SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DEGASTROL 15 mg Micropellet Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains;
Active substance:
Lansoprazole ..... 15 mg

Excipient(s):
Sucrose ..... 100.474 mg
Sodium lauryl sulphate ..... 0.007 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Micropellet capsule.
Size 3, opaque, hard gelatin capsules with a cream colored body and orange cap containing white-creamy-white, odorless pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Duodenal and gastric ulcer,
- Treatment and prophylaxis of reflux esophagitis,
- Eradication of *Helicobacter pylori* (*H. pylori*) concurrently given with appropriate antibiotic therapy for treatment of *H. pylori*-associated ulcers.
- Treatment and prophylaxis of NSAID-associated duodenal and benign gastric ulcers in patients requiring continued NSAID treatment,
- Symptomatic gastro-esophageal reflux disease,
- Treatment of erosive esophagitis,
- Pathologic hypersecretory conditions including Zollinger-Ellison syndrome.

4.2 Posology and method of administration

Posology/frequency and duration of administration
Unless otherwise specified by physician, usual doses of lansoprazole are as follows:

Duodenal ulcer: The recommended dose is 30 mg once daily for 2 weeks. In patients not fully healed within this time, the medication is continued at the same dose for another 2 weeks.

Gastric ulcer: The recommended dose is 30 mg once daily for 4 weeks. The ulcer usually heals within 4 weeks, but in patients not fully healed within this time, the medication may be continued at the same dose for another 4 weeks.

Reflux esophagitis: The recommended dose is 30 mg once daily for 4 weeks. In patients not fully

healed within this time, the treatment may be continued at the same dose for another 4 weeks.

Prophylaxis of reflux esophagitis: The recommended dose is 15 mg once daily. The dose may be increased up to 30 mg daily as necessary.

Eradication of Helicobacter pylori: In combination therapy, consideration should be given to bacterial resistance, duration of treatment (usually 7 days but sometimes up to 14 days), and selection of the appropriate antibacterial agent.

The recommended dose of lansoprazole in combination with the following antibacterial agents is 30 mg twice daily for 7 days:

- Clarithromycin 250-500 mg twice daily + amoxicillin 1 g twice daily
- Clarithromycin 250 mg twice daily + metronidazole 400-500 mg twice daily

H. pylori eradication rates of up to 90% are obtained when clarithromycin is combined with lansoprazole and amoxicillin or metronidazole. 6 months after successful eradication treatment, the risk of re-infection is low and relapse is therefore unlikely.

Treatment of NSAID (non-steroidal anti-inflammatory drug) associated duodenal and benign gastric ulcers in patients requiring continuous NSAID treatment: The recommended dose is 30 mg once daily for 4 weeks. In patients not fully healed the treatment may be continued for another 4 weeks. For patients at risk or with ulcers that are difficult to heal, a longer course of treatment and/or a higher dose should probably be used.

Prophylaxis of NSAID associated gastric and duodenal ulcers in patients at risk (age >65 or history of gastric or duodenal ulcer) requiring prolonged NSAID treatment: The recommended dose is 15 mg once daily. If the treatment fails a dose of 30 mg once daily should be used.

Symptomatic gastro-esophageal reflux disease: The recommended dose is 15 mg or 30 mg once daily. Relief of symptoms is obtained rapidly. Individual adjustment of dosage should be considered. If the symptoms are not relieved within 4 weeks with a daily dose of 30 mg lansoprazol, additional treatment is recommended.

Pathologic hypersecretory conditions including Zollinger-Ellison syndrome: The recommended initial dose is 60 mg once daily. The dose should be adjusted according to the patient's need and the treatment should be continued for as long as necessary. Daily doses of up to 180 mg have been used. If the required daily dose exceeds 120 mg, it should be given in two divided doses.

Method of administration:
For the desired effect, DEGASTROL micropellet capsules should be taken once a day in the morning on an empty stomach (except for the treatment of Helicobacter pylori eradication, where it is taken twice a day, morning and evening).

Lansoprazole should be taken at least 30 minutes before food (see section 5.2). Capsules should be swallowed as a whole with liquid.

Patients should be informed not to open, chew or crush capsules.

According to studies and clinical practice, capsules can be used as follows in patients with difficulty swallowing capsules and in patients:

- The capsule is opened. The micropellets are mixed with a small amount of water, apple/tomato juice or sprinkled on a soft food (e.g. yoghurt, apple puree) and swallowed.
- The capsule is opened. For administration by nasogastric tube, the micropellets are mixed with 40 mL of apple juice (see section 5.2.).

The medication should be administered immediately after preparation of the suspension or mixture. The micropellets should not be chewed or crushed. Use in other drinks and liquids is not recommended as clinical studies have not been conducted.

Additional information on special populations:
Renal impairment:
There is no need for a dose adjustment in patients with renal impairment.

Hepatic impairment:
Patients with moderate or severe liver disease should be kept under regular supervision and the daily dose should be halved (see sections 4.4 and 5.2).

Pediatric population:
In paediatric patients aged 1-11 years:
In paediatric patients ≤30 kg, the recommended dose for short-term treatment of symptomatic gastroesophageal reflux disease and erosive esophagitis is 15 mg once daily for up to 12 weeks.

In paediatric patients over 30 kg, the recommended dose is 30 mg once daily for up to 12 weeks.

In patients aged 12-17 years:
The recommended dose in gastroesophageal reflux disease is 15 mg once daily for up to 8 weeks. The recommended dose in erosive esophagitis is 30 mg once daily for up to 8 weeks.

Geriatric population:
Due to reduced clearance in the elderly an adjustment of dose may be necessary based on individual requirements. If there is no clinical requirement, the daily dose of 30 mg should not be exceeded.

4.3 Contraindications
DEGASTROL is contraindicated in patients with sensitivity to lansoprazole or other ingredients. Lansoprazole should not be administered with atazanavir (see section 4.5).

Proton pump inhibitors, including lansoprazole, are contraindicated with drugs containing rilpivirine.

4.4 Special warnings and precautions for use
In clinical studies, paediatric patients aged 1-11 years were not administered lansoprazole for more than 12 weeks. It is not known whether lansoprazole is safe and effective when used for longer than the recommended duration. The recommended dose and duration of use should not be exceeded in paediatric patients.

Lansoprazole therapy may mask signs of gastric malignancy. Therefore, patients should be

evaluated for the possibility of gastric malignancy before initiating therapy.

Lansoprazole should be used with caution in patients with moderate and severe hepatic dysfunction (see sections 4.2 and 5.2).

Acute tubulointerstitial nephritis:
Acute tubulointerstitial nephritis (TIN) has been observed in patients taking PPIs and can occur at any point during PPI therapy. Patients may present with signs and symptoms ranging from symptomatic hypersensitivity reactions to non-specific symptoms of reduced renal function (e.g. malaise, nausea, anorexia). In reported case series, some patients have been diagnosed on biopsy and in the absence of non-renal symptoms (e.g. fever, rash or arthralgia). Lansoprazole should be discontinued and patients with suspected acute TIN should be evaluated.

Cyanocobalamin (vitamin B12) deficiency:
Daily treatment with any acid-suppressing drug for a prolonged period (e.g. longer than three years) may lead to malabsorption of cyanocobalamin caused by hypo- or achlorhydria. There are rare reports in the literature of cyanocobalamin deficiency occurring with acid suppressive therapy. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed in patients treated with lansoprazole. Cyanocobalamin deficiency should be considered in patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, in people with reduced body stores or risk factors that reduce vitamin B12 absorption on long-term treatment (such as the elderly) or if relevant clinical symptoms are observed.

Interaction with methotrexate:
The literature indicates that concomitant use of proton pump inhibitors with methotrexate (primarily at high doses) may increase and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. Temporary discontinuation of the proton pump inhibitor may be considered in some patients with high-dose methotrexate administration.

Fundic gland polyps:
Proton pump inhibitor usage is associated with an increased risk of fundic gland polyps, which increases with long-term use, especially after one year. Most proton pump inhibitor recipients who develop fundic gland polyps have been asymptomatic and fundic gland polyps have been identified incidentally at endoscopy. The shortest duration of proton pump inhibitor therapy appropriate to the condition being treated should be used.

Risk of heart valve thickening in paediatric patients less than one year of age:
Lansoprazole is not approved in paediatric patients less than one year of age. Non-clinical studies in young rats with lansoprazole have shown an adverse effect of heart valve thickening. The risk of heart valve damage has not been reported in patients one year of age and older.

Lansoprazole, like all proton pump inhibitors (PPIs), may increase the number of bacteria normally present in the gastrointestinal tract. This may increase the risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and, especially in hospitalised patients, *Clostridium difficile*.

In patients suffering from gastro-duodenal ulcers, the possibility of *H. pylori* infection as an

etiological factor should be considered.

In patients with gastro-duodenal ulcer complaints, the possibility of H.pylori infection as an etiological factor should be considered.

If lansoprazole is used in combination with antibiotics for eradication therapy of *H. pylori*, the product information of these antibiotics should also be followed.

Because of limited safety data for patients on maintenance treatment for longer than 1 year, regular review of the treatment and a comprehensive risk/benefit assessment should be performed

Very rarely cases of colitis have been reported in patients taking lansoprazole. Therefore, in the case of severe and/or persistent diarrhea, discontinuation of therapy should be considered.

Except in patients treated for eradication of infection, if diarrhoea persists, lansoprazole should be discontinued because of the possibility of microscopic colitis with thickening of the collagen bundle or infiltration of inflammatory cells seen in the submucosa of the large intestine. In the majority of cases, the symptoms of microscopic colitis resolve with discontinuation of lansoprazole.

Co-administration of lansoprazole with HIV protease inhibitors whose absorption is dependent on acidic intragastric pH, such as atazanavir and nelfinavir, is not recommended due to a significant reduction in their bioavailability (see section 4.5). If co-administration of lansoprazole with HIV protease inhibitors is unavoidable, close clinical monitoring is recommended.

The treatment for the prevention of peptic ulceration of patients in need of continuous NSAID treatment should be restricted to high risk patients (e.g. previous gastrointestinal bleeding, perforation or ulcer, advanced age, concomitant use of medication known to increase the likelihood of upper GI adverse events [e.g. corticosteroids or anticoagulants], the presence of a serious co-morbidity factor or the prolonged use of NSAID maximum recommended doses).

Bone fracture:
Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk of osteoporosis-related fractures of the hip, wrist or spine. Proton pump inhibitors, especially when used at high doses and for prolonged periods (>1 year), may moderately increase the risk of hip, wrist and spine fractures, predominantly in the elderly or in the presence of other known risk factors. Patients should receive the lowest dose and shortest duration of PPI therapy appropriate for the condition for which they are being treated. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10-40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and should receive adequate vitamin D and calcium.
Hypomagnesemia:
Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Severe symptoms of hypomagnesaemia, such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmias, may occur, but they may start insidiously and be overlooked. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI therapy. For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically during

treatment.

Interactions with diagnostic investigations for neuroendocrine tumors:
Serum chromogranine A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.

Increased levels of chromogranin A (CgA) may interfere with investigations for neuroendocrine tumours. To prevent this interaction, lansoprazole treatment should be stopped at least 5 days before CgA measurements. If CgA and gastrin levels have not returned to the reference range after the first measurement, measurements should be repeated 14 days after discontinuation of proton pump inhibitor treatment.

Subacute cutaneous lupus erythematosus:
Proton pump inhibitors are associated with very infrequent cases of subacute cutaneous lupus erythematosus. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping DEGASTROL. Having previously developed subacute cutaneous lupus erythematosus after treatment with a proton pump inhibitor increases the risk of the same condition occurring with other proton pump inhibitors.

Excipient warning
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

DEGASTROL contains less than 1 mmol sodium (23 mg) in each micropellet capsule, i.e. it is actually ‘sodium-free’.

4.5 Interactions with other medicinal products and other forms of interaction

<u>Effects of lansoprazole on other medicinal products</u>

Medicinal products with pH dependent absorption:
Lansoprazole may interfere with the absorption of other medicinal products where gastric pH is an important determinant of oral bioavailability.

HIV protease inhibitors/antiretroviral drugs
Co-administration of lansoprazole with HIV protease inhibitors whose absorption is dependent on acidic intragastric pH, such as atazanavir and nelfinavir, is not recommended due to a significant reduction in their bioavailability (see section 4.4). One study showed that co-administration of lansoprazole (60 mg once daily) with 400 mg atazanavir in healthy volunteers led to a significant reduction in atazanavir exposure (approximately 90% reduction in AUC (area under the curve) and Cmax (maximum serum concentrations)).

Reduced exposure to certain antiretroviral drugs (e.g. rilpivirine, atazanavir and nelfinavir) when used concomitantly with lansoprazole may reduce the antiviral effect and promote the development of drug resistance.

Increased exposure to other antiretroviral drugs (e.g. saquinavir) when used concomitantly with lansoprazole may increase the toxicity of antiretroviral drugs.

There are other antiretroviral drugs that do not cause clinically significant interactions with lansoprazole.

Ketoconazole and itraconazole: The absorption of ketoconazole and itraconazole from the gastrointestinal tract is enhanced by the presence of gastric acid. Administration of lansoprazole may result in sub-therapeutic concentrations of ketoconazole and itraconazole and the combination should be avoided.

Mycophenolate mofetil (MMF): Co-administration of PPIs in healthy volunteers and transplant patients receiving MMF has been reported to reduce exposure to the active metabolite mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at increased gastric pH. The clinical significance of reduced MPA exposure on organ rejection in organ transplant patients receiving lansoprazole and MMF has not been determined. Lansoprazole should be used with caution in organ transplant patients receiving MMF.

Digoxin: Co-administration of lansoprazole and digoxin may lead to increased digoxin plasma levels. The plasma levels of digoxin should therefore be monitored and the dose of digoxin adjusted if necessary when initiating and ending lansoprazole treatment.

Medicinal products metabolized by P450 enzymes:
Lansoprazole may increase plasma concentrations of medicinal products that are metabolized by CYP3A4. Caution is advised when combining lansoprazole with medicinal products which are metabolized by this enzyme and have a narrow therapeutic window.

Warfarin: There are reports of increased INR and prothrombin time in patients taking PPIs and warfarin together. Increases in INR and prothrombin time can cause abnormal bleeding and even death. Patients co-treated with lansoprazole and warfarin may need to be monitored for increased INR and prothrombin time.

Theophylline: Lansoprazole reduces the plasma concentration of theophylline, which may decrease the expected clinical effect at the dose. Caution is advised when combining the two drugs.

Tacrolimus: Co-administration of lansoprazole increases the plasma concentrations of tacrolimus (a CYP3A and P-gp substrate). Lansoprazole exposure increased the mean exposure of tacrolimus by up to 81%. Monitoring of tacrolimus plasma concentrations is advised when concomitant treatment with lansoprazole is initiated or ended.

Drugs transported by P-glycoprotein:
Lansoprazole has been observed to inhibit the transport protein, P-glycoprotein (P-gp) *in vitro*. The clinical relevance of this is unknown.

Combination therapy with clarithromycin and amoxicillin: Co-administration of clarithromycin with other drugs can lead to serious adverse reactions, including potentially fatal arrhythmias, and is contraindicated. Amoxicillin also has drug interactions.

Interactions with neuroendocrine tumour investigations: CgA levels are elevated secondary to PPI-

induced decreases in gastric acidity. Increased CgA levels may cause false positive results in diagnostic investigations for neuroendocrine tumours.

Effects of other drugs on lansoprazole
CYP2C19 or CYP3A4 inhibitors
Increased exposure to lansoprazole is expected when used in combination with potent inhibitors.
Fluvoxamine: A dose reduction may be considered when combining lansoprazole with the CYP2C19 inhibitor fluvoxamine. The plasma concentrations of lansoprazole increase up to 4-fold**.**

Drugs that induce CYP2C19 and CYP3A4
Enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin and St John's Wort *(Hypericum perforatum)* can markedly reduce the serum concentrations of lansoprazole.

Others
Methotrexate: Concomitant use with high doses of methotrexate may increase and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.

Sucralfate/Antacids: Sucralfate/antacids may decrease the bioavailability of lansoprazole. Therefore, lansoprazole should be taken at least one hour after taking these drugs.

No studies showing clinically significant interactions of lansoprazole with NSAIDs have been conducted.

Interaction with the secretin stimulation test: A hyper-response in gastrin secretion in response to the secretin stimulation test is falsely suggestive of gastrinoma. Lansoprazole treatment should be temporarily stopped for at least 28 days before the evaluation to allow gastrin levels to return to baseline values.

False positive urine tests for THC:
False positive urine screening tests for tetrahydrocannabinol (THC) have been reported in patients receiving PPIs. An alternative confirmation method should be considered to confirm positive results.

Additional information on special population
No data available.

Pediatric population
No data available.

4.6 Fertility, pregnancy and lactation

General recommendation
Pregnancy category is B

Women of child-bearing potential/Birth control (Contraception)
Effective contraception control is not required in women of child-bearing potential.

Pregnancy
For lansoprazole, no clinical data on exposed pregnancies are available.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy/embryonal/fetal development/parturition or post-natal development. Therefore, the use of lansoprazole during pregnancy is not recommended.

Breast-feeding
Animal studies have shown excretion of lansoprazole and its metabolites in the milk; however, it is not known whether lansoprazole is excreted in human breast milk. Because many drugs are excreted in human breast milk, because of the potential for serious adverse reactions in nursing infants, and because of the potential for carcinogenicity shown in animal studies, a decision should be made whether breastfeeding should be stopped or whether DEGASTROL treatment should be stopped/avoided.

Reproductive ability/Fertility
No human data on the effect of lansoprazole on fertility are available. Lansoprazole at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

In teratogenicity studies which have been performed in pregnant rats at oral doses up to 150 mg/kg/day (40 times the recommended human dose based on body surface area) and pregnant rabbits at oral doses up to 30 mg/kg/day (16 times the recommended human dose based on body surface area) orally, no evidence of impaired fertility or harm to the fetus was revealed.

4.7 Effects on ability to drive and use machines
Adverse effects such as dizziness, vertigo, visual disturbances and somnolence may occur (see section 4.8). Under these conditions the ability to react may be decreased.

4.8 Undesirable effects
The most frequently reported adverse effects associated with lansoprazole and probably drug-related adverse reactions in clinical trials are listed below according to the organ system classification and frequency.

Adverse effects are classified in each organ system class based on the following convention: Very common ≥1/10; common ≥1/100 to <1/10, uncommon ≥1/1,000 to <1/100; rare ≥1/10,000 to <1/1,000; very rare <1/10,000 and not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Uncommon: Thrombocytopenia, eosinophilia, leucopoenia
Rare: Anemia
Very rare: Agranulocytosis pancytopenia

Immune system diseases
Rare: Angioedema
Very rare: Anaphylactic shock

Metabolism and nutrition disorders
Not known: Hypomagnesemia (see section 4.4), hypocalcaemia, hypokalaemia

Psychiatric disorders
Uncommon: Depression

Rare: Insomnia, hallucination, confusion
Not known: Visual hallucinations

Nervous system disorders
Common: Headache, dizziness
Rare: Restlessness, vertigo, paresthesia, somnolence, tremor

Eye disorders
Rare: Visual disturbances

Gastrointestinal disorders
Common: Nausea, diarrhea, stomachache, constipation, vomiting, flatulence, dry mouth or throat, fundic gland polyps (benign)
Rare: Glossitis, candidiasis of esophageal, pancreatitis, taste disturbances
Very rare: Colitis, stomatitis

Hepatobiliary disorders
Common: Increase in liver enzyme levels
Rare: Hepatitis, jaundice

Skin and subcutaneous tissue disorders
Common: Urticaria, itching, rash
Rare: Petechiae, purpura, hair loss, erythema multiforme, photosensitivity
Very rare: Stevens-Johnson Syndrome, toxic epidermal necrolysis
Not known: Subacute cutaneous lupus erythematosus (see section 4.4)

Musculoskeletal disorders, connective tissue and bone diseases
Uncommon: Arthralgia, myalgia, fracture of the hip, wrist or spine (see section 4.4)

Renal and urinary disorders
Rare: Interstitial nephritis

Reproductive system and breast disorders
Rare: Gynecomasty

General disorders and administration site conditions
Common: Fatigue
Uncommon: Edema
Rare: Fever, hyperhidrosis, anorexia, impotence

Investigations
Very rare: Increase in cholesterol and triglyceride levels, hyponatremia

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

The effects of overdose on lansoprazole in humans are not known (although the acute toxicity is likely to be low); consequently, instruction for treatment cannot be given. However, daily doses of up to 180 mg of lansoprazole orally and up to 90 mg of lansoprazole intravenously have been administered in trials without significant undesirable effects.

Please refer to section 4.8 for possible symptoms of lansoprazole overdose.

In one reported overdose, a patient received 600 mg of lansoprazole with no adverse effect. Oral lansoprazole doses of up to 5000 mg/kg in rats [approximately 1300 times the 30 mg human dose based on body surface area (BSA)] and 5000 mg/kg in mice (675.7 times the 30 mg human dose based on BSA) did not produce deaths or any clinical signs.

In cases of suspected overdose, the patient should be kept under observation. Lansoprazole is not eliminated by hemodialysis. If necessary, gastric emptying, charcoal and symptomatic therapy is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton pump inhibitors
ATC code: A02BC03

Lansoprazole is a gastric proton pump inhibitor. It inhibits the final stage of gastric acid formation by inhibiting the activity of H^+/K^+-ATPase of the parietal cells in the stomach. The inhibition is dose-dependent and reversible, and the effect applies to both basal and stimulated secretion of gastric acid. Lansoprazole is concentrated in the parietal cells and becomes active in their acidic environment, whereupon it reacts with the sulphydryl group of H^+/K^+-ATPase causing inhibition of the enzyme activity.

Effects on gastric acid secretion:
Lansoprazole is a specific inhibitor of the parietal cell proton pump. A single oral dose of lansoprazole inhibits pentagastrin-stimulated gastric acid secretion by about 80%. After repeated daily administration for seven days, approximately 90% inhibition of gastric acid secretion is achieved. It has a corresponding effect on the basal secretion of gastric acid. A single oral dose of 30 mg reduces basal secretion by about 70%, and the patient's symptoms are consequently relieved beginning from the very first dose. After eight days of repeated administration the reduction is approximately 85%. A rapid relief of symptoms is obtained by a single capsule (30 mg) daily, and most patients with duodenal gastric recover within 2 weeks, patients with gastric ulcer and reflux esophagitis within 4 weeks. By reducing gastric acidity, lansoprazole creates an environment in which appropriate antibiotics can be effective against *H. pylori.*

Decreased gastric acidity due to any reason including lansoprazole might be expected to increase gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pomp inhibitors may lead to a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and possibly *Clostridium difficile* in hospitalized patients.

During treatment with antisecretory medicinal products, serum gastrin increases in response to decreased acid secretion. In addition, CgA increases due to decreased gastric acidity. The increased

CgA level may affect research for neuroendocrine tumours.

Current published evidence suggests that proton pump inhibitors should be discontinued 5 days to 2 weeks before CgA measurements. This is to allow CgA levels, which may spuriously rise following PPI treatment, to return to the reference range.

5.2 Pharmacokinetic properties

General properties
Absorption:
As Lansoprazole has a non-acid-resistant chemical structure, in order to prevent it from undergoing a chemical change in the stomach and increase its systemic bioavailability, it is administered in enteric-coated formulation allowing intestinal absorption.

Absorption of lansoprazole administered orally in enteric-coated formulation is rapid and the maximum serum concentration is attained within 1.7 hours. Lansoprazole does not accumulate in the body and its pharmacokinetics are unaltered by multiple dosing. Lansoprazole is rapidly absorbed and after 1.7 hours of oral administration C_{max} values are attained and its bioavailability is 80%. Presence of food in the stomach slows the absorption of lansoprazole. Both the C_{max} and AUC are diminished by about 50 % if it is administered 30 minutes after food, compared to the fasting condition. The mean plasma half-life in healthy subjects was 1.5 (±1) hours.

Distribution:
Lansoprazole is 97% bound to proteins. Plasma protein binding is constant over the concentration range of 0.05-5 mcg/ml concentration interval.

Biotransformation:
Lansoprazole is extensively metabolized in the liver; two metabolites (hydroxylated sulfinyl and sulfone) have been identified in measurable quantities in plasma. These metabolites have very little or no antisecretory activity. The metabolism of lansoprazole is mainly catalysed by the enzyme CYP2C19, with the enzyme CYP3A4 also contributing to metabolism.
Lansoprazole is thought to be transformed into two active metabolites which inhibit acid secretion through H+/K+ ATPase at the secretory surface of the parietal cell, and these metabolites could not be demonstrated in the blood. These metabolites are not present in the systemic circulation.

Elimination:
The elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion. The plasma elimination half-life is less than 2 hours while the acid inhibitory effect lasts more than 24 hours. The elimination half-life is 2 to 3 hours in the elderly.

Following single dose oral administration of lansoprazole, virtually no unchanged drug was excreted in the urine. In one study, following a single oral dose of ^{14}C-lansoprazole, approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the feces. This implies a significant biliary excretion of the lansoprazole metabolites.

Linearity/Non-linearity:
Maximum serum concentrations (C_{max}) and the area under the curve (AUC) are proportional in doses from 15 to 60 mg after single oral administration.

Characteristics in patients

Renal impairment:

After administration of 60 mg of lansoprazole in patients with severe renal insufficiency, plasma protein binding decreased by 1-1.5%. Patients with renal insufficiency had a shortened elimination half-life and decreased total AUC (free and bound to proteins). However, the AUC for free lansoprazole in plasma was not related to the degree of renal impairment; and the C_{max} and T_{max} were not different than those from healthy subjects. No dosage adjustment is required in patients with renal impairment.

Hepatic impairment:

In patients with various degrees of hepatic impairment, the mean plasma half-life was prolonged from 1.5 hours to 3.2-7.2 hours. In patients with hepatic insufficiency, the mean AUC values at steady state increased up to 500%. The dose of lansoprazole should be reduced in patients with severe hepatic impairment.

Geriatric population:

The clearance of lansoprazole is decreased in the elderly, elimination half-life increases 50% to 100%. Because, the mean half-life in the elderly is between 1.9 to 2.9 hours, repeated once daily dosing does not result in its accumulation. Peak plasma levels did not change in the elderly.

Pediatric population:

The evaluation of the pharmacokinetics in children aged 1–17 years of age showed a similar exposure as compared to adults with doses of 15 mg for those below 30 kg of weight and 30 mg for those above. The investigation of a dose of 17 mg/m^2 body surface or 1 mg/kg body weight also resulted in comparable exposure of lansoprazole in children aged 2-3 months up to one year of age compared to adults.

Higher exposure to lansoprazole in comparison to adults has been seen in infants below the age of 2-3 months with doses of both 1 mg/kg and 0.5 mg/kg body weight given as a single dose.

CYP2C19 poor metabolizers:

CYP2C19 is subject to genetic polymorphism and 2-6% of the population, called poor metabolizers, They are homozygote for a mutant CYP2C19 allele and therefore lacks a functional CYP2C19 enzyme. The exposure of lansoprazole is several-fold higher in poor metabolizers than in extensive metabolizers.

5.3 Preclinical safety data

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

In two rat carcinogenicity studies, lansoprazole produced dose-related gastric ECL (enterochromaffin-like) cell hyperplasia and ECL cell carcinoids associated with hypergastrinemia due to inhibition of acid secretion. Intestinal metaplasia was also observed, as were Leydig cell hyperplasia and benign Leydig cell tumors. After 18 months of treatment retinal atrophy was observed. This was not seen in monkeys, dogs or mice.

In mouse carcinogenicity studies, liver tumours and rete testis adenoma as well as dose-dependent gastric ECL cell hyperplasia developed.

The clinical relevance of these findings is unknown.

Juvenile animal studies:
In rat pups, lansoprazole was administered from postnatal day 7 (age equivalent to newborn humans) to postnatal day 62 (age equivalent to approximately 14 years in humans).

Studies in juvenile rats (8-week study, 6-week toxicokinetic dose titration study, developmental susceptibility study) showed an increased incidence of heart valve thickening. After a 4-week drug-free recovery period, the findings were reversed. Rat pups younger than postnatal day 21 (equivalent to approximately 2 years in humans) were more susceptible to the development of heart valve thickening. The safety margin for expected human exposure is in the range of 3 to 6 times the exposure in the juvenile studies based on AUC at the no-observed-effect level (NOEL) (8-week study, 6-week toxicokinetic dose titration study) or the lowest observed-effect level (LOEL) (developmental sensitisation study).

These studies also demonstrated changes in male reproductive tissue (testis and epididymis). In addition, growth retardation was recorded in male or female rats. However, this resulted in delayed femoral growth plate thickness only in males.

The relevance of these findings in paediatric patients is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Sodium lauryl sulfate
Methyl hydroxypropylcellulose
Talc
Titanium dioxide (E171)
Polyethylene glycol 6000
Polysorbate 80
Polyacrylate
Sugar spheres
    Sucrose
    Maize starch
Meglumine
Mannitol

Gelatin capsule no 3:
Gelatin (from bovine bone)
Titanium dioxide (E171)
Quinoline yellow (E104)
Erythrosine (E127)
Yellow iron oxide (E172)

6.2 Incompatibilities

There are no known incompatibilities.

6.3 Shelf life
48 months.

6.4 Special precautions for storage
Store at room temperature below 25°C and tightly closed.
Capsules should be used within 1 month once opened. If this period is exceeded, any remaining medication should not be used.
Close the bottle tightly after every use.

6.5 Nature and contents of packaging
White opaque HDPE bottle closed with a child-resistant white opaque PP cap with aluminum seal in a cardboard box.
Each bottle contains 28 capsules.

6.6 Special precautions for disposal and other handling
Any unused medicinal products or waste materials should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)

185/40

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 26.03.1998
Date of last renewal :

10. DATE OF REVISION OF THE TEXT