Item 8.7.4: Commercial Marketing Experience and Foreign Regulatory Actions

Sweden
Translation

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FASS text

Pantoloc®
Nycomed

Enterotablets 40 mg

Acid blocking substance - proton pump inhibitor A02B C02

Declaration. 1 tablet contains: Pantoprazol. natr.sesquihydr. respond. pantoprazol. 40 mg, mannitol. 42.7 mg, colourants (E171, E172) et constit. q.s.

Indications. Short-term treatment of duodenal ulcers, gastric ulcers and reflux oesophagitis.

Dosage. The tablets should be swallowed whole with a small amount of water before breakfast. They must not be chewed or broken.

Duodenal ulcers. Normal dosage for small ulcers is one tablet (40 mg) per day for two weeks. In smokers, for example, and those with larger ulcers, treatment for four weeks can be necessary.

Stomach ulcers. Normal dosage for small ulcers is one tablet (40 mg) per day for four weeks. In smokers, for example, and those with larger ulcers, treatment for eight weeks can be necessary.

Patients whose peptic ulcers are associated with Helicobacter pylori should be treated with antimicrobial agents. In combination with Pantoloc 40 mg twice daily, the combination clarithromycin 250 mg and tinidazole 500 mg both twice daily have shown good effect.

Reflux oesophagitis. Normal dosage for low grade reflux oesophagitis is one tablet (40 mg) per day for four weeks. In smokers, for example, and those with more pronounced reflux oesophagitis, treatment for eight weeks can be necessary.

Since pantoprazole does not accumulate significantly, normal dosage can be recommended to patients with reduced kidney function.

Warnings or special precautions for use. Patients with severe reduced liver function.
Suspected ulcer disease should be verified using X-rays or endoscopy early on in the anamnesis to avoid inadequate treatment.
In the case of stomach ulcers, malignancy should be ruled out.

Interactions. Interaction studies have been carried out between pantoprazole and pharmaceuticals which are metabolized via the cytochrome P-450 system. No interaction could be shown during simultaneous treatment with antipyrine, carbamazepine, coffein, diazepam, diclofenac, digoxin, phenytoin, nifedipin, phenprocumone, and theophylline. Pantoprazole does not affect the pharmacodynamics of warfarin, and does neither interact with antacids or sequential oral contraceptives containing levonorgesterel and oestrogen.

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Pregnancy. Category B:3. See special section marked g. Clinical experience in pregnant women is limited.
A weak foeto-toxic effect has been seen in animal experiments. Therefore, during pregnancy and until there is further experience, Pantoloc should only be given after due consideration.

Breastfeeding. Group IVa. Information is not available on whether pantoprazole passes over into the mother's milk.

Side-effects: The most common symptoms which have been reported inclinical trials with pantoprazole have been diarrhoea and headache, with a frequency of 1.5% each, in most cases, these side-effects are temporary.

Common (>1/100)	*General:* Headache, tiredness *GI:* Diarrhoea, nausea/vomiting, constipation, abdominal pain and gas formation
Less common (1/100-1/1000)	*General:* Dizziness *Skin:* Rash, itching

Pharmacodynamics. 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 a chiral substance which exists as a raceme where both enantiomers are equipotent.

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.

Pharmacokinetics. The pharmacokinetic documentation is based on the raceme. Bioavailibility is about 77% (65-85%). Maximum plasma concentrations of 2-3 micrograms/ml are achieved about 2.5 hours after the administration of a single oral dose of 40 mg. The distribution volume is about 0.15 l/kg and the protein binding is about 98%.

The half-life in plasma is about 1 hour (0.9-1.08). The kinetics are linear and the plasma levels following repeated dosage are the same as after a single dose. Clearance is about 0.1 l/hr/kg.

Pantoprazole is primarily metabolized in the liver. It is unknown which enzyme system is involved in the metabolization of pantoprazole. The main metabolite,

dimethylpantoprazole, is inactive and is conjugated with sulphate. Its half-life is about 1.5 hours, i.e. somewhat longer than for pantoprazole. The metabolites of pantoprazole are eliminated to 80% in the urine and the rest in the faeces.

The intra-individual variability in plasma levels is about 35%. In 2% of the population studied, the half-life of pantoprazole following repeated dosage is about 2-10 hours and AUC values are about 3-8 times greater than in other individuals. The underlying cause for these findings is unclear. The accumulation of pantoprazole and its main metabolite is limited in these patients at normal doses and the altered pharmacokinetics are not expected to have any clinical relevance.

These properties are not connected to debrisoquin hydroxylase and it is unclear if they are connected to S-mephenytoin hydroxylase activities. The bioavailibility in patients with serious cirrhosis of the liver is unchanged although C_{max} is 2-3 times greater and AUC values are 5-8 times greater than in healthy volunteers, probably due to changed clearance. Since pantoprazole is not significantly accumulated, normal doses can be recommended for patients with reduced liver function. In elder patients, a marginal increase in the half-life can be seen. This is not cause for any dose adjustment. Pantoprazole is only dialysed to a very small extent.

Manufacturer. Byk Gulden.

Packages and prices.
Enterotablets 40 mg
14 pcs.
28 pcs.
56 pcs.
100 pcs.

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United Kingdom
Original Language

SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

Protium (or Panselect)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pantoprazole sodium sesquihydrate 45.1 mg
(equivalent to pantoprazole 40 mg)

3. PHARMACEUTICAL FORM

Enteric-coated tablet for oral use

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

- duodenal ulcer
- gastric ulcer
- moderate and severe reflux oesophagitis

Note

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

4.2 Posology and Method of Administration

The recommended oral dosage is one enteric-coated tablet per day. Protium should not be chewed or crushed, and should be swallowed whole with water either before or during breakfast.

In most patients, freedom from symptoms is achieved rapidly.

As sufficient experience with long-term administration in man is lacking, the length of a course of treatment with Protium should not exceed 8 weeks.

Duodenal ulcer:

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

Gastric ulcer:

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

Gastro-Oesophageal Reflux:

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

Elderly:

No dose adjustment is necessary in the elderly.

Patients with impaired renal function:

No dose adjustment is necessary in patients with renal impairment.

Patients with hepatic cirrhosis:

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

Children:

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

4.3 Contra-indications

Protium may not be used in cases of known hypersensitivity to any of its constituents.

4.4 Special Warnings and Precautions for Use

None

4.5 Interactions with other Medicaments and other forms of Interaction

No drug interactions have been reported so far (see also section 5.2)

4.6 Pregnancy and Lactation

Use during pregnancy:

There is no information about the safety of pantoprazole during pregnancy in humans. Animal experiments have revealed no signs of foetal damage, but reproduction studies have revealed reduced litter weight and delayed development of the skeleton at doses above 15 mg/kg.

During pregnancy, Protium should not be used unless the benefit exceeds the potential risk.

Use during lactation

There is no information about the safety of pantoprazole during breast-feeding in humans. In the rat, not more than 0.02% of the administered dose is excreted via the breast milk.

During breast-feeding, Protium should not be used unless the benefit exceeds the potential risk.

4.7 Effects on Ability to Drive and Use Machines

Pantoprazole does not affect the ability to drive and use machines.

4.8 Undesirable Effects

Treatment with Protium can occasionally lead to headache (1.3%) or diarrhoea (1.5%).

Skin rashes (0.4%), pruritus (0.5%) and dizziness (0.7%) were observed rarely.

4.9 Overdose

There are no known symptoms of overdosage in man. However, pantoprazole is very specific in action and no particular problems are anticipated. Doses up to 240 mg i.v. were administered without obvious adverse effects.

As pantoprazole is extensively protein bound, it is not readily dialysable. Apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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

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

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

Pantoprazole has the same effect whether administered orally or intravenously.

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

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

5.2 Pharmacokinetic Properties

General Pharmacokinetics

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

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

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

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

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

Characteristics in patients/special groups of subjects

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

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

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

Preclinical Safety Data

Acute toxicity

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

In the rat, the corresponding values were around 240 mg/kg for i.v. administration and 900 mg/kg for oral administration.

Chronic toxicity

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

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

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

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

Carcinogenicity

In a 2-year carcinogenicity study in rats - which corresponds to lifetime treatment for rats - ECL cell carcinoids were found. The mechanism leading to the formation of gastric carcinoids by substituted benzimidazoles has been carefully investigated and allows the conclusion that it is a secondary reaction to the massively elevated serum gastrin levels occurring in the rat during treatment. In addition, rats have more ECL cells in the mucosa of the glandular stomach than man,so that a larger number of responder cells for the increased gastrin values can become active.

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

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

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

Mutagenicity

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

Reproduction toxicology

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Crospovidone, mannitol, hydroxypropyl methylcellulose, poly (ethylacrylate, methacrylic acid) 1:1, anhydrous sodium carbonate, propylene glycol, polyvidone K90, calcium stearate, triethyl citrate, polyvidone K25, titanium dioxide (E 171), polysorbate 80, sodium lauryl sulphate, yellow iron oxide (E 172).

6.2 Incompatibilities

None

6.3 Shelf Life

Pantoprazole tablets are stable over a period of 3 years.

6.4 Special Precautions for Storage

Blister packaging:	Store below 25°C
PE-bottle:	Store below 30°C

6.5 Nature and Contents of Container

Protium is distributed in PE-bottles or alternatively in PVC/PVDC/Alu blisters, packed in carton boxes.

Dose units: 14, 28 enteric-coated tablets
2 tablet starter pack

6.6 Instructions for Use/Handling

None

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7. MARKETING AUTHORISATION HOLDER

Byk Gulden
Lomberg Chemische Fabrik GmbH
Byk Gulden Straße 2
D-78467 Konstanz
Germany
(0)7531 84-0

8. MARKETING AUTHORISATION NUMBER

PL 04889/0010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

4 June 1996

10. DATE OF (PARTIAL) REVISION OF THE TEXT

November 1996

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 25, 1999

FROM: Lilia Talarico, M.D., Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180 /S/

SUBJECT: Secondary Review, Summary Memo

TO: NDA 20-987

THROUGH: Florence Houn, M.D., Director, Office of Drug Evaluation III

Pantoprazole is a substitute benzimidazole that binds covalently to the H^+K^+-ATPase causing irreversible inhibition of the proton pump activity and gastric acid secretion. Restoration of activity requires *de novo* protein synthesis of the proton pump. Proton pump inhibitors are effective in the treatment of symptoms and mucosal damage resulting from hypersecretion of gastric acid such as gastroesophageal reflux disease (GERD) and associated reflux esophagitis (RE) and erosive esophagitis (EE).

In June 1998, the sponsor submitted NDA 20-987 requesting approval of Pantoprazole for short term treatment (4 to 8 weeks) for the healing of erosive esophagitis associated with GERD and relief of associated symptoms. The results of two clinical trials were presented in the NDA in support of approval of the above indication.

Study GMR 32022 (3001A1-300 US) was a multicenter, randomized, double-blind clinical trial that compared three doses of Pantoprazole (10, 20 and 40 mg) to placebo in 603 patients with symptomatic EE. Treatment was continued for up to 8 weeks. The primary efficacy endpoint was endoscopic resolution of esophageal erosions to grade 1 or less at week 4 or at week 8 if esophageal erosions were still present at week 4. Secondary efficacy endpoint was resolution of the reflux symptoms. Overall, 603 patients were enrolled in the study and 538 patients completed the study. Except for the censoring of patients with healed esophageal lesions at week 4 without any subsequent evaluation, the study design was otherwise adequate. The study was well-executed in terms of randomization, blinding and data collection.

After 4 weeks of treatment statistically significant dose-response relationship and therapeutic gain over placebo were demonstrated: overall, the healing rates were 42%, 55% and 72% for 10, 20 and 40 mg Pantoprazole dosing respectively compared to 13.6% for placebo (p-value vs placebo all <0.001). No significant increase in efficacy was observed at week 8.

In terms of symptomatic improvement of EE, the dose regimen of 40 mg provided the fastest relief (within the first week of therapy) and was effective in the highest percentage of patients.

Pantoprazole was generally safe and well tolerated at all doses. One cardiac death occurred in the 10 mg group. No significant laboratory abnormalities were observed.

Study GMR-32023 (300A1-301-US) was a multicenter, randomized, double-blind study to compare the clinical efficacy and safety of pantoprazole 20 mg or 40 mg once daily to Nizatidine 150 mg twice daily for 4 to 8 weeks in patients with symptomatic and erosive esophagitis. Overall, 244 patients were enrolled and 215 completed the study. In general, the study design appeared to be adequate and well controlled and the study was well executed.

The primary efficacy endpoint (resolution of esophageal erosion) and the secondary efficacy endpoint (resolution of symptoms of EE) were as described in study –300US. After 4 weeks of treatment, both dose regimens of Pantoprazole 20 and 40 mg were statistically superior to Nazitidine in healing of esophageal erosions: 60%. 65%, and 20.5% respectively. No significant difference was observed between the pantoprazole 20mg and 40 mg dose. The results were similar after 8 weeks of treatment.
For patients with more severe disease (grade 3 EE), both dose regimens of Pantoprazole were significantly more effective than Nazitidine. Again, no greater efficacy was observed with the higher dose of Pantoprazole.

With respect to EE symptoms, both doses of Pantoprazole were more effective than Nazitidine. The 40 mg dose was not more effective than the 20 mg dose.

Both doses of Pantoprazole were generally safe and well tolerated. The incidence of adverse events was not different among the three treatment groups.
Review of the 4 month Safety Update has not revealed an increased incidence of serious adverse events or the occurrence of unexpected adverse events.

Based on the strong evidence of the efficacy and the acceptable safety profile in terms of incidence and severity of adverse events reported during the clinical trials, approval of Pantoprazole 40 mg qd for 4-8 weeks for the healing of erosive esophagitis and the relief of symptoms associated with GERD was recommended.

The preclinical pharmacology data and the results of the animal toxicology studies that were provided in the NDA were addressed by the Medical reviewer, Dr. Gallo-Torres in his medical review. However, at that time, the review by the Agency's Pharmacology/ Toxicology reviewer was not yet available.

The Pharmacology reviewer, Dr. Timothy Robison has reviewed the previous carcinogenicity data and additional animal data from studies performed

Comparison of the findings of the 2-year carcinogenicity studies of pantoprazole and two marketed proton pump inhibitors omeprazole and lansoprazole indicated that only neuroendocrine tumors of stomach (benign and malignant) were observed with all compounds, and testicular adenoma was observed with lansoprazole. Stomach adenocarcinoma, squamous cell papilloma and carcinoma, thyroid adenomas and carcinomas, and liver adenomas and carcinomas were reported only for the animals receiving pantoprazole.

Two-year carcinogenicity studies were repeated in Fisher F-344 rats. The report of a study was submitted in April 1996. The maximum dose of pantoprazole used in this study was 50 mg/kg based on the sponsor's belief that the dose of 200 mg/kg used in the studies with S-D rats was in excess of the MTD. This assumption was not corroborated

by a 90-day oral dose ranging study performed in Fisher rats receiving pantoprazole up to 200 mg/kg. The tumors found in the Fisher F-344 rats carcinogenicity study included neuroendocrine tumors (benign and malignant) and granulocytic leukemia.

Studies to assess the tumor promotion potential of pantoprazole in liver, thyroid, stomach, and forestomach were performed in rats.

The tumor promoting activity of pantoprazole was assessed in the stomach and forestomach of S-D rats using N-methyl-N-nitroso-guanidine (MNNG) as initiating carcinogen. For the purpose of evaluating the tumor promoting potential of pantoprazole, the MNNG+ pantoprazole group was compared to MNNG+vehicle group. A third group received pantoprazole alone and the control group received no therapy. The results were submitted in May 1998.
Mortality was increased in the groups receiving MNNG and a variety of pathologic findings occurred in all three treated groups. Squamous epithelial hyperplasia was evident in the groups receiving pantoprazole. Adenocarcinomas occurred in 35% of female rats treated with MNNG+pantoprazole as compared to 5% of female rats that received MNNG+vehicle, however the incidence rates of adenocarcinomas in male rats receiving MNNG with or without pantoprazole was similar.

The tumor promoting activity of pantoprazole in liver and thyroid in S-D rats was assessed using N-nitroso-N-methylurea (NMU). The positive control group received phenobarbital after NMU. Mortality was increased and a variety of pathologic findings were observed. Tumor incidence in thyroid was low in the positive control of NMU+phenobarbital and mainly in female rats invalidating the study.
Increased incidence of combined hepatocellular neoplasms and foci of cellular alteration was observed in female rats receiving NMU+ pantoprazole, however this was not the case for male rats suggesting that the finding in female rats may have been due to the high mortality of study animals.

Comparative toxicokinetic studies were performed to assess the hyperplastic and hyperthrophic changes in the liver by pantoprazole, lansoprazole and omeprazole. The assessment of potential for DNA damage included 32P-Post-labeling experiments.. Hepatocyte proliferation was measured by determining BrdU incorporation into hepatic nuclei and identification of proliferating cell nuclear antigen. Hepatocyte proliferation was observed in rats receiving pantoprazole or omeprazole, but not in rats receiving lansoprazole. Light and electronic microscopy did not show significant difference in hepatocyte hyperthrophy among different treatment groups.

In conclusion, a quantitative and qualitative difference in incidence of tumors was observed in rats treated with pantoprazole compared to other proton pump inhibitors. Furthermore, covalent DNA binding was demonstrated and presence of DNA adducts in liver DNA was observed on ———— obtained from rats treated with pantoprazole. Tumors were also documented in animals during 6 and 12 months chronic toxicity studies of pantoprazole.

/S/
Lilia Talarico, M.D.

cc:
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APPEARS THIS WAY
ON ORIGINAL