50 Gastro-resistant tablets
56 Gastro-resistant tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

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

EXP:

Tablet container: Shelf life after first opening: 28 days.

9. SPECIAL STORAGE CONDITIONS

Tablet container: Do not store above 25 °C.
Blister: Do not store above 30 °C.

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

DiaMed GmbH
Kaiser-Wilhelm-Ring 4 – 6
48145 Münster
Germany

12. MARKETING AUTHORISATION NUMBER(S)

PL 32652/0003

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

---

16. INFORMATION IN BRAILLE

Dialoc 20 mg

PARTICULARS TO APPEAR ON THE INNER PACKAGING

Label tablet container

1. NAME OF THE MEDICINAL PRODUCT

Dialoc 20 mg
Gastro-resistant tablets
Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant tablet contains 20 mg pantoprazole (as pantoprazole sodium sesquihydrate 22.55 mg).

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 Gastro-resistant tablets
14 Gastro-resistant tablets
28 Gastro-resistant tablets
50 Gastro-resistant tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

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

EXP:

Shelf life after first opening: 28 days.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

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

---

11. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

DiaMed GmbH
Kaiser-Wilhelm-Ring 4 – 6
48145 Münster
Germany

12. MARKETING AUTHORISATION NUMBER(S)

PL 32652/0003

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

---

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE INNER PACKAGING

Label Blister

1. NAME OF THE MEDICINAL PRODUCT

Dialoc 20 mg
Gastro-resistant tablets
Pantoprazole

2. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

DiaMed GmbH

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton label

1. NAME OF THE MEDICINAL PRODUCT

Dialoc 40 mg
Gastro-resistant tablets
Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant tablet contains 40 mg pantoprazole (as pantoprazole sodium sesquihydrate 45.1 mg).

3. LIST OF EXCIPIENTS

Contains lactose and tartrazine. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 Gastro-resistant tablets
14 Gastro-resistant tablets
28 Gastro-resistant tablets
50 Gastro-resistant tablets
56 Gastro-resistant tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

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

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8. EXPIRY DATE

EXP:

Tablet container: Shelf life after first opening: 28 days.

9. SPECIAL STORAGE CONDITIONS

Tablet container: Do not store above 25 °C.

Blister: Do not store above 30 °C.

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

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11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

DiaMed GmbH
Kaiser-Wilhelm-Ring 4 – 6
48145 Münster
Germany

12. MARKETING AUTHORISATION NUMBER(S)

PL 32652/0004

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

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16. INFORMATION IN BRAILLE

Dialoc 40 mg

PARTICULARS TO APPEAR ON THE INNER PACKAGING

Label tablet container

1. NAME OF THE MEDICINAL PRODUCT

Dialoc 40 mg
Gastro-resistant tablets
Pantoprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant tablet contains 40 mg pantoprazole (as pantoprazole sodium sesquihydrate 45.1 mg).

3. LIST OF EXCIPIENTS

Contains lactose and tartrazine. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 Gastro-resistant tablets
14 Gastro-resistant tablets
28 Gastro-resistant tablets
50 Gastro-resistant tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use.

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

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8. EXPIRY DATE

EXP:

Shelf life after first opening: 28 days.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.

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

11. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

DiaMed GmbH
Kaiser-Wilhelm-Ring 4 – 6
48145 Münster
Germany

12. MARKETING AUTHORISATION NUMBER(S)

PL 32652/0004

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

---

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE INNER PACKAGING

Label Blister

1. NAME OF THE MEDICINAL PRODUCT

Dialoc 40 mg
Gastro-resistant tablets
Pantoprazole

2. NAME AND ADDRESS OF MARKETING AUTHORISATION HOLDER

DiaMed GmbH

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. OTHER

Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the applications for:

- Pantodia/Dialoc 20 mg Gastro-resistant Tablets for the management of mild reflux disease and prevention of gastroduodenal ulceration

And

- Pantodia/Dialoc 40mg Gastro-resistant Tablets, for the treatment of peptic ulceration, moderate to severe reflux oesophagitis, hypersecretory conditions including Zollinger-Ellison Syndrome and, in combination with appropriate antibiotic therapy, eradication of *Helicobacter pylori* infection in patients with peptic ulceration

Could be approved.

These are applications made under the decentralised procedure (DCP), according to Article 10.1 of Directive 2001/83, as amended, claiming to be generic medicinal products of Pantoloc 40mg Gastro-resistant Tablet, which were originally granted licences to Nycomed Pharma GmbH (Austria) on 29th June 1995. The corresponding medicinal products which are authorised in the RMS are Protium 20mg and 40mg gastro-resistant tablets (Nycomed GmbH).

The UK is the Reference Member State (RMS) in these Decentralised Procedures, and the Concerned Member States (CMS) are:

Poland, Romania, and Slovenia (UK/H/1802/01-02/DC)
Austria, Belgium, Denmark, Finland, The Netherlands, Norway, Poland and Sweden (UK/H/1803/01-02/DC)

Pantodia/Dialoc is a proton pump inhibitor, i.e. it inhibits the gastric H^+/K^+-ATPase enzyme, which is responsible for acid secretion in the parietal cells of the stomach. The action is specific and dose-proportional. It is used for the treatment of acid related disease like upper gastrointestinal ulceration and oesophageal reflux disease and (in conjunction with antibiotics) the eradication of *Helicobacter pylori*.

No new preclinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release

of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 21st April 2010. The licences were granted in the UK on 24th May 2010.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Pantodia/Dialoc 20mg and 40mg Gastro-resistant Tablets
Name(s) of the active substance(s) (INN)	Pantoprazole sodium sesquihydrate
Pharmacotherapeutic classification (ATC code)	Proton Pump Inhibitor (A02BC02)
Pharmaceutical form and strength(s)	Gastro-resistant Tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/1802-3/01-02/DC
Reference Member State	United Kingdom
Member States Concerned	UK/H/1802/01-02/DC: Poland, Romania, and Slovenia UK/H/1803/01-02/DC: Austria, Belgium, Denmark, Finland, The Netherlands, Norway, Poland and Sweden
Marketing Authorisation Number(s)	PL 32652/0001-4
Name and address of the authorisation holder	DiaMed GmbH, Kaiser-Wilhelm-ring 4-6, 48145 Munster, Germany

III SCIENTIFIC OVERVIEW AND DISCUSSION

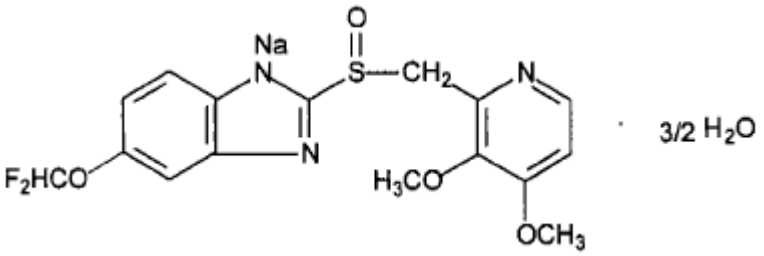
III.1 QUALITY ASPECTS

S. DRUG SUBSTANCE

INN: Pantoprazole sodium sesquihydrate

Chemical Name: 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl]methyl]sulphinyl] -1H-benzimidazole sodium salt sesquihydrate

Structure:



Molecular Formula: $C_{16}H_{14}F_2N_3NaO_4S.3/2H_2O$

Molecular Weight: 432.38g.mol

Appearance: White to off-white powder. It is freely soluble in water, methanol and ethanol (96%), practically insoluble in hexane.

All aspects of the manufacture and control of the active substance pantoprazole sodium sesquihydrate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

P. DRUG PRODUCT

Other ingredients

Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose (E460i), lactose monohydrate, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, Opadry II 85F32081 Yellow (polyvinyl alcohol, macrogol 3350, titanium dioxide (E171), iron oxide yellow (E172), quinoline yellow aluminium lake (E104), sodium lauryl sulphate, polysorbate 80), methacryl acid-ethyl acrylate copolymer, triethyl citrate (E1505) and talc (E553b)

All excipients comply with their respective European Pharmacopoeia monographs with the exception of Opadry II 85F32081 Yellow which complies with an in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate and calcium stearate, none of the excipients are sourced from animal or human origin. The suppliers of lactose monohydrate has confirmed that it is sourced from healthy animals, under the same conditions as milk for human consumption and the calcium stearate is sourced from vegetable. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to formulate robust, stable tablets that were containing qualitatively and quantitatively the same active ingredient as

Pantoloc Gastro-resistant Tablets (Nycomed Pharma GmbH, Austria), and exhibiting the same bioavailability in order to comply with the regulations pertaining to generic medicinal product applications.

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and originator products.

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 are 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
All strengths of tablets are packaged in either
1. aluminium-aluminium foil blisters in pack sizes of 7, 14, 28 or 56 gastro-resistant tablets or
2. HDPE bottles with HDPE or PP screw cap closure with desiccant, in pack sizes of 7, 14, 28 or 50 gastro-resistant tablets.

The marketing authorisation holder has stated that they do not intend to market all pack sizes for all product licences at the present time. However, they have committed to submitting mock-ups for any pack sizes to the regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations 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 with a storage condition ‘Do not store above 30°C’ is set for the blister packs and 3 years with a storage condition of ‘Do not store above 25°C’ is set for the bottles. These are acceptable.

Bioequivalence/bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

SPC, PIL, Labels

The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet 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.

Pharmacovigilance System and Risk Management Plan
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for these products.

MAA forms
The MAA forms are pharmaceutically satisfactory.

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

Conclusion
The grant of marketing authorisation is recommended

III.2 PRE-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of pantoprazole sodium sesquihydrate are well-known, no further preclinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

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

There are no objections to the approval of these products from a preclinical viewpoint.

III.3 CLINICAL ASPECTS
Pharmacokinetics
To support these applications the applicant has submitted two bioequivalence studies performed under fasting and fed conditions.

1. *A randomized, single dose, open-label, two period, two-sequence, blinded crossover, comparative bioavailability study on Pantoprazole 40mg gastro-resistant tablets compared with Eupantol 40mg gastro-resistant tablets in 36 healthy, adults, under fasting conditions. Of these, the protocol pre-specified that the first 30 would be analysed; the remaining 6 were reserves to replace possible drop-outs.*

2. *A randomized, single dose, open-label, two period, two-sequence, blinded crossover, comparative bioavailability study on Pantoprazole 40mg gastro-resistant tablets compared with Eupantol 40mg gastro-resistant tablets in 36 healthy, adults, under fed conditions. Of these, the protocol pre-specified that the first 30 would be analysed; the remaining 6 were reserves to replace possible drop-outs.*

Serial blood samples for plasma pantoprazole assay were taken prior to dosing then at 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 5, 6, 8,10,12, 16 and 24 hours post dose.

Each study period was separated by an adequate 7-day washout corresponding to more than 10 times the expected half life of the moiety to be measured.

Results

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) under fasting condition

PARAMETER	GEOMETRIC LS MEANS		RATIO	90% CONFIDENCE LIMITS		POWER OF THE STUDY (%)
	TEST	REFERENCE		LOWER	UPPER	
C_{max}	2672.9	2875.5	92.95	86.06	100.39	>99
AUC_T	5443.7	5196.7	104.75	99.82	109.93	100
AUC_∞ **	5789.0	5551.1	104.29	99.43	109.38	100

** n = 29

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) under fed condition

PARAMETER	GEOMETRIC LS MEANS		RATIO	90% CONFIDENCE LIMITS		POWER OF THE STUDY (%)
	TEST	REFERENCE		LOWER	UPPER	
C_{max}	2344.7	2530.7	92.65	82.61	103.92	>99
AUC_T	4033.1	4114.5	98.02	92.40	103.98	>99
AUC_∞ **	4290.3	4296.1	99.86	94.43	105.61	>99

** n=28

The single dosing studies with the 40mg tablet, under both fed and fasting conditions, show bioequivalence compared to the reference product and results can be extrapolated to the lower strength 20mg tablet, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

Pharmacodynamics
The pharmacodynamic characteristics of pantoprazole have been well-studied in the past. There would be no particular concerns for a generic medicinal product.

Clinical Efficacy
No new data have been submitted and none are required.

Clinical Safety
No new data have been submitted and none are required.

SPC, PIL and Labels
The SPC, PIL and labels are medically acceptable. The SPCs are consistent with those for the originator products.

Expert Reports
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

6. Conclusion
The grant of marketing authorisation is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Pantodia/Dialoc 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
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant's Pantoprazole 40mg Gastro-resistant Tablets and its respective reference product. As the 20mg strength of the product meet the criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) the results and conclusions of the bioequivalence study on the 40mg strength can be extrapolated to the other strength of tablet.

No new or unexpected safety concerns arise from these applications.

The SPC PIL and labelling are satisfactory and consistent with those of the reference products.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicants' products and the originator products 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.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome