Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Razolager 15 mg hard gastro-resistant capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 15 mg of lansoprazole

Excipients with known effect
Each 15 mg capsule contains 100.47 mg of sucrose (as in sugar spheres).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard gastro-resistant capsule

Size 3 (approx. 16 mm), opaque**,** yellow hard gelatin capsule containing white or almost white spherical microgranules.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

• 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 ulcers and duodenal ulcers in patients at risk (see section 4.2) requiring continued therapy
• Symptomatic gastro-oesophageal reflux disease
• Zollinger-Ellison syndrome.

Razolager is indicated in adults.

4.2 Posology and method of administration

Posology
For optimal effect, Razolager 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.

Treatment of duodenal ulcer:
The recommended dose is 30 mg once daily for 2 weeks. In patients not fully healed within this time, the treatment 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 treatment maybe continued at the same dose for another 4 weeks.

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

Eradication of *Helicobacter 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:
The recommended dose is 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:
The recommended dose is 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 dosage 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

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

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).

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 also section 5.2) and it is currently unknown to what extent the results from studies in young animals are relevant to human use (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 oral use. Razolager should be taken at least 30 minutes before food (see section 5.2). Capsules should be swallowed whole with liquid.

Patients with difficulty swallowing: studies and clinical practice suggest that the capsules may be opened and the granules mixed with a small amount of water, apple/tomato juice or sprinkled onto a small amount of soft food (e.g. yoghurt, apple puree) to ease administration. Capsules may also be opened and granules mixed with 40 ml of apple juice for administration through a nasogastric tube (see section 5.2). After preparing the suspension or mixture, the drug should be administered immediately.

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

Malignant gastric cancer

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 and HIV protease inhibitors for which absorption is dependent on the acid pH of the stomach, such as atazanavir and nelfinavir, is not recommended due to the significant reduction in their bioavailability (see section 4.5).

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

Like all proton pump inhibitors (PPIs), lansoprazole may increase counts of bacteria normally present in the gastrointestinal tract. This can increase the risk of gastrointestinal infections caused by bacteria such as *Salmonella*, *Campylobacter* and *Clostridium difficile*.

In patients suffering from gastro-duodenal ulcers, 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*, 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.

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 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 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.

Hypomagnesaemia

Rare cases of severe hypomagnesaemia has been reported in patients treated with proton-pump inhibitors (PPI) 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 can 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 other medicines that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Influence on vitamin B12 absorption

Lansoprazole, like any acid-reducing medicine, may lead to reduced absorption of vitamin B12 (cyanocobalamin) as a result of hypo- or achlorhydria.
This should be taken into account for patients with reduced storage capacity or risk factors for inadequate vitamin B12 absorption who are receiving long-term therapy or where relevant clinical symptoms have been observed.

Severe adverse skin 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 healthcare 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.

Interference with laboratory tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, Razolager 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.

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.

Excipients with known effects
Razolager contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per 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 medicinal products where gastric acidity (pH) is critical to oral bioavailability.

HIV protease inhibitors:
Co-administration of lansoprazole and HIV protease inhibitors for which absorption is dependent on the acid pH of the stomach, such as atazanavir and nelfinavir, is not recommended due to the 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 a high dose of methotrexate can increase and prolong serum levels of methotrexate and/or its metabolite, which may lead to methotrexate toxicity. A temporary discontinuation of the treatment with lansoprazole should be considered when a high dose of methotrexate is used.

Warfarin:
Concomitant administration of lansoprazole 60 mg and warfarin had no effect on the pharmacokinetics of warfarin or INR. However, there have been reports of increased INR and prothrombin time in patients using PPIs and warfarin concomitantly. Increases in INR and prothrombin time can lead to abnormal bleedings and even death. Patients who have to be treated with lansoprazole and warfarin concomitantly should be monitored for an increase of the INR and prothrombin time, especially when initiating or ending the 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 drugs 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. Patients receiving lansoprazole concomitantly with theophylline should be monitored regularly.

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. The plasma concentrations of lansoprazole increase up to 4-fold.

Medicinal products which induces 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 and antacids may decrease the bioavailability of lansoprazole. Therefore lansoprazole should be taken at least 1 hour after taking these medicinal products.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Only limited data are available on the use of lansoprazole during pregnancy. 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, the use of lansoprazole during pregnancy should be avoided.

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 breastfeeding to the child and the benefit of lansoprazole therapy to the woman.

Fertility
No data are available on the effect of lansoprazole on fertility. Fertility in male and female rats 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

Tabular summary of adverse reactions

Frequencies are defined as 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), not known (cannot be estimated from the available data). It is not possible to state the frequency of all adverse reactions reported in the post-marketing setting, which is why they are listed under "Not known".

Within each frequency grouping, adverse reactions are presented in order of decreasing severity.

Frequency System organ class	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders		Thrombocytopenia*, eosinophilia, leucopenia*	Anaemia	Agranulocytosis*, pancytopenia*	
Immune system disorders			Angiodema	Anaphylactic shock	
Metabolism and nutrition disorders			Anorexia		Hypomagnesaemia* hypocalcaemia*† and hypokalaemia*†
Psychiatric disorders		Depression	Insomnia, hallucination, confusion		Visual hallucinations
Nervous system disorders	Headache, dizziness		Restlessness, vertigo, paresthesia, 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, hyperhidrosis	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, impotence		
General disorders and administration site conditions	Fatigue	Oedema	Fever		
Investigations				Increase in cholesterol and triglyceride levels, hyponatremia	

* 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 180mg of lansoprazoleorally 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: Drugs for acid related disorders, 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.

Pharmacodynamic effects

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.
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
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 bioavailabilty by about 50%.

Studies have shown that granules from opened capsules give equivalent AUC as the intact capsule if the granules are suspended in a small amount of orange juice, apple juice, or tomato juice mixed with a tablespoon of apple or pear puree or sprinkled on a tablespoon of yoghurt, pudding or cottage cheese. Equivalent AUC has also been shown for granules suspended in apple juice administered through a naso-gastric tube.

Distribution
The plasma protein binding is 97%.

Biotransformation
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.

Elimination
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 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 paediatric population 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 there is a greater increase 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 homozygote 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

Nonclinical 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.

Studies in juvenile animals:

Studies in juvenile rats (8-week study, 6-week toxicokinetic dose titration study, developmental sensitivity study) covering the paediatric population under the age of 12 years showed an increased incidence of cardiac valve thickening. The findings either resolved or improved after a 4-week recovery period during which no medicinal products were administered. Juvenile rats aged 21 days or under (equivalent to a human age of approximately 2 years) were more sensitive to the development of cardiac valve thickening. The margin of safety for the expected exposure in humans is in the range of 3 to 6 times the exposure in juvenile animal studies based on AUC at the NOEL (no-observed-effect level) (8-week study, 6-week toxicokinetic dose titration study) or LOEL (lowest-observed-effect level) (developmental sensitivity study).
The relevance of these results for children under the age of 12 years is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gastro-resistant granules
Sugar spheres (maize starch and sucrose)
Sodium laurilsulfate
Meglumine
Mannitol
Hypromellose
Macrogol
Talc
Polysorbate 80
Titanium dioxide (E171)
Methacrylic acid – ethyl acrylate copolymer 1:1,

Capsule shell
Gelatin
Titanium dioxide (E171)

Sodium laurilsulfate
Quinoline yellow (E104)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Alu/OPA/PVC blister with Al/PVC/PVDC non-peelable foil or Al/PETP/PVC peelable foil packs containing 7, 14, 15, 28, 30, 35, 56, 60 and 98 capsules.

Alu/OPA/PVC/PET calendar pack ***(peelable or non-peelable)*.**
28 and 98 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Viatris Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23266/074/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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