What is in Pantoloc?

Each Pantoloc tablet contains pantoprazole as the active ingredient. Other non-medicinal ingredients are: crospovidone, methylhydroxypropylcellulose, yellow iron oxide, mannitol, poly(ethylacrylate, methacrylic acid) 1:1, propylene glycol, anhydrous sodium carbonate, polyvidone K90, calcium stearate, triethyl citrate, polyvidone K25, polysorbate 80, sodium lauryl sulphate and titanium dioxide.

Check with your doctor whether you might be allergic to any of the above ingredients.

What should I tell my doctor before taking Pantoloc?

Tell your doctor:

- about all health problems you have now or have had in the past;
- about all other medicines you take, including ones you can get without a prescription;
- if you are allergic to "non-medicinal" substances which may be present in "Pantoloc" (See "What is in Pantoloc?");
- if you are pregnant, plan to become pregnant or are breastfeeding.

How do I take Pantoloc properly?

Your doctor has recommended you take Pantoloc tablets for a specific number of weeks. Keep taking Pantoloc until you have finished all your tablets, as recommended by your doctor. Do not stop even when you start to feel better. If you stop taking Pantoloc too soon, your symptoms may return.

If you forget to take one dose of Pantoloc, take a tablet as soon as you remember, unless it is almost time for your next dose. If it is, do not take the missed tablet at all. Never double-up on a dose to make up for the one you have missed, just go back to your regular schedule.

Pantoloc may be taken in the morning, with or without food. Swallow the tablet(s) whole, with water. Do not crush or chew the tablet(s).

Are there any side effects?

Like any medication, Pantoloc may cause side effects in some people. When side effects have been reported, they have been generally mild and did not last a long time. Headache and diarrhea are the most common side effects; less often rash, itchiness and dizziness can occur. If any of these become troublesome, consult your doctor. If you experience any unusual or unexpected symptoms while using Pantoloc, consult your doctor.

What should I do in case of overdose?

If you or someone you know takes a lot more than the recommended dose (an overdose) you should contact a doctor or pharmacist immediately. No severe symptoms have been seen up to now in cases of overdose. Doses up to 240 mg of an injectable solution of pantoprazole have been administered and were well tolerated.

Where should I keep Pantoloc?

Keep your tablets at room temperature (15 to 30°C) and in a safe place, where children cannot reach them.

Important Note:

This information is intended to alert you to some of the times when you should call your doctor. Other situations which cannot be predicted may arise while you are taking medicines. Nothing should stop you from calling your doctor with any questions or concerns you have about using Pantoloc.

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PHARMACOLOGY

ANIMAL PHARMACOLOGY

Pharmacodynamics:

Pantoprazole is a proton pump inhibitor. It inhibits H^+,K^+-ATPase, the enzyme responsible for gastric acid secretion in the parietal cells of the stomach, in a dose-dependent manner. The drug is a substituted benzimidazole that accumulates in the acid canaliculi of parietal cells after absorption. There, pantoprazole is converted into the active form, a cyclic sulfenamide that binds selectively to the proton translocating region of the H^+,K^+-ATPase. Pantoprazole's selectivity is due to the fact that it only exerts its maximal effect in a strongly acidic environment (pH < 3). Pantoprazole remains mostly inactive at higher pH values. As pantoprazole action is distal to the receptor levels, it can inhibit gastric acid secretion irrespective of the nature of the stimulus (acetylcholine, histamine, gastrin).

In vivo, pantoprazole produced marked and long-lasting inhibiton of basal and stimulated gastric acid secretion with median effective dose (ED_{50}) values ranging from 0.2 -2.4 mg/kg in rats and dogs. In addition to the administration of single doses, pantoprazole has been tested upon repeated oral adminstration (e.g. during 24-h pH-metry in dogs performed under pentagastrin stimulation). While a dose of 1.2 mg/kg did not significantly elevate pH on Day 1, pH rose to values between 4 and 7 after a 5-day dosing regimen. This effect was no longer observed 18 hours after the last drug administration. In various gastric ulcer models in the rat, pantoprazole showed antiulcer activity.

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In parallel to the profound inhibition of gastric acid secretion, pantoprazole induced a dose-dependent increase in serum gastrin levels up to values above 1000 pg/mL from a control level of about 100 pg/mL. As a consequence of persisting hypergastrinemia in rats after high/doses of pantoprazole, hyperplastic changes were observed in the fundic mucosa with an increased density of enterochromaffin-like (ECL) cells. These changes were reversible during drug-free recovery periods.

In a battery of standard high-dose pharmacology tests, no influence of pantoprazole was detected on the central and peripheral nervous system. In conscious dogs as well as anaesthetized cats receiving single i.v. doses up to 10 mg/kg pantoprazole, no consistent changes with respect to respiratory rate, ECG, EEG, blood pressure and heart rate were observed. Higher doses led to modest and transient reductions in blood pressure and variable changes in heart rate. No influence of pantoprazole was found on renal function and on autonomic functions, such as pancreatic and bile secretion, gastrointestinal motility and body temperature.

Nc consistent changes in the effects of ethanol, pentobarbitone, or hexobarbitone were induced by pantoprazole; only doses over 300 mg/kg prolonged the effects of diazepam.

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Pharmacokinetics:

Absorption and Distribution

Pantoprazole is absorbed rapidly in both rat and dog. Peak plasma levels are attained within 15 to 20 minutes in the rat and after about 1 hour in the dog. Oral bioavailability is 33% in the rat and 49 % in the dog. Following absorption, autoradiography and quantitative tissue distribution experiments have shown that pantoprazole is rapidly distributed to extravascular sites. Following administration of pantoprazole, distribution of radioactivity in the blood and most organs is found to be uniform initially. After 16 hours, radiolabelled pantoprazole is predominantly detected in the stomach wall. After 48 hours, all the administered radioactivity is found to have been excreted. Penetration of the blood-brain barrier by radiolabelled pantoprazole is very low. Protein binding in the rat and dog is 95% and 86%, respectively.

Metabolism and Excretion

Pantoprazole is extensively metabolized. Oxidations and reductions at different sites of the molecule, together with Phase II reactions (sulfation and glucuronidation) and combinations thereof result in the formation of various metabolites. In rats and dogs, 29-33% of the dose is excreted as urinary metabolites, and the remainder as biliary/fecal metabolites. Almost no parent compound can be found in the excreta.

Mammoglandular passage and transplacental transport has been investigated in the rat using radiolabelled pantoprazole. A maximum of 0.23% of the administered dose is

excreted in the milk. Radioactivity penetrates the placenta with 0.1-0.2% of the dose /g fetal tissue on the first day after oral administration.

HUMAN PHARMACOLOGY

Pharmacodynamics:

Pantoprazole is a potent inhibitor of gastric acid secretion. This was demonstrated by use of a gastric acid aspiration technique as well as by continuous intragastric pH monitoring. Using the aspiration technique it was also shown that pantoprazole caused a dose-dependent reduction of secreted gastric acid volume.

Table 1: Percent inhibition of pentagastrin-stimulated acid output (PSAO) in healthy volunteers following single oral doses of Pantoprazole vs. placebo during 4 to 7 hours post dosing.

Dose	Mean %Inhibition of PSAO
6 mg	13%
10 mg	24%
20 mg	27%
40 mg	42%
60 mg	54%
80 mg	80%
100 mg	82%

With 40 mg administered orally, effective inhibition of gastric acid secretion was achieved. Pantoprazole 40 mg was significantly superior to standard H_2-blocker therapy (300 mg ranitidine at night) with regard to median 24-hour and daytime pH; however, not for nighttime measurements.

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Table 2: Effects of one week oral treatment in healthy volunteers with placebo, Pantoprazole 40 mg in the morning, and standard ranitidine therapy with 300 mg in the evening

Time of Day		Median pH	
	Placebo	Pantoprazole 40 mg	Ranitidine 300 mg
08.00-08.00 (24h)	1.6	4.2*	2.7
08.00-22.00 (Day Time)	1.8	4.4*	2.0
22.00-08.00 (Night Time)	1.3	3.1	3.7

* $p<0.05$ vs ranitidine

Increasing the once daily dose from 40 mg to 80 mg pantoprazole did not result in a significantly higher median 24-hour pH.

Table 3: Effect of oral Pantoprazole in healthy volunteers on median 24 hour pH on Day 7 (40 vs 80 mg).

40 mg	80 mg	
3.8	3.85	n.s.

Hence, once daily administration of 40 mg pantoprazole should be sufficient for the treatment of most patients with acid-related diseases.

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Pharmacokinetics:

After oral intake, pantoprazole is absorbed with a bioavailability of 77% relative to i.v. dosing. Maximum serum concentrations of pantoprazole are reached within approximately 2.5 hours after oral intake. Following a dose of 40 mg, mean maximum serum concentrations of approximately 2 μg/mL and 3 μg/mL are reached after 2 to 3 hours. There is no food effect on AUC (bioavailability) and C_{max}. However, time to reach maximum serum concentrations is slightly increased when the drug is given together with a high caloric breakfast. Taking into account the long duration of action of pantoprazole, which by far exceeds the time period over which serum concentrations are measurable, this observed variation in t_{max} is considered to be of no clinical importance.

Pantoprazole is approximately 98% bound to serum protein.

Despite its relatively short elimination half-life of approximately 1 hour, the antisecretory effect increases during repeated once daily administration, demonstrating that the duration of action markedly exceeds the serum elimination half-life. This means that there is no direct correlation between the serum concentrations and the pharmacodynamic action.

Morning administration of pantoprazole was significantly superior to evening dosing with regard to 24 hour intragastric pH, hence morning dosing should be recommended for the treatment of patients. Since the intake of the drug before a breakfast did not

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influence C_{max} and AUC, which characterize rate and extent of absorption, no specific requirements for intake of pantoprazole in relation to breakfast are necessary.

Pantoprazole undergoes metabolic transformation in the liver. Approximately 82% of the oral dose is removed by renal excretion, and the remainder via feces. The main serum metabolites (M1-M3) are sulphate conjugates formed after demethylation at the pyridine moiety, the sulphoxide group being either retained (M2, main metabolite), or oxidized to a sulphone (M1), or reduced to a sulphide (M3). These metabolites also occur in the urine (main metabolite M2). Conjugates with glucuronic acid are also found in the urine.

Pantoprazole shows linear pharmacokinetics, i.e., AUC and C_{max} increase in proportion with the dose within the dose-range of 10 to 80 mg after both i.v. and oral administration. Elimination half-life, clearance and volume of distribution are considered to be dose-independent. Following repeated i.v. or oral administration, the AUC of pantoprazole was similar to a single dose.

A slight increase in AUC (12%) and C_{max} (7%) for pantoprazole occurs in elderly volunteers when compared with younger volunteers. The daily dose in elderly patients, as a rule, should not exceed the recommended dosage regimens.

The half-life increased to between 7 and 9 h, the AUC increased by a factor of 5 to 7, and the C_{max} increased by a factor of 1.5 in patients with liver cirrhosis compared with

healthy subjects. Pantoprazole should not be administered to patients with mild to moderate liver impairment unless the expected benefits outweigh the potential risks.

No dose reduction is required when pantoprazole is administered to patients with impaired kidney function, because the difference in AUC between patients who underwent dialysis and those who did not is 4%. No induction of the CYP 450 system by pantoprazole was observed during chronic administration with antipyrine as a marker. Also, no inhibition of metabolism was observed after concomitant administration of pantoprazole with either diazepam, phenytoin, nifedipine, theophylline, digoxin or oral contraceptives. Concomitant administration of pantoprazole with warfarin has no influence on the anticoagulatory effect of warfarin.

TOXICOLOGY

ACUTE TOXICITY

In acute toxicity studies in mice the mean lethal dose (LD_{50}) values for pantoprazole were found to be around 390 mg/kg bodyweight for i.v. administration and around 700 mg/kg bodyweight for oral administration.

In the rat the corresponding values were around 250 mg/kg for i.v. administration and > 1000 mg/kg for oral administration.

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Table 4: Acute toxicity studies of Pantoprazole

SPECIES	SEX	ROUTE	ca. LD_{50}* (mg/kg)
Mouse	M	p.o.	>100
	F	p.o.	747
Mouse	M	i.v.	399
	F	i.v.	395
Rat	M	p.o.	1343
	F	p.o.	1037
Rat	M	i.v.	330
	F	i.v.	343
Dog	M/F	p.o.	300-1000**
	M/F	i.v.	150-300

* Doses refer to the sodium salt administered in solution

** sodium salt as dry powder in gelatine capsules

The symptoms seen after lethal oral or i.v. doses were similar in rats and mice: the animals displayed ataxia, reduced activity, hypothermia and prostration. Surviving animals recovered uneventfully. Salivation, tremor, lethargy, prostration and coma were seen in dogs at lethal oral doses, with death occurring on the following day. Ataxia, tremor and a prone position were noted at sublethal oral and i.v. doses, but the survivors recovered quickly and appeared fully normal after the 2-week observation period.

CHRONIC TOXICITY

Daily oral doses of pantoprazole in the 1- and 6-month SD rat repeated-dose studies were 1, 5, 20, and 500 mg/kg and 0.8, 4, 16 and 320 mg/kg, respectively; doses for the 1 month rat i.v. study were 1, 5, and 30 mg/kg.

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A 12-month toxicity study in SD rats was conducted using daily oral doses of 5, 50, and 300 mg/kg. Daily oral doses in the 1- and 6 month (beagle) dog studies were 7.5, 15,30, and 100 mg/kg and 5, 15, 30, and 60 mg/kg respectively. In the 12-month oral study in dogs, 2.5, 15, and 60 mg/kg were administered daily.

Hypergastrinemia was dose-related and was observed at all doses investigated in the studies mentioned above, but was reversible upon cessation of treatment. Drug-related effects on the stomach included increased stomach weights and morphologic changes of the mucosa. In the 6-month rat study, increased stomach weight and some cellular changes were detected at all doses. In the 1-month rat study, gastric changes were detected at 5 mg/kg but not at 1 mg/kg. In dogs, increased stomach weight was observed at all doses studied. There were no gastric cellular changes detected at oral doses of 7.5 or 5 mg/kg in the 1- and 6-month dog studies, respectively. In both species, most gastric effects were reversible after a 4- or 8-week recovery period. Hypergastinemia and gastric changes were considered to be the consequence of the pharmacological action of the compound, namely prolonged and profound inhibition of acid secretion.

Increased liver weight in the rat experiments was considered to be a consequence of the induction of hepatic drug metabolizing systems and was found to be associated with centrilobular hepatocellular hypertrophy at 320 mg/kg in the 6-month study and at 50 and 300 mg/kg after 12 months of treatment. Increased liver weights were also detected at a dose of 16 mg/kg in male rats in the 6-month study and at 500 mg/kg, but not 20 mg/kg, in the 1-month study. Increased liver weight was noted in male dogs of all dose groups in

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the 1-month study, though only at 100 mg/kg in females on the same study. Both males and females had increased liver weights after 6 months administration of 30 or 60 mg/kg, but not as 15 mg/kg. In the 12-month study, liver weights were increased only in the female dogs dosed with 60 mg/kg. There were no hepatic lesions that correlated with increased liver weight in the dog studies. In dogs, the increase in liver weight was attributed to an activation of hepatic drug metabolizing systems as mentioned for rats.

Thyroid activation in animal experiments is due to the rapid metabolization of thyroid hormones in the liver and has been described in a similar form for other drugs. Thyroid weights were increased in both sexes at 500 mg/kg in the 1-month rat study and at 320 mg/kg in the rat 6-month study. Thyroid follicular cell hypertrophy was noted in females at these doses, in rats treated with 50 and 300 mg/kg in the 12 month study and also in a few females at 16 in the 6 month study. There were no thyroid effects in rats at or below an oral dose of 5 mg/kg even after 1 year. In the dog, no effects were seen on the thyroid after 4 weeks. Only slight, but not dose-dependent, increases in thyroid weights were seen after 6 months, but no changes were observed histologically. In the 12 month study, the relative thyroid weights in the 60 mg/kg group were only slightly higher than those of the control dogs, and changes were detected histologically in only a few animals under 15 and 60 mg/kg. In both species, changes were reversible.

Increased serum cholesterol values were noted in all groups in the 6- and 12 month dog studies and in all groups in the 12 month rat study. The increases were slight and were reversible after cessation of treatment.

In dog studies, oral doses of pantoprazole of 15 mg/kg or above caused a transient pulmonary edema in a proportion of naive dogs during the first week of drug administration. Pulmonary edema caused death in a few dogs after repeated oral doses of 15 mg/kg or above. There is strong evidence that the pulmonary toxicity is due to a thiol metabolite which does not occur in man. No evidence of pulmonary edema was detected in dogs at an oral dose of 7.5 mg/kg nor at 60 mg/kg when administered daily for 6 or 12 months after a 1 week dose escalation phase.

CARCINOGENICITY

Two carcinogenicity studies had been conducted:

- A 24 month oral study was conducted at doses of 0.5, 5, 50 and 200 mg/kg/day in SD rat.
- A 24 month oral study was conducted at doses of 5, 25 and 150 mg/kg/day in B6C3F1 mouse.

Pantoprazole, dissolved in distilled water, was administered once a day by oral gavage to groups of 50 male and 50 female B6C3F1 mice at doses of 5, 25, or 150 mg/kg. An identical control group was dosed with distilled water (pH 10), while a second identical control group received no treatment at all. In the rat study, pantoprazole was administered

once a day by oral gavage to groups of 70 male and 70 female SD rats at doses of 0.5, 5, 50, and 200 mg/kg. A control group of 70 males and 70 females received the vehicle.

In the 2 year carcinogenicity study in rats, which corresponds to a lifetime treatment for rats, neuroendocrine neoplasms were found in the stomach at doses of 50 mg/kg/day and above in males and at 0.5 mg/kg/day and above in females. Tumor formation occurred late in the life of the animals (only after 17 months treatment), whereas no tumors were found in rats treated with an even higher dose for 1 year. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated, and it is considered to be due to high levels of serum gastrin observed in the rat during chronic treatment.

ECL-cell neoplasms were not observed in either the carcinogenicity study in the mouse (24 months) or in the chronic studies in the dog. In clinical studies, where pantoprazole was administered at doses up to 80 mg, ECL-cell density remained almost unchanged.

Microscopy of the rat and mouse tissues gave evidence for an increase in liver tumors. In the rat experiment, the incidence of benign liver tumors in the 50 and 200 mg/kg groups and the incidence of hepatocellular carcinoma was increased in the males and females of the 200 mg/kg group. There was a slightly higher incidence of hepatocellular adenomas and carcinomas in the female mice of the 150 mg/kg group than in either of the 2 control groups. Other changes in the liver morphology were present as well. Centrilobular hepatocellular hypertrophy increased in incidence and severity with increasing dose, and

hepatocellular necrosis was increased in the highest dose in the rat and mouse studies. Hepatocellular tumors are common in mice, and the incidence found for the female 150 mg/kg group was within historical control ranges for this strain. The liver tumor incidences in rats treated with 50 mg/kg and in the male rats treated with 200 mg/kg were also within historical control incidences for the rat. These tumors occurred late in the life of the animals and were primarily benign. The nongenotoxic mechanism of rodent liver tumor formation after prolonged treatment with pantoprazole is associated with enzyme induction leading to hepatomegaly and centrilobular hypertrophy and is characterized by tumor induction in low incidences at high doses only. As pantoprazole acts in a similar fashion to phenobarbital, causing reversible centrilobular hepatocellular hypertrophy and enzyme induction in short-term studies, it is probable that the mechanism of action for induction of the liver tumors seen in long-term rodent studies is also the same. Hepatocellular tumors at high doses in rodents are not indicative of human carcinogenic risk.

A slight increase in neoplastic changes of the thyroid was observed in rats receiving pantoprazole at 200 mg/kg/day. The incidences of these tumors were within the historical control ranges for this rat strain. No thyroid neoplasms were observed in the 12-month study. The no-effect dose for both male and female rats is 50 mg/kg, which is 100 times the human dose. The effect of pantoprazole on the thyroid is secondary to the effects on liver enzyme induction, which lead to enhanced metabolism of thyroid hormones in the liver. As a consequence, increased TSH is produced, which has a trophic effect on the

thyroid gland. Clinical studies have demonstrated that neither liver enzyme induction nor changes in thyroid hormonal parameters occur in man after therapeutic doses of pantoprazole.

Tumors induced in rats and mice by pantoprazole were the result of nongenotoxic mechanisms which are not relevant to humans. Tumors were induced in rodents at dosages that provide higher exposure than with human therapeutic use. Based on kinetic data, the exposure to pantoprazole in rats receiving 200 mg/kg was 22.5 times higher than that found in humans receiving 40 mg oral doses. In mice receiving 150 mg/kg, exposure to pantoprazole was 2.5 times higher than that in humans.

MUTAGENICITY

Pantoprazole was negative in five mutagenicity studies: Ames test, chromosome aberration test in human lymphocytes *in vitro*, gene mutation test in Chinese hamster ovary cells *in vitro* and two micronucleus tests in mice *in vivo*. The three *in vitro* tests were conducted both in the presence and absence of metabolic activation. In addition, the potential of pantoprazole to induce DNA repair synthesis was tested *in vitro* in an assay using rat hepatocytes. None of the tests indicated genotoxic activity.

In addition, two *in vitro* cell transformation assays using different cell types were performed to aid in the interpretation of the rodent carcinogenicity studies; in neither test did pantoprazole enhance the morphologic transformation of the cell types used.

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REPRODUCTION AND TERATOLOGY

Pantoprazole was not teratogenic to rats or rabbits at doses up to 450 and 40 mg/kg/day (gavage), 20 and 15 mg/kg/day (i.v. injection), respectively.

Treatment of male rats with pantoprazole up to 500 mg/kg p.o. for 127 days did not affect fertility. Treatment of pregnant rats induced dose-dependent fetotoxic effects: increased pre- and postnatal deaths (450 mg/kg/day), reduced fetal weight and delayed skeletal ossification (150 mg/kg/day), and reduced pup weight (15 mg/kg/day). These results may be explained by maternal toxicity of pantoprazole at high dose and/or placental transfer of pantoprazole.

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

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

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Germany
Translation

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SUMMARY OF PRODUCT CHARACTERISTICS (SPC) - tablet - H.p. - eradication

1. NAME OF THE MEDICINAL PRODUCT

"Tradename"®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One gastro-resistant tablet contains
Pantoprazole sodium sesquihydrate 45.1 mg
(equivalent to pantoprazole 40 mg)

3. PHARMACEUTICAL FORM

Gastro-resistant tablet for oral use

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- in combination with two appropriate antibiotics (see "Posology") for the eradication of H. pylori in patients with peptic ulcers with the objective of reducing the recurrence of duodenal and gastric ulcers caused by this microorganism.
- duodenal ulcer
- gastric ulcer
- moderate and severe reflux esophagitis

4.2 Posology and method of administration

- recommended dosage:

In Helicobacter pylori positive patients with gastric and duodenal ulcers, eradication of the germ by a combination therapy should be achieved. Depending upon the resistance pattern, the following combinations can be recommended for the eradication of H. pylori:

a) twice daily one gastro-resistant tablet "Tradename"
+ twice daily 1000 mg amoxycillin
+ twice daily 500 mg clarithromycin

b) twice daily one gastro-resistant tablet "Tradename"
+ twice daily 500 mg metronidazole
+ twice daily 500 mg clarithromycin

c) twice daily one gastro-resistant tablet "Tradename"
+ twice daily 1000 mg amoxycillin
+ twice daily 500 mg metronidazole

If combination therapy is not an option, e.g. if the patient has tested negative for Helicobacter pylori, the following dosage guidelines apply for "Tradename" monotherapy:

For the treatment of gastric and duodenal ulcer and reflux esophagitis one gastro-resistant tablet of "Tradename" per day. In individual cases the dose may be doubled (increase to 2

gastro-resistant tablets "Tradename" daily) especially when there has been no response to other treatment.

In patients with severe liver impairment the dose has to be reduced to 1 tablet (40 mg pantoprazole) every other day. Furthermore, in these patients the liver enzymes should be monitored during "Tradename" therapy. In case of a rise of the liver enzymes "Tradename" should be discontinued.

The daily dose of 40 mg pantoprazole should not be exceeded in elderly patients or in those with impaired renal function. An exception is combination therapy for eradication of H. pylori, where also elderly patients should receive the usual pantoprazole dose (2x40 mg/day) during 1-week treatment.

- general instructions:

"Tradename" gastro-resistant tablets should not be chewed or crushed, and should be swallowed whole with water 1 hour before breakfast. In combination therapy for eradication of Helicobacter pylori infection, the second "Tradename" tablet should be taken before the evening meal. The combination therapy is implemented for 7 days in general and can be prolonged to up to two weeks maximum. If, to ensure healing of the ulcers, further treatment with pantoprazole is indicated, the dosage recommendations for duodenal and gastric ulcers should be considered.

A duodenal ulcer generally heals within 2 weeks. If a 2-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

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

As experience with long-term administration in man is insufficient treatment with "Tradename" should not exceed 8 weeks.

4.3 Contra-indications

"Tradename" should generally not be used in cases of known hypersensitivity to one of the constituents of "Tradename" or of the combination partners.

"Tradename" must not be used in combination treatment for eradication of H.p. in patients with moderate to severe hepatic or renal dysfunction since currently no data are available on the efficacy and safety of "Tradename" in combination treatment of these patients.

4.4 Special warnings and special precautions for use

Pantoprazole is not indicated for mild gastrointestinal complaints such as nervous dyspepsia.

In the case of combination therapy, the summaries of product characteristics of the respective drugs should be observed.

Prior to treatment the possibility of malignancy of gastric ulcer or a malignant disease of the esophagus should be excluded as the treatment with pantoprazole may alleviate the symptoms of malignant ulcers and can thus delay diagnosis.

Diagnosis of reflux esophagitis should be confirmed by endoscopy.

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

4.5 Interaction with other medicaments and other forms of interaction

"Tradename" may reduce the absorption of drugs whose bioavailability is pH-dependent (e.g. ketoconazole).

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

There were also no interactions with concomitantly administered antacids.

Human kinetic interaction studies have been performed administering pantoprazole concomitantly with the respective antibiotics (clarithromycin, metronidazole, amoxycillin). No clinically relevant interactions were found.

4.6 Pregnancy and lactation

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

4.7 Effects on ability to drive and use of machines

There are no known effects on the ability to drive and use machines.

4.8 Undesirable effects

Treatment with „Tradename" can occasionally lead to headache or diarrhoea.

There were rare reports of nausea, upper abdominal pain, flatulence, skin rash, pruritus and dizziness.

Edema, fever, the onset of depression and disturbances in vision (blurred vision) were reported in individual cases.

4.9 Overdose

There are no known symptoms of overdosage in man.

Doses up to 240 mg i.v. were administered over 2 minutes and were well tolerated.
In the case of overdosage with clinical signs of intoxication, the usual rules of intoxication therapy apply.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Item 8.7.4: Commercial Marketing Experience and Foreign Regulatory Actions

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

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

5.2 Pharmacokinetic properties

- General pharmacokinetics

Pantoprazole is rapidly absorbed and the maximal plasma concentration is achieved even after one single 40 mg oral dose. On average at about 2.5 h p.a. the maximum serum concentrations of about 2 - 3 µg/ml are achieved, and these values remain constant after multiple administration. Volume of distribution is about 0.15 l/kg and clearance is about 0.1 l/h/kg. Terminal half-life is about 1 h. There were a few cases of subjects with delayed elimination. Because of the specific activation of pantoprazole in the parietal cell the elimination half-life does not correlate with the much longer duration of action (inhibition of acid secretion).

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

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

- Bioavailability

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

- Characteristics in patients/special groups of subjects

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

Although for patients with liver cirrhosis (classes A and B according to Child) the half-life values increased to between 7 and 9 h and the AUC values increased by a factor of 5 - 7, the maximum serum concentration only increased slightly by a factor of 1.5 compared with healthy subjects.

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

5.3 Preclinical Safety Data

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

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

In the two-year studies an increased number of liver tumors was observed in rats and female mice and was interpreted as being due to pantoprazole's high metabolic rate in the liver. From mutagenicity studies, cell transformation tests and a DNA binding study it is concluded that pantoprazole has no genotoxic potential.

A slight increase of neoplastic changes of the thyroid was observed in the group of rats receiving the highest dose. The occurrence of these neoplasms is associated with the pantoprazole-induced changes in the breakdown of thyroxine in the rat liver. As the therapeutic dose in man is low, no side effects to the thyroid glands are expected.

Investigations revealed no evidence of impaired fertility or teratogenic effects.
Penetration of the placenta was investigated in the rat and was found to increase with advanced gestation. As a result, concentration of pantoprazole in the foetus is increased shortly before birth.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

One gastro-resistant tablet contains:

active ingredient:
pantoprazole sodium sesquihydrate 45.1 mg
(equivalent to pantoprazole 40.0 mg)

inactive constituents:

sodium carbonate
D-mannitol (≙ 0.0036 BU)
crospovidone
polyvidone K90
calcium stearate
methylhydroxypropylcellulose
polyvidone K25
titanium dioxid E 171
yellow iron oxid E 172
propylene glycol
poly(ethylacrylate, methacrylic acid) 1:1

polysorbate 80
sodium lauryl sulfate
triethyl citrate
printing ink

6.2 Incompatibilities

None

6.3 Shelf life

3 years

6.4 Special precautions for storage

None

6.5 Nature and contents of container

Bottles and closures made of polyethylene; blister made of transparent hard PVC film, coated with PVDC on one side. Aluminium cover foil, lacquered with VCVAC/acrylate on one side.

Packs with	15 enteric-coated tablets 30 enteric-coated tablets 60 enteric-coated tablets 100 enteric-coated tablets
Hospital pack with	140 enteric-coated tablets 140 (10x14) enteric-coated tablets 700 (5x140) enteric-coated tablets
Sample pack with	15 enteric-coated tablets

6.6 Instructions for use/handling

None

7. MARKETING AUTHORIZATION HOLDER

Name or style and permanent address or registered place of business of the holder of the marketing authorization

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8. MARKETING AUTHORIZATION NUMBER

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

10. DATE OF (PARTIAL) REVISION OF THE TEXT

December 1997