Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lanzol 15 mg hard gastro-resistant capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gastro-resistant capsule contains 15 mg of lansoprazole.

Excipient(s) with known effect
Each hard gastro-resistant capsule contains up to 108.7 mg of sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard Gastro-resistant capsule.

Opaque, yellow hard gelatine capsule, containing white to almost white pellets with enteric coating.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lanzol gastro-resistant capsules are indicated for:

- Treatment of duodenal and gastric ulcer.
- Treatment of reflux oesophagitis
- Prophylaxis of reflux oesophagitis
- Eradication of *Helicobacter pylori (H. pylori)* concurrently given with appropriate antibiotic therapy for treatment of *H.pylori*-associated ulcers
- Treatment of NSAID-associated benign gastric and duodenal ulcers in patients requiring continued NSAID-treatment
- Prophylaxis of NSAID-associated gastric and duodenal ulcers in patients at risk (see section 4.2) requiring continued therapy
- Symptomatic gastro-oesophageal reflux disease
- Zollinger-Ellison syndrome.

4.2 Posology and method of administration

Posology

Treatment of duodenal ulcer
The recommended dose is 30 mg once daily for 2 weeks. In patients not fully healed within this time, the medicinal product is continued at the same dose for another two weeks.

Treatment of 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 medicinal product may be continued at the same dose for another 4 weeks.

Reflux oesophagitis
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 oesophagitis
15 mg once daily. The dose may be increased up to 30 mg daily as necessary.

Eradication of H. pylori

When selecting appropriate combination therapy, consideration should be given to official local guidance regarding bacterial resistance, duration of treatment (most commonly 7 days but sometimes up to 14 days), and appropriate use of antibacterial agents.

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

Six months after successful eradication treatment, the risk of re-infection is low and relapse is therefore unlikely.

Use of a regimen including lansoprazole 30 mg twice daily, amoxicillin 1 g twice daily and metronidazole 400–500 mg twice daily has also been examined. Lower eradication rates were seen using this combination than in regimens involving clarithromycin. It may be suitable for those who are unable to take clarithromycin as part of an eradication therapy, when local resistance rates to metronidazole are low.

Treatment of NSAID associated benign gastric and duodenal ulcers in patients requiring continued NSAID treatment
30 mg once daily for four weeks. In patients not fully healed the treatment may be continued for another four 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 (such as age > 65 or history of gastric or duodenal ulcer) requiring prolonged NSAID treatment
15 mg once daily. If the treatment fails the dose 30 mg once daily should be used.

Symptomatic gastro-oesophageal reflux disease
The recommended dose is 15 mg or 30 mg daily. Relief of symptoms is obtained rapidly. Individual adjustment of dose should be considered. If the symptoms are not relieved within 4 weeks with a daily dose of 30 mg, further examinations are recommended.

Zollinger-Ellison syndrome
The recommended initial dose is 60 mg once daily. The dose should be individually adjusted 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.

Special populations

Hepatic impairment
Patients with moderate or severe liver disease should be kept under regular supervision and a 50 % reduction of the daily dose is recommended (see section 4.4 and 5.2).

Renal impairment
There is no need for a dose adjustment in patients with impaired renal function.

Elderly
Due to reduced clearance of lansoprazole in the elderly an adjustment of dose may be necessary based on individual requirements. A daily dose of 30 mg should not be exceeded in the elderly unless there are compelling clinical indications.

Paediatric population
The use of lansoprazole is not recommended in children as clinical data are limited (see section 5.2) and juvenile animal studies have findings of currently unknown human relevance (see section 5.3). Treatment of small children below one year of age should be avoided as available data have not shown beneficial effects in the treatment of gastro-oesophageal reflux disease.

Method of administration
For optimal effect, Lanzol should be taken once daily in the morning, except when used for *H. pylori* eradication when treatment should be twice a day, once in the morning and once in the evening. Lanzol should be taken at least 30 minutes before food (see section 5.2). Capsules should be swallowed whole with liquid.

For patients with difficulty swallowing:
The capsules may be emptied, but the contents may not be chewed or ground.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Gastric malignancy

In common with other anti-ulcer therapies, the possibility of malignant gastric tumour should be excluded when treating a gastric ulcer with lansoprazole because lansoprazole can mask the symptoms and delay the diagnosis.

HIV protease inhibitors

Co-administration of lansoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir and nelfinavir, due to 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.

Hypomagnesaemia

Severe hypomagnesaemia has been rarely reported in patients treated with proton pump inhibitors (PPIs) like lansoprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur, but they may begin insidiously and be overlooked. Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8). In most affected patients, hypomagnesaemia (and hypomagnesaemia associated hypocalcaemia and/or hypokalaemia) improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with digoxin or medicinal products that may cause hypomagnesaemia (e.g. diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Influence on vitamin B_{12} absorption

Lansoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B_{12} (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, patients with reduced body stores or risk factors for reduced vitamin B_{12} absorption (such as the elderly) on long-term therapy or if relevant clinical symptoms are observed.

Hepatic impairment

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

Gastrointestinal infections caused by bacteria

Lansoprazole, like all PPIs, might increase the counts 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 aetiological factor should be considered.

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

Long-term treatment

Because of limited safety data for patients on maintenance treatment for longer than 1-year, regular review of the treatment and a thorough risk/benefit assessment should regularly be performed in these patients.

Gastrointestinal disorders

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

With the exception of patients treated for the eradication of *H. pylori* infection, if diarrhoea persists, administration of lansoprazole should be discontinued, due to the possibility of microscopic colitis with thickening of the collagen bundle or infiltration of inflammatory cells noted in the large intestine submucosa. In the majority of cases, symptoms of microscopic colitis resolve upon discontinuation of lansoprazole.

Co administration with NSAIDs

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 medicinal product 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 fractures

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. 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 they should have an adequate intake of vitamin D and calcium.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with lansoprazole with frequency not known (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, lansoprazole should be withdrawn immediately and an alternative treatment considered.

Subacute cutaneous lupus erythematosus (SCLE)

Proton pump inhibitors are associated with very infrequent cases of SCLE. 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 lansoprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors (see section 4.8).

Renal impairment

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking lansoprazole and may occur at any point during lansoprazole therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.

Lansoprazole should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

Interference with laboratory tests

Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, lansoprazole treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

Lanzol contains sucrose and sodium

This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

This medicinal product contains less than 1 mmol (23 mg) sodium, per hard gastro-resistant capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of lansoprazole on other medicinal products

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
Co-administration of lansoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH, such as atazanavir and nelfinavir, due to significant reduction in their bioavailability (see section 4.4).

A study has shown that co-administration of lansoprazole (60 mg once daily) with atazanavir 400 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 90% decrease in AUC and C_{max}).

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.

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.

Methotrexate
Concomitant use with high-dose Methotrexate may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. Therefore, in settings where high- dose methotrexate is used a temporary withdrawal of lansoprazole may need to be considered.

Warfarin
Co-administration of lansoprazole 60 mg and warfarin did not affect the pharmacokinetics of warfarin or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with lansoprazole and warfarin concomitantly may need to be monitored for increase in INR and prothrombin time, especially when initiating or ending concomitant treatment.

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

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 medicinal products. Patient monitoring should be taken in co-administration of lansoprazole with theophylline.

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.

Medicinal products 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.

Effects of other medicinal products on lansoprazole

Medicinal products which inhibit CYP2C19

Fluvoxamine
A dose reduction may be considered when combining lansoprazole with the CYP2C19 inhibitor fluvoxamine. A study shows that the plasma concentrations of lansoprazole increase up to 4-fold.

Medicinal products which induce CYP2C19 and CYP3A4
Enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin, and St John´s wort (*Hypericum perforatum*) can markedly reduce the plasma concentrations of lansoprazole.

Others

Sucralfate/antacids
Sucralfate/antacids may decrease the bioavailability of lansoprazole. Therefore, lansoprazole should be taken at least 1 hour after taking these medicinal products.

Non-steroidal anti-inflammatory medicinal products
No clinically significant interactions of lansoprazole with nonsteroidal anti-inflammatory drugs have been demonstrated, although no formal interactions studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited amount of data from the use of lansoprazole in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

As a precautionary measure, it is preferable to avoid the use of lansoprazole during pregnancy.

Breast-feeding

It is not known whether lansoprazole is excreted in human breast milk. Animal studies have shown excretion of lansoprazole in milk.

A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with lansoprazole should be made taking into account the benefit of breast-feeding for the child and the benefit of lansoprazole therapy for the woman.

Fertility

No human data on the effects of lansoprazole on fertility are available. In male and female rats, fertility was not affected by lansoprazole.

4.7 Effects on ability to drive and use machines

Adverse drug reactions 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

Tabulated list of adverse reactions

Frequencies are defined as common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). For all adverse reactions reported from post marketing

experience, it is not possible to apply any Adverse Reaction frequency and therefore they are mentioned with a "not known" frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders		Thrombocytopaenia*, eosinophilia, leukopenia*	Anaemia	Agranulocytosis*, pancytopaenia*	
Immune system disorders				Anaphylactic shock*	
Metabolism and nutritional disorders					Hyponatremia*, hypomagnesaemia* (see section 4.4), hypocalcaemia* †, and hypokalaemia*†
Psychiatric disorders		Depression	Insomnia, hallucination, confusion		Visual hallucinations
Nervous system disorders	Headache, dizziness		Restlessness, vertigo, paraesthesia, somnolence, tremor		
Eye disorders			Visual disturbances		
Gastrointestinal disorders	Nausea, diarrhoea, stomach ache, constipation, vomiting, flatulence, dry mouth or throat, fundic gland polyps (benign)		Glossitis, candidiasis of the oesophagus, pancreatitis, taste disturbances	Colitis*, stomatitis	
Hepatobiliary disorders	Increase in liver enzyme levels		Hepatitis, jaundice		
Skin and subcutaneous tissue disorders	Urticaria, itching, rash		Petechiae, purpura, hair loss, erythema multiforme, photosensitivity	Steven-Johnson syndrome*, toxic epidermal necrolysis*	Subacute cutaneous lupus erythematosus* (see section 4.4), and drug reaction with eosinophilia and systemic symptoms
Musculoskeletal and connective tissue disorders		Arthralgia, myalgia, fracture of the hip, wrist or spine (see section 4.4)			
Renal and urinary disorders			Tubulointerstitial nephritis (with possible progression to renal failure)		
Reproductive system and breast disorders			Gynaecomastia		
General disorders and administration	Fatigue	Oedema	Fever, hyperhidrosis, angioedema,		

site conditions			anorexia, impotence		
Investigations				Increase in cholesterol and triglyceride levels, hyponatraemia	

* Adverse reactions that have been observed during post approval of dexlansoprazole (as these reactions are reported voluntarily from a population of uncertain size, frequency cannot be estimated from the available data)
† Hypocalcaemia and/or hypokalaemia may be related to the occurrence of hypomagnesaemia (see section 4.4)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 HPRA Pharmacovigilance; website: www.hpra.ie.

4.9 Overdose

The effects of overdose on lansoprazole in humans are not known (although the acute toxicity is likely to be low) and, 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 the case of suspected overdose the patient should be monitored. Lansoprazole is not significantly eliminated by haemodialysis. 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.

Mechanism of action

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.

Effect 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, about 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 patients' symptoms are consequently relieved starting from the very first dose. After eight days of repeated administration the reduction is about 85%. A rapid relief of symptoms is obtained by one capsule (30 mg) daily, and most patients with duodenal ulcer recover within 2 weeks, patients with gastric ulcer and reflux oesophagitis within 4 weeks. By reducing gastric acidity, lansoprazole creates an environment in which appropriate antibiotics can be effective against *H. pylori*.

During treatment with antisecretory medicinal products, serum gastrin increases in response to the decreased acid secretion. Also, CgA increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours (see section 4.4).

Available published evidence suggests that proton pump inhibitors should be discontinued between 5 days and 2 weeks prior to CgA measurements. This is to allow CgA levels that might be spuriously elevated following PPI treatment to return to reference range.

5.2 Pharmacokinetic properties

Lansoprazole is a racemate of two active enantiomers that are biotransformed into the active form in the acidic environment of the parietal cells. As lansoprazole is rapidly inactivated by gastric acid, it is administered orally in enteric-coated form(s) for systemic absorption.

Absorption and distribution

Lansoprazole exhibits high (80–90%) bioavailability with a single dose. Peak plasma levels occur within 1.5 to 2.0 hours. Intake of food slows the absorption rate of lansoprazole and reduces the bioavailability by about 50%. The plasma protein binding is 97%.

Biotransformation and elimination

Lansoprazole is extensively metabolised by the liver and the metabolites are excreted by both the renal and biliary route. The metabolism of lansoprazole is mainly catalysed by the enzyme CYP2C19. The enzyme CYP3A4 also contributes to the metabolism. The plasma elimination half-life ranges from 1 to 2 hours following single or multiple doses in healthy subjects. There is no evidence of accumulation following multiple doses in healthy subjects. Sulphone, sulphide and 5-hydroxyl derivatives of lansoprazole have been identified in plasma. These metabolites have very little or no antisecretory activity.

A study with ^{14}C labelled lansoprazole indicated that approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the faeces.

Special patient populations

Elderly
The clearance of lansoprazole is decreased in the elderly, with elimination half-life increased approximately 50% to 100%. Peak plasma levels were not increased in the elderly.

Paediatric 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 1.0 mg/kg and 0.5 mg/kg body weight given as a single dose.

Hepatic impairment
The exposure of lansoprazole is doubled in patients with mild hepatic impairment and much more increased in patients with moderate and severe hepatic impairment.

CYP2C19 poor metabolisers
CYP2C19 is subject to genetic polymorphism and 2–6 % of the population, called poor metabolisers (PMs), are homozygotes for a mutant CYP2C19 allele and therefore lacks a functional CYP2C19 enzyme. The exposure of lansoprazole is several-fold higher in PMs than in extensive metabolisers (EMs).

5.3 Preclinical safety data

Preclinical data reveal no special hazards 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 cell hyperplasia and ECL cell carcinoids associated with hypergastrinaemia due to inhibition of acid secretion.

Intestinal metaplasia was also observed as were Leydig cell hyperplasia and benign Leydig cell tumours. After 18 months of treatment retinal atrophy was observed. This was not seen in monkeys, dogs or mice.

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

The clinical relevance of these findings is unknown.

Juvenile Animal Studies

Studies in juvenile rats (8-week study, 6-week toxicokinetic dose titration study, developmental sensitivity study) covering the paediatric population less than 12 years of age have shown an increased incidence of cardiac valve thickening. The findings reversed or trended towards reversibility after a 4-week drug free recovery period. Juvenile rats younger than postnatal day 21 (age equivalent to approximately 2 years in humans) were more sensitive to the development of cardiac valve thickening. The safety margin to the expected human exposure is in the range of 3- to 6-fold the exposure in juvenile studies based on the AUC at the no-observed-effect level (NOEL) (8-week study, 6-week toxicokinetic dose titration study) or lowest-observed-effect level (LOEL) (developmental sensitivity study).

The relevance of these findings to paediatric patients less than 12 years of age is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methacrylic Acid-Ethyl Acrylate Copolymer (1:1) Dispersion 30%
Hypromellose
Macrogol 6000
Mannitol (E421)
Meglumine
Polysorbate 80
Sodium laurilsulphate
Sugar spheres (sucrose and maize starch)
Talc
Titanium dioxide (E171)

Capsule shell:
Gelatin
Titanium dioxide (E171)
Quinoline yellow (E104)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25ºC
Store in the original package in order to protect from moisture.

In addition for HDPE containers:
Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Aluminium/Aluminium blister
7, 10, 14, 15, 20, 28, 30, 35, 50, 56, 60, 84, 98, 100 and 250 capsules

HDPE container
28 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/067/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 11 March 2005

Date of last renewal: 07 November 2008

10 DATE OF REVISION OF THE TEXT

May 2025