ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nexium Control 20 mg gastro-resistant tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 20 mg esomeprazole (as magnesium trihydrate)

Excipient(s) with known effect
Each gastro-resistant tablet contains 28 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant tablet.

A light pink, oblong, biconvex, film-coated, gastro-resistant tablet of 14 mm x 7 mm engraved with '20 mG' on one side and 'A/EH' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nexium Control is indicated for the short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitation) in adults.

4.2 Posology and method of administration

Posology
The recommended dose is 20 mg esomeprazole (one tablet) per day.

It might be necessary to take the tablets for 2-3 consecutive days to achieve improvement of symptoms. The duration of treatment is up to 2 weeks. Once complete relief of symptoms has occurred, treatment should be discontinued.

If no symptom relief is obtained within 2 weeks of continuous treatment, the patient should be instructed to consult a doctor.

Special populations
Patients with renal impairment
Dose adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency, such patients should be treated with caution (see section 5.2).

Patients with hepatic impairment
Dose adjustment is not required in patients with mild to moderate liver impairment. However, patients with severe liver impairment should be advised by a doctor before taking Nexium Control (see sections 4.4 and 5.2).

Elderly patients (≥65 years old)
Dose adjustment is not required in elderly patients.

Paediatric population
There is no relevant use of Nexium Control in the paediatric population below 18 years of age for the indication of "short-term treatment of reflux symptoms (e.g., heartburn and acid regurgitation)".

Method of administration
The tablets should be swallowed whole with half a glass of water. The tablets must not be chewed or crushed.

Alternatively, the tablet can be dispersed in half a glass of non-carbonated water. No other liquids should be used as the enteric coating may be dissolved. The water should be stirred until the tablet disintegrates. The liquid with the pellets should be drunk immediately or within 30 minutes. The glass should be rinsed with half a glass of water and the water drunk. The pellets should not be chewed or crushed.

4.3 Contraindications

Hypersensitivity to the active substance, substituted benzimidazoles or to any of the excipients listed in section 6.1.
Esomeprazole must not be used concomitantly with nelfinavir (see section 4.5).

4.4 Special warnings and precautions for use

General
Patients should be instructed to consult a doctor if:

- They have significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena and when gastric ulcer is suspected or present, malignancy should be excluded as treatment with esomeprazole may alleviate symptoms and delay diagnosis.
- They have had previous gastric ulcer or gastrointestinal surgery.
- They have been on continuous symptomatic treatment of indigestion or heartburn for 4 or more weeks.
- They have jaundice or severe liver disease.
- They are aged over 55 years with new or recently changed symptoms.

Patients with long-term recurrent symptoms of indigestion or heartburn should see their doctor at regular intervals. Patients over 55 years taking any non-prescription indigestion or heartburn remedy on a daily basis should inform their pharmacist or doctor.

Patients should not take Nexium Control as a long term preventive medicinal product.

Treatment with proton pump inhibitors (PPIs) may lead to a slightly increased risk of gastrointestinal infections such as *Salmonella and Campylobacter* and in hospitalised patients, also possibly *Clostridium difficile* (see section 5.1).

Patients should consult their doctor before taking this medicinal product if they are due to have an endoscopy or urea breath test.

Combination with other medicinal products
Co-administration of esomeprazole with atazanavir is not recommended (see section 4.5). If the combination of atazanavir with a PPI is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir. Esomeprazole 20 mg should not be exceeded.

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with medicinal products metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole. The clinical relevance of this interaction is uncertain. The use of esomeprazole with clopidogrel should be discouraged (see section 4.5).

Patients should not take another PPI or H_2 antagonist concomitantly.

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

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 Nexium Control. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Severe cutaneous adverse reactions (SCARs)
Severe cutaneous adverse reactions (SCARs) such as erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) which can be life-threatening or fatal, have been reported very rarely in association with esomeprazole treatment.

Patients should be advised of the signs and symptoms of the severe skin reaction EM/SJS/TEN/DRESS and should seek medical advice from their physician immediately when observing any indicative signs or symptoms. Esomeprazole should be discontinued immediately upon signs and symptoms of severe skin reactions and additional medical care/close monitoring should be provided as needed. Re-challenge should not be undertaken in patients with EM/SJS/TEN/DRESS.

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

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium free’.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Effects of esomeprazole on the pharmacokinetics of other medicinal products
As esomeprazole is one enantiomer of omeprazole it is reasonable to advise about interactions reported with omeprazole.

Protease inhibitors
Omeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during

omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP2C19.

For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, C_{max} and C_{min}). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg once a day) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared with the exposure observed with atazanavir 300 mg/ritonavir 100 mg once a day without omeprazole 20 mg once a day. Co-administration of omeprazole (40 mg once a day) reduced mean nelfinavir AUC, C_{max} and C_{min} by 36–39 % and mean AUC, C_{max} and C_{min} for the pharmacologically active metabolite M8 was reduced by 75-92%. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended and concomitant administration with esomeprazole and nelfinavir is contraindicated (see section 4.3 and 4.4).

For saquinavir (with concomitant ritonavir), increased serum levels (80-100%) have been reported during concomitant omeprazole treatment (40 mg once a day). Treatment with omeprazole 20 mg once a day had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir).

Treatment with esomeprazole 20 mg once a day had no effect on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg once a day had no effect on the exposure of lopinavir (with concomitant ritonavir).

Methotrexate
When given together with PPIs, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Tacrolimus
Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and the dose of tacrolimus adjusted if needed.

Medicinal products with pH dependent absorption
Gastric acid suppression during treatment with esomeprazole and other PPIs might decrease or increase the absorption of medicinal products with a gastric pH dependent absorption. The absorption of medicinal products taken orally such as ketoconazole, itraconazole and erlotinib can decrease during treatment with esomeprazole and the absorption of digoxin can increase during treatment with esomeprazole.

Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects). Digoxin toxicity has been rarely reported. However, caution should be exercised when esomeprazole is given at high doses in elderly patients. Therapeutic monitoring of digoxin should then be reinforced.

Medicinal products metabolised by CYP2C19
Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with medicinal products metabolised by CYP2C19, such as warfarin, phenytoin, citalopram, imipramine, clomipramine, diazepam, etc., the plasma concentrations of these medicinal products may be increased and a dose reduction could be needed. In case of clopidogrel, a prodrug which is transformed into its active metabolite via CYP2C19, the plasma concentrations of the active metabolite may be decreased.

Warfarin
Concomitant administration of 40 mg esomeprazole to warfarin-treated patients in a clinical study showed that coagulation times were within the accepted range. However, post-marketing, a few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment. Monitoring is recommended when initiating and ending concomitant esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

Clopidogrel
Results from studies in healthy subjects have shown a pharmacokinetic (PK)/pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg orally daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%.

In a study in healthy subjects, there was a decreased exposure by almost 40% of the active metabolite of clopidogrel when a fixed dose combination of esomeprazole 20 mg + acetylsalicylic acid 81 mg was given with clopidogrel compared to clopidogrel alone. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the same in both groups.

Inconsistent data on the clinical implications of this PK/PD interaction in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of esomeprazole-and clopidogrel should be discouraged.

Phenytoin
Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Voriconazole
Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C_{max} and AUC_{τ} by 15% and 41%, respectively.

Cilostazol
Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

Cisapride
In healthy volunteers, concomitant administration of 40 mg esomeprazole resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole.

Diazepam
Concomitant administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam.

Investigated medicinal products with no clinically relevant interaction
Amoxicillin and quinidine
Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin and quinidine.

Naproxen or rofecoxib
Studies evaluating concomitant administration of esomeprazole and either naproxen or rofecoxib did not identify any clinically relevant pharmacokinetic interactions during short-term studies.

Effects of other medicinal products on the pharmacokinetics of esomeprazole

Medicinal products which inhibit CYP2C19 and/or CYP3A4

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg twice a day (b.i.d.)), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP 3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUC_t by 280%. A dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Medicinal products which induce CYP2C19 and/or CYP3A4

Medicinal products known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort *(Hypericum perforatum)*) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity of esomeprazole.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

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

Breast-feeding

It is unknown whether esomeprazole/metabolites are excreted in human milk. There is insufficient information on the effects of esomeprazole in newborns/infants. Esomeprazole should not be used during breast-feeding.

Fertility

Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

4.7 Effects on ability to drive and use machines

Esomeprazole has minor influence on the ability to drive or use machines. Adverse reactions such as dizziness and visual disturbances are uncommon (see section 4.8). If affected, patients should not drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Headache, abdominal pain, diarrhoea and nausea are among those adverse reactions that have been most commonly reported in clinical studies (and also from post-marketing use). In addition, the safety profile is similar for different formulations, treatment indications, age groups and patient populations. No dose-related adverse reactions have been identified.

Tabulated list of adverse reactions

The following adverse reactions have been identified or suspected in the clinical studies programme for esomeprazole and post-marketing. The reactions are classified according to MedDRA frequency 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); not known (cannot be estimated from the available data).

	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders			leukopenia, thrombocytope-nia	agranulocytosis, pancytopenia	
Immune system disorders			hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock		
Metabolism and nutrition disorders		peripheral oedema	hyponatraemia		hypomagne-saemia; severe hypomagne-saemia can correlate with hypocalcae-mia; hypomagne-saemia may also result in hypokalaem-ia
Psychiatric disorders		insomnia	agitation, confusion, depression	aggression, hallucinations	
Nervous system disorders	headache	dizziness, paraesthesia, somnolence	taste disturbance		
Eye disorders			blurred vision		
Ear and labyrinth disorders		vertigo			
Respiratory, thoracic and mediastinal disorders			bronchospasm		
Gastrointestinal disorders	abdominal pain, constipa-tion, diarrhoea, flatulence, nausea/ vomiting, fundic gland polyps (benign)	dry mouth	stomatitis, gastrointestinal candidiasis		microscopic colitis
Hepatobiliary disorders		increased liver enzymes	hepatitis with or without jaundice	hepatic failure, hepatic encephalopathy in patients with pre-existing liver disease	

	Common	Uncommon	Rare	Very rare	Not known
Skin and subcutaneous tissue disorders		dermatitis, pruritus, rash urticaria	alopecia, photosensitivity	erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), Drug reaction with eosinophilia and systemic symptoms (DRESS)	Subacute cutaneous lupus erythematosus (see section 4.4).
Musculoskeletal and connective tissue disorders			arthralgia, myalgia	muscular weakness	
Renal and urinary disorders				Interstitial nephritis	
Reproductive system and breast disorders				gynaecomastia	
General disorders and administration site disorders			malaise, increased sweating		

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 the HPRA Pharmacovigilance website: www.hpra.ie

4.9 Overdose

There is very limited experience to date with deliberate overdose. The symptoms described in connection with 280 mg esomeprazole were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialysable. Treatment should be symptomatic and general supportive measures should be utilised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for acid related disorders, proton pump inhibitors,
ATC code: A02BC05.

Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity.

Mechanism of action
Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+K^+-ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Pharmacodynamic effects
After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five.

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic gastroesophageal reflux disease (GERD) patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours respectively were for esomeprazole 20 mg 76%, 54% and 24%. Corresponding proportions for esomeprazole 40 mg were 97%, 92% and 56%.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

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.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long-term treatment with esomeprazole.

Decreased gastric acidity due to any means including PPIs, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with PPIs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and in hospitalised patients, also possibly *Clostridium difficile*.

Clinical efficacy
Esomeprazole 20 mg has been demonstrated to effectively treat frequent heartburn in subjects receiving one dose per 24 hours over 2 weeks. In two multicenter, randomized, double-blind, placebo-controlled pivotal studies 234 subjects with a recent history of frequent heartburn were treated with 20 mg esomeprazole for 4 weeks. Symptoms associated with acid reflux (such as heartburn and acid regurgitation) were evaluated retrospectively over a 24 hour period. In both studies esomeprazole 20 mg was significantly better compared to placebo for the primary endpoint, complete resolution of heartburn, defined as no heartburn episodes during the last 7 days prior to the final visit (33.9% - 41.6% vs. placebo 11.9 – 13.7%, ($p<0.001$). The secondary endpoint of complete resolution of heartburn, defined as no heartburn on the patient's diary card for 7 consecutive days, was statistically significant at both week 1 (10.0% - 15.2% vs placebo 0.9% - 2.4%, $p = 0.014$, $p<0.001$) and week 2 (25.2% - 35.7% vs placebo 3.4% - 9.0%, $p<0.001$).

Other secondary endpoints were supportive of the primary endpoint, including relief of heartburn at week 1 and week 2, percentage of 24 hour days without heartburn at week 1 and week 2, mean heartburn severity at week 1 and week 2, and time to initial and sustained resolution of heartburn over a 24 hour period and during the night compared to placebo. Approximately 78% of the subjects on 20 mg esomeprazole reported first resolution of heartburn within the first week of treatment compared to 52 – 58% for placebo. Time to sustained resolution of heartburn, defined as when 7 consecutive days of no heartburn was first recorded, was significantly shorter in the esomeprazole 20 mg group (39.7% - 48.7% by day 14 vs placebo 11.0% - 20.2%). The median time to first resolution of

night-time heartburn was 1 day, statistically significant compared to placebo in one study (p=0.048) and approaching significance in the other (p=0.069). About 80% of nights were heartburn free during all time periods and 90% of nights were heartburn free by week 2 of each clinical study, compared to 72.4 – 78.3% for placebo. The investigators' assessments of heartburn resolution were consistent with the subjects' assessments, showing statistically significant differences between esomeprazole (34.7% - 41.8%) compared to placebo (8.0% - 11.4%). The investigators also found esomeprazole to be significantly more effective than placebo in resolving acid regurgitation (58.5% - 63.6% vs placebo 28.3% - 37.4%) during the week 2 evaluation.

Following Overall Treatment Evaluation (OTE) of patients at week 2, 78.0-80.7% of patients on esomeprazole 20 mg, compared to 72.4 – 78.3% for placebo, reported their condition as improved. The majority of these rated the importance of this change to be Important to Extremely Important in performing their activities of daily living (79 - 86% at week 2).

5.2 Pharmacokinetic properties

Absorption
Esomeprazole is acid labile and is administered orally as enteric-coated granules. *In vivo* conversion to the R-isomer is negligible. Absorption of esomeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively. Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution
The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 l/kg body weight. Esomeprazole is 97% plasma protein bound.

Biotransformation
Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

Elimination
The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 l/h after a single dose and about 9 l/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration. The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent compound is found in urine.

Linearity/non-linearity
The pharmacokinetics of esomeprazole has been studied in doses up to 40 mg b.i.d. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a more than dose proportional increase in AUC after repeated administration. This time and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite.

Special patient populations

Poor metabolisers

Approximately 2.9±1.5% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were 60% higher.

These findings have no implications for the posology of esomeprazole.

Gender

Following a single dose of 40 mg esomeprazole the mean are under the plasma concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the posology of esomeprazole.

Hepatic impairment

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once-daily dosing.

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Elderly patients (≥65 years old)

The metabolism of esomeprazole is not significantly changed in elderly patients (71-80 years of age).

5.3 Preclinical safety data

Non-clinical data reveal no particular hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and toxicity to reproduction and development. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Carcinogenicity studies in the rat with the racemic mixture have shown gastric ECL-cell hyperplasia and carcinoids. These gastric effects in the rat are the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid and are observed after long-term treatment in the rat with inhibitors of gastric acid secretion.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol monostearate 40-55
Hydroxypropylcellulose
Hypromellose 2910 (6 mPa·s)
Reddish-brown iron oxide (E172)
Yellow iron oxide (E172)
Magnesium stearate
Methacrylic acid ethylacrylate copolymer (1:1) dispersion 30 per cent
Cellulose microcrystalline
Synthetic Paraffin

Macrogol 6000
Polysorbate 80
Crospovidone (Type A)
Sodium stearyl fumarate
Sugar spheres (sucrose and maize starch)
Talc
Titanium dioxide (E171)
Triethyl citrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium blister. Pack sizes of 7, 14 and 28 gastro-resistant tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Haleon Ireland Dungarvan Limited,
Knockbrack,
Dungarvan,
Co. Waterford,
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/860/001
EU/1/13/860/002
EU/1/13/860/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 August 2013
Date of latest renewal: 25 June 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Nexium Control 20 mg gastro-resistant hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant hard capsule contains 20 mg esomeprazole (as magnesium trihydrate)

Excipient(s) with known effect
Each gastro-resistant hard capsule contains 11.5 mg sucrose and 0.01 mg allura red AC (E129).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gastro-resistant hard capsule. (Gasto-resistant capsule).

Capsule approximately 11 x 5 mm, with a clear body, and an amethyst cap imprinted with "NEXIUM 20 MG" in white. The capsule has a yellow centre band, and contains yellow and purple enteric coated pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nexium Control is indicated for the short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitation) in adults.

4.2 Posology and method of administration

Posology
The recommended dose is 20 mg esomeprazole (one capsule) per day.

It might be necessary to take the capsules for 2-3 consecutive days to achieve improvement of symptoms. The duration of treatment is up to 2 weeks. Once complete relief of symptoms has occurred, treatment should be discontinued.

If no symptom relief is obtained within 2 weeks of continuous treatment, the patient should be instructed to consult a doctor.

Special populations
Patients with renal impairment
Dose adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency, such patients should be treated with caution (see section 5.2).

Patients with hepatic impairment
Dose adjustment is not required in patients with mild to moderate liver impairment. However, patients with severe liver impairment should be advised by a doctor before taking Nexium Control (see sections 4.4 and 5.2).

Elderly patients (≥65 years old)
Dose adjustment is not required in elderly patients.

Paediatric population
There is no relevant use of Nexium Control in the paediatric population below 18 years of age for the indication of "short-term treatment of reflux symptoms (e.g., heartburn and acid regurgitation)".

Method of administration
The capsules should be swallowed whole with half a glass of water. The capsules must not be chewed, crushed or opened.

4.3 Contraindications

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

Esomeprazole must not be used concomitantly with nelfinavir (see section 4.5).

4.4 Special warnings and precautions for use

General
Patients should be instructed to consult a doctor if:

- They have significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena and when gastric ulcer is suspected or present, malignancy should be excluded as treatment with esomeprazole may alleviate symptoms and delay diagnosis.
- They have had previous gastric ulcer or gastrointestinal surgery.
- They have been on continuous symptomatic treatment of indigestion or heartburn for 4 or more weeks.
- They have jaundice or severe liver disease.
- They are aged over 55 years with new or recently changed symptoms.

Patients with long-term recurrent symptoms of indigestion or heartburn should see their doctor at regular intervals. Patients over 55 years taking any non-prescription indigestion or heartburn remedy on a daily basis should inform their pharmacist or doctor.

Patients should not take Nexium Control as a long term preventive medicinal product.

Treatment with proton pump inhibitors (PPIs) may lead to a slightly increased risk of gastrointestinal infections such as *Salmonella and Campylobacter* and in hospitalised patients, also possibly *Clostridium difficile* (see section 5.1).

Patients should consult their doctor before taking this medicinal product if they are due to have an endoscopy or urea breath test.

Combination with other medicinal products
Co-administration of esomeprazole with atazanavir is not recommended (see section 4.5). If the combination of atazanavir with a PPI is judged unavoidable, close clinical monitoring is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir. Esomeprazole 20 mg should not be exceeded.

Esomeprazole is a CYP2C19 inhibitor. When starting or ending treatment with esomeprazole, the potential for interactions with medicinal products metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole. The clinical relevance

of this interaction is uncertain. The use of esomeprazole with clopidogrel should be discouraged (see section 4.5).

Patients should not take another PPI or H_2 antagonist concomitantly.

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

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 Nexium Control. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Severe cutaneous adverse reactions (SCARs)
Severe cutaneous adverse reactions (SCARs) such as erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) which can be life-threatening or fatal, have been reported very rarely in association with esomeprazole treatment.

Patients should be advised of the signs and symptoms of the severe skin reaction EM/SJS/TEN/DRESS and should seek medical advice from their physician immediately when observing any indicative signs or symptoms. Esomeprazole should be discontinued immediately upon signs and symptoms of severe skin reactions and additional medical care/close monitoring should be provided as needed. Re-challenge should not be undertaken in patients with EM/SJS/TEN/DRESS.

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

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium free’.

Allura red AC (E129)
This medicinal product contains azo colouring agent, Allura red AC (E129), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Effects of esomeprazole on the pharmacokinetics of other medicinal products
As esomeprazole is one enantiomer of omeprazole it is reasonable to advise about interactions reported with omeprazole.

Protease inhibitors
Omeprazole has been reported to interact with some protease inhibitors. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the protease inhibitors. Other possible interaction mechanisms are via inhibition of CYP2C19.

For atazanavir and nelfinavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. Co-administration of omeprazole (40 mg once daily) with atazanavir 300 mg/ritonavir 100 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, C_{max}, and C_{min}). Increasing the atazanavir dose to 400 mg did not compensate for the impact of omeprazole on atazanavir exposure. The co-administration of omeprazole (20 mg once a day) with atazanavir 400 mg/ritonavir 100 mg to healthy volunteers resulted in a decrease of approximately 30% in the atazanavir exposure as compared with the exposure observed with atazanavir 300 mg/ritonavir 100 mg once a day without omeprazole 20 mg once a day. Co-administration of omeprazole (40 mg once a day) reduced mean nelfinavir AUC, C_{max}, and C_{min} by 36 - 39 % and mean AUC, C_{max}, and C_{min} for the pharmacologically active metabolite M8 was reduced by 75 - 92%. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and atazanavir is not recommended and concomitant administration with esomeprazole and nelfinavir is contraindicated (see section 4.3 and 4.4).

For saquinavir (with concomitant ritonavir), increased serum levels (80-100%) have been reported during concomitant omeprazole treatment (40 mg once a day). Treatment with omeprazole 20 mg once a day had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir).

Treatment with esomeprazole 20 mg once a day had no effect on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg once a day had no effect on the exposure of lopinavir (with concomitant ritonavir).

Methotrexate
When given together with PPIs, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Tacrolimus
Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus. A reinforced monitoring of tacrolimus concentrations as well as renal function (creatinine clearance) should be performed, and the dose of tacrolimus adjusted if needed.

Medicinal products with pH dependent absorption
Gastric acid suppression during treatment with esomeprazole and other PPIs might decrease or increase the absorption of medicinal products with a gastric pH dependent absorption. The absorption of medicinal products taken orally such as ketoconazole, itraconazole and erlotinib can decrease during treatment with esomeprazole and the absorption of digoxin can increase during treatment with esomeprazole.

Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects). Digoxin toxicity has been rarely reported. However, caution should be exercised when esomeprazole is given at high doses in elderly patients. Therapeutic monitoring of digoxin should then be reinforced.

Medicinal products metabolised by CYP2C19
Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with medicinal products metabolised by CYP2C19, such as warfarin, phenytoin, citalopram, imipramine, clomipramine, diazepam, etc., the plasma concentrations of these medicinal products may be increased and a dose reduction could be needed. In case of clopidogrel, a prodrug which is transformed into its active metabolite via CYP2C19, the plasma concentrations of the active metabolite may be decreased.

Warfarin
Concomitant administration of 40 mg esomeprazole to warfarin-treated patients in a clinical study showed that coagulation times were within the accepted range. However, post-marketing, a few isolated cases of elevated INR of clinical significance have been reported during concomitant treatment. Monitoring is recommended when initiating and ending concomitant esomeprazole treatment during treatment with warfarin or other coumarine derivatives.

Clopidogrel
Results from studies in healthy subjects have shown a pharmacokinetic (PK)/pharmacodynamic (PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg orally daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40%, and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%.

In a study in healthy subjects, there was a decreased exposure by almost 40% of the active metabolite of clopidogrel when a fixed dose combination of esomeprazole 20 mg + acetylsalicylic acid 81 mg was given with clopidogrel compared to clopidogrel alone. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the same in both groups.

Inconsistent data on the clinical implications of this PK/PD interaction in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution, concomitant use of esomeprazole-and clopidogrel should be discouraged.

Phenytoin
Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Voriconazole
Omeprazole (40 mg once daily) increased voriconazole (a CYP2C19 substrate) C_{max} and AUC_{τ} by 15% and 41%, respectively.

Cilostazol
Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively.

Cisapride
In healthy volunteers, concomitant administration of 40 mg esomeprazole resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life($t_{1/2}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole.

Diazepam
Concomitant administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C19 substrate diazepam.

Investigated medicinal products with no clinically relevant interaction
Amoxicillin and quinidine
Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin and quinidine.

Naproxen or rofecoxib
Studies evaluating concomitant administration of esomeprazole and either naproxen or rofecoxib did not identify any clinically relevant pharmacokinetic interactions during short-term studies.

Effects of other medicinal products on the pharmacokinetics of esomeprazole

Medicinal products which inhibit CYP2C19 and/or CYP3A4

Esomeprazole is metabolised by CYP2C19 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg twice a day (b.i.d.)), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUC_t by 280%. A dose adjustment of esomeprazole is not regularly required in either of these situations. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Medicinal products which induce CYP2C19 and/or CYP3A4

Medicinal products known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort *(Hypericum perforatum)*) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity of esomeprazole.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

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

Breast-feeding

It is unknown whether esomeprazole/metabolites are excreted in human milk. There is insufficient information on the effects of esomeprazole in newborns/infants. Esomeprazole should not be used during breast-feeding.

Fertility

Animal studies with the racemic mixture omeprazole, given by oral administration do not indicate effects with respect to fertility.

4.7 Effects on ability to drive and use machines

Esomeprazole has minor influence on the ability to drive or use machines. Adverse reactions such as dizziness and visual disturbances are uncommon (see section 4.8). If affected, patients should not drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Headache, abdominal pain, diarrhoea and nausea are among those adverse reactions that have been most commonly reported in clinical studies (and also from post-marketing use). In addition, the safety profile is similar for different formulations, treatment indications, age groups and patient populations. No dose-related adverse reactions have been identified.

Tabulated list of adverse reactions

The following adverse reactions have been identified or suspected in the clinical studies programme for esomeprazole and post-marketing. The reactions are classified according to MedDRA frequency 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); not known (cannot be estimated from the available data).

	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders			leukopenia, thrombocytopenia	agranulocytosis, pancytopenia	
Immune system disorders			hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock		
Metabolism and nutrition disorders		peripheral oedema	hyponatraemia		hypomagnesaemia; severe hypomagnesaemia can correlate with hypocalcaemia; hypomagnesaemia may also result in hypokalaemia
Psychiatric disorders		insomnia	agitation, confusion, depression	aggression, hallucinations	
Nervous system disorders	headache	dizziness, paraesthesia, somnolence	taste disturbance		
Eye disorders			blurred vision		
Ear and labyrinth disorders		vertigo			
Respiratory, thoracic and mediastinal disorders			bronchospasm		
Gastrointestinal disorders	abdominal pain, constipation, diarrhoea, flatulence, nausea/ vomiting, fundic gland polyps (benign)	dry mouth	stomatitis, gastrointestinal candidiasis		microscopic colitis
Hepatobiliary disorders		increased liver enzymes	hepatitis with or without jaundice	hepatic failure, hepatic encephalopathy in patients with pre-existing liver disease	

	Common	Uncommon	Rare	Very rare	Not known
Skin and subcutaneous tissue disorders		dermatitis, pruritus, rash urticaria	alopecia, photosensitivity	erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), Drug reaction with eosinophilia and systemic symptoms (DRESS)	Subacute cutaneous lupus erythematosus (see section 4.4).
Musculoskeletal and connective tissue disorders			arthralgia, myalgia	muscular weakness	
Renal and urinary disorders				Interstitial nephritis	
Reproductive system and breast disorders				gynaecomastia	
General disorders and administration site disorders			malaise, increased sweating		

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 the HPRA Pharmacovigilance website: www.hpra.ie

4.9 Overdose

There is very limited experience to date with deliberate overdose. The symptoms described in connection with 280 mg esomeprazole were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively plasma protein bound and is therefore not readily dialysable. Treatment should be symptomatic and general supportive measures should be utilised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for acid related disorders, proton pump inhibitors,
ATC code: A02BC05.

Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity.

Mechanism of action
Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+K^+-ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Pharmacodynamic effects

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five.

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic gastroesophageal reflux disease (GERD) patients. The proportion of patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours respectively were for esomeprazole 20 mg 76%, 54%, and 24%. Corresponding proportions for esomeprazole 40 mg were 97%, 92%, and 56%.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

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.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long-term treatment with esomeprazole.

Decreased gastric acidity due to any means including PPIs, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with PPIs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and in hospitalised patients, also possibly *Clostridium difficile*.

Clinical efficacy

Esomeprazole 20 mg has been demonstrated to effectively treat frequent heartburn in subjects receiving one dose per 24 hours over 2 weeks. In two multicentre, randomised, double-blind, placebo-controlled pivotal studies 234 subjects with a recent history of frequent heartburn were treated with 20 mg esomeprazole for 4 weeks. Symptoms associated with acid reflux (such as heartburn and acid regurgitation) were evaluated retrospectively over a 24 hour period. In both studies esomeprazole 20 mg was significantly better compared to placebo for the primary endpoint, complete resolution of heartburn, defined as no heartburn episodes during the last 7 days prior to the final visit (33.9% - 41.6% vs. placebo 11.9 - 13.7%, ($p<0.001$). The secondary endpoint of complete resolution of heartburn, defined as no heartburn on the patient's diary card for 7 consecutive days, was statistically significant at both week 1 (10.0% - 15.2% vs. placebo 0.9% - 2.4%, $p = 0.014$, $p<0.001$) and week 2 (25.2% - 35.7% vs. placebo 3.4% - 9.0%, $p<0.001$).

Other secondary endpoints were supportive of the primary endpoint, including relief of heartburn at week 1 and week 2, percentage of 24 hour days without heartburn at week 1 and week 2, mean heartburn severity at week 1 and week 2, and time to initial and sustained resolution of heartburn over a 24 hour period and during the night compared to placebo. Approximately 78% of the subjects on 20 mg esomeprazole reported first resolution of heartburn within the first week of treatment compared to 52 - 58% for placebo. Time to sustained resolution of heartburn, defined as when 7 consecutive days of no heartburn was first recorded, was significantly shorter in the esomeprazole 20 mg group (39.7% - 48.7% by day 14 vs. placebo 11.0% - 20.2%). The median time to first resolution of night-time heartburn was 1 day, statistically significant compared to placebo in one study ($p=0.048$) and approaching significance in the other ($p=0.069$). About 80% of nights were heartburn free during all time periods and 90% of nights were heartburn free by week 2 of each clinical study, compared to 72.4 - 78.3% for placebo. The investigators' assessments of heartburn resolution were consistent with

the subjects' assessments, showing statistically significant differences between esomeprazole (34.7% - 41.8%) compared to placebo (8.0% - 11.4%). The investigators also found esomeprazole to be significantly more effective than placebo in resolving acid regurgitation (58.5% - 63.6% vs. placebo 28.3% - 37.4%) during the week 2 evaluation.

Following Overall Treatment Evaluation (OTE) of patients at week 2, 78.0 - 80.7% of patients on esomeprazole 20 mg, compared to 72.4 - 78.3% for placebo, reported their condition as improved. The majority of these rated the importance of this change to be Important to Extremely Important in performing their activities of daily living (79 - 86% at week 2).

5.2 Pharmacokinetic properties

Absorption
Esomeprazole is acid labile and is administered orally as enteric-coated granules. *In vivo* conversion to the R-isomer is negligible. Absorption of esomeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68% respectively. Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution
The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 l/kg body weight. Esomeprazole is 97% plasma protein bound.

Biotransformation
Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

Elimination
The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 l/h after a single dose and about 9 l/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration. The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of esomeprazole is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent compound is found in urine.

Linearity/non-linearity
The pharmacokinetics of esomeprazole has been studied in doses up to 40 mg b.i.d. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a more than dose proportional increase in AUC after repeated administration. This time and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite.

Special patient populations
Poor metabolisers
Approximately 2.9±1.5% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects

having a functional CYP2C19 enzyme (extensive metabolisers). Mean peak plasma concentrations were 60% higher.
These findings have no implications for the posology of esomeprazole.

Gender
Following a single dose of 40 mg esomeprazole the mean are under the plasma concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the posology of esomeprazole.

Hepatic impairment
The metabolism of esomeprazole in patients with mild to moderate liver dysfunction may be impaired. The metabolic rate is decreased in patients with severe liver dysfunction resulting in a doubling of the area under the plasma concentration-time curve of esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once-daily dosing.

Renal impairment
No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Elderly patients (≥65 years old)
The metabolism of esomeprazole is not significantly changed in elderly patients (71-80 years of age).

5.3 Preclinical safety data

Non-clinical data reveal no particular hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and toxicity to reproduction and development. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:
Carcinogenicity studies in the rat with the racemic mixture have shown gastric ECL-cell hyperplasia and carcinoids. These gastric effects in the rat are the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid and are observed after long-term treatment in the rat with inhibitors of gastric acid secretion.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Glycerol monostearate 40-55
Hydroxypropylcellulose
Hypromellose 2910 (6 mPa·s)
Magnesium stearate
Methacrylic acid - ethyl acrylate copolymer (1:1) dispersion 30 per cent
Polysorbate 80
Sugar spheres (sucrose and maize starch)
Talc
Triethyl citrate
Carmine (E120)
Indigo carmine (E132)
Titanium dioxide (E171)
Yellow iron oxide (E172)

Capsule shell
Gelatin
Indigo carmine (E132)
Erythrosine (E127)
Allura red AC (E129)

Printing ink
Povidone K-17
Propylene glycol
Shellac
Sodium hydroxide
Titanium dioxide (E171)

Band
Gelatin
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle with an induction seal closure and child resistant closure containing 14 gastro-resistant capsules. The bottle also contains a sealed container with silica gel desiccant.

Nexium Control capsules are available in pack sizes of 14 and 28 capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Haleon Ireland Dungarvan Limited,
Knockbrack,
Dungarvan,
Co. Waterford,
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/860/003
EU/1/13/860/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 August 2013
Date of latest renewal: 25 June 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Haleon Italy Manufacturing S.r.l.
Via Nettunense, 90
04011 Aprilia (LT)
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product not subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nexium Control 20 mg gastro-resistant tablets

esomeprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant tablet contains 20 mg esomeprazole (as magnesium trihydrate).

3. LIST OF EXCIPIENTS

Contains sucrose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 gastro-resistant tablets
14 gastro-resistant tablets
28 gastro-resistant tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

The tablets should be swallowed whole. Do not chew or crush the tablets.
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Haleon Ireland Dungarvan Limited,
Knockbrack,
Dungarvan,
Co. Waterford,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/860/001	7 gastro-resistant tablets
EU/1/13/860/002	14 gastro-resistant tablets
EU/1/13/860/004	28 gastro-resistant tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

For short–term treatment of reflux symptoms (heartburn, acid regurgitation) in adults, aged 18 or over.
Do not use if you are allergic to esomeprazole or any of the other ingredients of this medicine.
Talk to your pharmacist or doctor if:
You are taking any medicines listed in the package leaflet
You are over 55 and have new or recently changed reflux symptoms.
How to use
Take one tablet once a day. Do not exceed this dose.
May take 2-3 days for full effect.
If your symptoms worsen or do not improve after taking this medicine for 14 days in a row, contact your doctor.

Treats Heartburn & Acid Reflux

One tablet daily
Lasts 24 hours

16. INFORMATION IN BRAILLE

Nexium Control 20 mg Tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nexium Control 20 mg gastro-resistant tablets

esomeprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Haleon Ireland Dungarvan Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nexium Control 20 mg gastro-resistant hard capsules

esomeprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant hard capsule contains 20 mg esomeprazole (as magnesium trihydrate).

3. LIST OF EXCIPIENTS

Contains sucrose and Allura red AC (E129). See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 gastro-resistant hard capsules
2 x 14 gastro-resistant hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Haleon Ireland Dungarvan Limited,
Knockbrack,
Dungarvan,
Co. Waterford,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/860/003 14 gastro-resistant hard capsules
EU/1/13/860/005 2 x 14 gastro-resistant hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

For short–term treatment of reflux symptoms (heartburn, acid regurgitation) in adults, aged 18 or over.

Do not use if you are allergic to esomeprazole or any of the other ingredients of this medicine.

Talk to your pharmacist or doctor if:

- You are taking any medicines listed in the package leaflet.
- You are over 55 and have new or recently changed reflux symptoms.

How to use
Take one capsule once a day. Do not exceed this dose.
The capsules should be swallowed whole. Do not chew, crush or open capsule.
May take 2-3 days for full effect.
If your symptoms worsen or do not improve after taking this medicine for 14 days in a row, contact your doctor.

Treats Heartburn & Acid Reflux

Capsules

One capsule daily
Lasts 24 hours

16. INFORMATION IN BRAILLE

Nexium Control 20 mg Capsules

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Nexium Control 20 mg gastro-resistant capsules

esomeprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each gastro-resistant capsule contains 20 mg esomeprazole (as magnesium trihydrate).

3. LIST OF EXCIPIENTS

Contains sucrose and Allura red AC (E129).

4. PHARMACEUTICAL FORM AND CONTENTS

14 gastro-resistant capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

Keep the container tightly closed to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Haleon Ireland Dungarvan Limited,
Knockbrack,
Dungarvan,
Co. Waterford,
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/860/003 14 gastro-resistant hard capsules
EU/1/13/860/005 2 x 14 gastro-resistant hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Treats Heartburn & Acid Reflux

Take one capsule once a day. Do not exceed this dose.
Swallow whole. Do not chew, crush or open capsule.

Capsules

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Nexium Control 20 mg gastro-resistant tablets
esomeprazole

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
Always take this medicine exactly as described in this leaflet or as your pharmacist has told you.
- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- You must talk to a doctor if you do not feel better or if you feel worse after 14 days.

What is in this leaflet

1. What Nexium Control is and what it is used for
2. What you need to know before you take Nexium Control
3. How to take Nexium Control
4. Possible side effects
5. How to store Nexium Control
6. Contents of the pack and other information
   - Further helpful information

1. What Nexium Control is and what it is used for

Nexium Control contains the active substance esomeprazole. It belongs to a group of medicines called 'proton pump inhibitors'. They work by reducing the amount of acid that your stomach produces.

This medicine is used in adults for the short-term treatment of reflux symptoms (for example, heartburn and acid regurgitation).

Reflux is the backflow of acid from the stomach into the gullet ("foodpipe") which may become inflamed and painful. This may cause you symptoms such as a painful sensation in the chest rising up to your throat (heartburn) and a sour taste in the mouth (acid regurgitation).

Nexium Control is not meant to bring immediate relief. You may need to take the tablets for 2-3 days in a row before you feel better. You must talk to a doctor if you do not feel better or if you feel worse after 14 days.

2. What you need to know before you take Nexium Control

Do not take Nexium Control
- If you are allergic to esomeprazole or any of the other ingredients of this medicine (listed in section 6).
- If you are allergic to medicines containing other proton pump inhibitors (e.g. pantoprazole, lansoprazole, rabeprazole or omeprazole).
- If you are taking a medicine containing nelfinavir (used to treat HIV infection).
- If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking Nexium Control or other related medicines.

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking this medicine.

Warnings and precautions
Talk to your doctor before taking Nexium Control if:
- You have had a stomach ulcer or stomach surgery in the past.
- You have been taking treatment continuously for reflux or heartburn for 4 or more weeks.
- You have jaundice (yellowing of skin or eyes) or severe liver problems.
- You have severe kidney problems.
- You are aged over 55 years and have new or recently changed reflux symptoms or need to take a non-prescription indigestion or heartburn remedy treatment every day.
- You have ever had a skin reaction after treatment with a medicine similar to Nexium Control that reduces stomach acid. Serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported in association with Nexium Control treatment. Stop using Nexium Control and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.
- You are due to have an endoscopy or a urea breath test.
- You are due to have a specific blood test (Chromogranin A).

Tell your doctor immediately before or after taking this medicine, if you notice any of the following symptoms, which could be a sign of another, more serious, disease.
- You lose a lot of weight for no reason.
- You have problems or pain when swallowing.
- You get stomach pain or signs of indigestion such as nausea, fullness, bloating especially after food intake.
- You begin to vomit food or blood, which may appear as dark coffee grounds in your vomit.
- You pass black stools (blood-stained faeces).
- You have severe or persistent diarrhoea; esomeprazole has been associated with a small increased risk of infectious diarrhoea.
- You get a rash on your skin, especially in areas exposed to the sun tell your doctor as soon as you can, as you may need to stop your treatment with Nexium Control. Remember to also mention any other ill-effects like pain in your joints.

Seek urgent medical attention if you experience chest pain with light-headedness, sweating, dizziness or shoulder pain with shortness of breath. This could be a sign of a serious condition with your heart.

If any of the above apply to you (or you are not sure), talk to your doctor straight away.

Children and adolescents
This medicine should not be used by children and adolescents under 18 years of age.

Other medicines and Nexium Control
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because this medicine can affect the way some medicines work and some medicines can have an effect on it.

Do not take this medicine if you are also taking a medicine containing nelfinavir (used to treat HIV infection).

You should specifically tell your doctor or pharmacist if you are taking clopidogrel (used to prevent blood clots).

Do not take this medicine with other medicines that limit the amount of acid produced in your stomach such as proton pump inhibitors (e.g. pantoprazole, lansoprazole, rabeprazole or omeprazole) or an H_2 antagonist (e.g. ranitidine or famotidine).

You may take this medicine with antacids (e.g. magaldrate, alginic acid, sodium bicarbonate, aluminium hydroxide, magnesium carbonate or combinations of these) if needed.

Tell your doctor or pharmacist if you are taking any of the following medicines:
- Ketoconazole and itraconazole (used to treat infections caused by a fungus)
- Voriconazole (used to treat infections caused by a fungus) and clarithromycin (used to treat infections). Your doctor may adjust your dose of Nexium Control if you also have severe liver problems and are treated for a long period of time.
- Erlotinib (used to treat cancer)
- Methotrexate (used to treat cancer and rheumatic disorders)
- Digoxin (used for heart problems)
- Atazanavir, saquinavir (used to treat HIV infection)
- Citalopram, imipramine or clomipramine (used to treat depression)
- Diazepam (used to treat anxiety, relax muscles or in epilepsy)
- Phenytoin (used to treat epilepsy)
- Medicines that are used to thin your blood, such as warfarin. Your doctor may need to monitor you when you start or stop taking Nexium Control
- Cilostazol (used to treat intermittent claudication – a condition where poor blood supply to the leg muscles causes pain and difficulty in walking)
- Cisapride (used for indigestion and heartburn)
- Rifampicin (used to treat tuberculosis)
- Tacrolimus (in cases of organ transplantation)
- St. John's wort (*Hypericum perforatum*) (used to treat depression)

Pregnancy and breast-feeding
As a precautionary measure, you should preferably avoid the use of Nexium Control during pregnancy. You should not use this medicine during breast-feeding.
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Nexium Control has a low likelihood of affecting your ability to drive or use machines. However, side effects such as dizziness and visual disturbances may uncommonly occur (see section 4). If affected, you should not drive or use machines.

Nexium Control contains sucrose and sodium
Nexium Control contains sugar spheres, which contain sucrose, a type of sugar. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Nexium Control contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

3. How to take Nexium Control

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure.

How much to take
- The recommended dose is one tablet a day.
- Do not take more than this recommended dose of one tablet (20 mg) a day, even if you don't feel an improvement immediately.
- You may need to take the tablets for 2 or 3 days in a row before your reflux symptoms (for example, heartburn and acid regurgitation) get better.
- The treatment length is up to 14 days.

- When your reflux symptoms have completely gone you should stop taking this medicine.
- If your reflux symptoms get worse or do not improve after taking this medicine for 14 days in a row, you should consult a doctor.

If you have persistent or longstanding, frequently recurring symptoms even after treatment with this medicine, you should contact your doctor.

Taking this medicine
- You can take your tablet at any time of the day either with food or on an empty stomach.
- Swallow your tablet whole with half a glass of water. Do not chew or crush the tablet. This is because the tablet contains coated pellets, which stop the medicine from being broken down by the acid in your stomach. It is important not to damage the pellets.

Alternative method of taking this medicine
- Put the tablet in a glass of still (non-fizzy) water. Do not use any other liquids.
- Stir until the tablet breaks up (the mixture will not be clear) then drink the mixture straight away or within 30 minutes. Always stir the mixture just before drinking it.
- To make sure that you have drunk all of the medicine, rinse the glass very well with half a glass of water and drink it. The solid pieces contain the medicine – do not chew or crush them.

If you take more Nexium Control than you should
If you take more Nexium Control than recommended, talk to your doctor or pharmacist straight away. You may experience symptoms such as diarrhoea, stomach ache, constipation, feeling or being sick and weakness.

If you forget to take Nexium Control
If you forget to take a dose, take it as soon as you remember it, on the same day. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
If you notice any of the following serious side effects, stop taking Nexium Control and contact a doctor immediately:
- Sudden wheezing, swelling of your lips, tongue and throat, rash, fainting or difficulties in swallowing (severe allergic reaction, seen rarely)
- Reddening of the skin with blisters or peeling. There may also be severe blisters and bleeding in the lips, eyes, mouth, nose and genitals. This could be ‘Stevens-Johnson syndrome’ or ‘toxic epidermal necrolysis’, seen very rarely.
- Yellow skin, dark urine and tiredness, which can be symptoms of liver problems, seen rarely.
- Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome), seen very rarely.

Talk to your doctor as soon as possible if you experience any of the following signs of infection:
This medicine may in very rare cases affect the white blood cells leading to immune deficiency. If you have an infection with symptoms such as fever with a **severely** reduced general condition or fever with symptoms of a local infection such as pain in the neck, throat or mouth or difficulties in urinating, you must consult your doctor as soon as possible so that a lack of white blood cells (agranulocytosis) can be ruled out by a blood test. It is important for you to give information about your medicine at this time.

Other side effects include:

Common (may affect up to 1 in 10 people)
- Headache.
- Effects on your stomach or gut: diarrhoea, stomach ache, constipation, wind (flatulence).
- Feeling sick (nausea) or being sick (vomiting).
- Benign growths (polyps) in the stomach.

Uncommon (may affect up to 1 in 100 people)
- Swelling of the feet and ankles.
- Disturbed sleep (insomnia), feeling sleepy.
- Dizziness, tingling feelings such as “pins and needles”.
- Spinning feeling (vertigo).
- Dry mouth.
- Increased liver enzymes shown in blood tests that check how the liver is working.
- Skin rash, lumpy rash (hives) and itchy skin.

Rare (may affect up to 1 in 1,000 people)
- Blood problems such as a reduced number of white blood cells or platelets. This can cause weakness, bruising or make infections more likely.
- Low levels of sodium in the blood. This may cause weakness, being sick (vomiting) and cramps
- Feeling agitated, confused or depressed.
- Taste changes.
- Eyesight problems such as blurred vision.
- Suddenly feeling wheezy or short of breath (bronchospasm).
- An inflammation on the inside of the mouth.
- An infection called “thrush” which can affect the gut and is caused by a fungus.
- Hair loss (alopecia).
- Skin rash on exposure to sunshine.
- Joint pain (arthralgia) or muscle pain (myalgia).
- Generally feeling unwell and lacking energy.
- Increased sweating.

Very rare (may affect up to 1 in 10,000 people)
- Low numbers of red blood cells, white blood cells, and platelets (a condition called pancytopenia)
- Aggression
- Seeing, feeling or hearing things that are not there (hallucinations)
- Severe liver problems leading to liver failure and inflammation of the brain.
- Muscle weakness
- Severe kidney problems
- Enlarged breasts in men

Not known (frequency cannot be estimated from the available data)
- Low levels of magnesium in the blood. This may cause weakness, being sick (vomiting), cramps, tremor and changes in heart rhythm (arrhythmias). If you have very low levels of magnesium, you may also have low levels of calcium and/or potassium in your blood.
- Inflammation of the gut (leading to diarrhoea).
- Rash, possibly with pain in the joints.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system: In Ireland, HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie e-mail: medsafety@hpra.ie.
In Malta, ADR Reporting, www.medicinesauthority.gov.mt/adrportal
By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Nexium Control

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

Keep this medicine in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Nexium Control contains
- The active substance is esomeprazole. Each gastro-resistant tablet contains 20 mg esomeprazole (as magnesium trihydrate).
- The other ingredients are glycerol monostearate 40-55, hydroxypropylcellulose, hypromellose, reddish-brown iron oxide (E172), yellow iron oxide (E172), magnesium stearate, methacrylic acid ethylacrylate copolymer (1:1) dispersion 30 per cent, cellulose microcrystalline, synthetic paraffin, macrogol 6000, polysorbate 80, crospovidone (Type A), sodium stearyl fumarate, sugar spheres (sucrose and maize starch), talc, titanium dioxide (E171) and triethyl citrate (see section 2, “Nexium Control contains sucrose and sodium”).

What Nexium Control looks like and contents of the pack
Nexium Control 20 mg gastro-resistant tablets are light pink, oblong, biconvex, 14 mm x 7 mm, film-coated, engraved with ‘20 mG’ on one side and A/EH on the other side.

Nexium Control is available in pack sizes of 7, 14 and 28 gastro-resistant tablets in blisters.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Haleon Ireland Dungarvan Limited, Knockbrack, Dungarvan, Co. Waterford, Ireland

Manufacturer
Haleon Italy Manufacturing S.r.l., Via Nettunense, 90, 04011, Aprilia (LT), Italy.

This leaflet was last revised in January 2025

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

FURTHER HELPFUL INFORMATION

What are the symptoms of heartburn?
The normal symptoms of reflux are a painful sensation in the chest rising up to your throat (heartburn) and a sour taste in the mouth (acid regurgitation).

Why do you get these symptoms?

Heartburn can be a result of eating too much, eating high fat food, eating too quickly and drinking lots of alcohol. You may also notice that when you lie down, that your heartburn gets worse. If you are overweight or smoke you increase the probability of suffering from heartburn.

What can I do to help relieve my symptoms?

- Eat healthier food and try to avoid spicy and fatty foods and large meals late before bedtime.
- Avoid fizzy drinks, coffee, chocolate and alcohol.
- Eat slowly and eat smaller portions.
- Try to lose weight.
- Stop smoking.

When should I seek advice or help?

- You should seek urgent medical advice if you experience chest pain with light-headedness, sweating, dizziness or shoulder pain with shortness of breath.
- If you experience any of the symptoms detailed in Section 2 of this leaflet and it advises you to talk to your doctor or pharmacist.
- If you are suffering from any of the side effects detailed in Section 4 which require medical attention.

Package leaflet: Information for the user

Nexium Control 20 mg gastro-resistant hard capsules
esomeprazole

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
Always take this medicine exactly as described in this leaflet or as your pharmacist has told you.
- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- You must talk to a doctor if you do not feel better or if you feel worse after 14 days.

What is in this leaflet

1. What Nexium Control is and what it is used for
2. What you need to know before you take Nexium Control
3. How to take Nexium Control
4. Possible side effects
5. How to store Nexium Control
6. Contents of the pack and other information
   - Further helpful information

1. What Nexium Control is and what it is used for

Nexium Control contains the active substance esomeprazole. It belongs to a group of medicines called 'proton pump inhibitors'. They work by reducing the amount of acid that your stomach produces.

This medicine is used in adults for the short-term treatment of reflux symptoms (for example, heartburn and acid regurgitation).

Reflux is the backflow of acid from the stomach into the gullet ("foodpipe") which may become inflamed and painful. This may cause you symptoms such as a painful sensation in the chest rising up to your throat (heartburn) and a sour taste in the mouth (acid regurgitation).

Nexium Control is not meant to bring immediate relief. You may need to take the capsules for 2-3 days in a row before you feel better. You must talk to a doctor if you do not feel better or if you feel worse after 14 days.

2. What you need to know before you take Nexium Control

Do not take Nexium Control
- If you are allergic to esomeprazole or any of the other ingredients of this medicine (listed in section 6).
- If you are allergic to medicines containing other proton pump inhibitors (e.g. pantoprazole, lansoprazole, rabeprazole or omeprazole).
- If you are taking a medicine containing nelfinavir (used to treat HIV infection).
- If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking Nexium Control or other related medicines.

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking this medicine.

Warnings and precautions

Talk to your doctor before taking Nexium Control if:
- You have had a stomach ulcer or stomach surgery in the past.
- You have been taking treatment continuously for reflux or heartburn for 4 or more weeks.
- You have jaundice (yellowing of skin or eyes) or severe liver problems.
- You have severe kidney problems.
- You are aged over 55 years and have new or recently changed reflux symptoms or need to take a non-prescription indigestion or heartburn remedy treatment every day.
- You have ever had a skin reaction after treatment with a medicine similar to Nexium Control that reduces stomach acid. Serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported in association with Nexium Control treatment. Stop using Nexium Control and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.
- You are due to have an endoscopy or a urea breath test.
- You are due to have a specific blood test (Chromogranin A).

Tell your doctor immediately before or after taking this medicine, if you notice any of the following symptoms, which could be a sign of another, more serious, disease.
- You lose a lot of weight for no reason.
- You have problems or pain when swallowing.
- You get stomach pain or signs of indigestion such as nausea, fullness, bloating especially after food intake.
- You begin to vomit food or blood, which may appear as dark coffee grounds in your vomit.
- You pass black stools (blood-stained faeces).
- You have severe or persistent diarrhoea; esomeprazole has been associated with a small increased risk of infectious diarrhoea.
- You get a rash on your skin, especially in areas exposed to the sun tell your doctor as soon as you can, as you may need to stop your treatment with Nexium Control. Remember to also mention any other ill-effects like pain in your joints.

Seek urgent medical attention if you experience chest pain with light-headedness, sweating, dizziness or shoulder pain with shortness of breath. This could be a sign of a serious condition with your heart.

If any of the above apply to you (or you are not sure), talk to your doctor straight away.

Children and adolescents
This medicine should not be used by children and adolescents under 18 years of age.

Other medicines and Nexium Control
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because this medicine can affect the way some medicines work and some medicines can have an effect on it.

Do not take this medicine if you are also taking a medicine containing nelfinavir (used to treat HIV infection).

You should specifically tell your doctor or pharmacist if you are taking clopidogrel (used to prevent blood clots).

Do not take this medicine with other medicines that limit the amount of acid produced in your stomach such as proton pump inhibitors (e.g. pantoprazole, lansoprazole, rabeprazole or omeprazole) or an H_2 antagonist (e.g. ranitidine or famotidine).

You may take this medicine with antacids (e.g. magaldrate, alginic acid, sodium bicarbonate, aluminium hydroxide, magnesium carbonate or combinations of these) if needed.

Tell your doctor or pharmacist if you are taking any of the following medicines:
- Ketoconazole and itraconazole (used to treat infections caused by a fungus).
- Voriconazole (used to treat infections caused by a fungus) and clarithromycin (used to treat infections). Your doctor may adjust your dose of Nexium Control if you also have severe liver problems and are treated for a long period of time.
- Erlotinib (used to treat cancer).
- Methotrexate (used to treat cancer and rheumatic disorders).
- Digoxin (used for heart problems).
- Atazanavir, saquinavir (used to treat HIV infection).
- Citalopram, imipramine or clomipramine (used to treat depression).
- Diazepam (used to treat anxiety, relax muscles or in epilepsy).
- Phenytoin (used to treat epilepsy).
- Medicines that are used to thin your blood, such as warfarin. Your doctor may need to monitor you when you start or stop taking Nexium Control.
- Cilostazol (used to treat intermittent claudication – a condition where poor blood supply to the leg muscles causes pain and difficulty in walking).
- Cisapride (used for indigestion and heartburn).
- Rifampicin (used to treat tuberculosis).
- Tacrolimus (in cases of organ transplantation).
- St. John's wort (*Hypericum perforatum*) (used to treat depression).

Pregnancy and breast-feeding
As a precautionary measure, you should preferably avoid the use of Nexium Control during pregnancy. You should not use this medicine during breast-feeding.
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
Nexium Control has a low likelihood of affecting your ability to drive or use machines. However, side effects such as dizziness and visual disturbances may uncommonly occur (see section 4). If affected, you should not drive or use machines.

Nexium Control contains sucrose, sodium and allura red AC (E129)
Nexium Control contains sugar spheres, which contain sucrose, a type of sugar. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Nexium Control contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium free'.

Nexium Control contains azo colouring agent, Allura red AC (E129), which may cause allergic reactions.

3. How to take Nexium Control

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure.

How much to take
- The recommended dose is one capsule a day.
- Do not take more than this recommended dose of one capsule (20 mg) a day, even if you don't feel an improvement immediately.
- You may need to take the capsules for 2 or 3 days in a row before your reflux symptoms (for example, heartburn and acid regurgitation) get better.
- The treatment length is up to 14 days.

- When your reflux symptoms have completely gone you should stop taking this medicine.
- If your reflux symptoms get worse or do not improve after taking this medicine for 14 days in a row, you should consult a doctor.

If you have persistent or longstanding, frequently recurring symptoms even after treatment with this medicine, you should contact your doctor.

Taking this medicine
- You can take your capsule at any time of the day either with food or on an empty stomach.
- Swallow your capsule whole with half a glass of water. Do not chew, crush or open the capsule. This is because the capsule contains coated pellets, which stop the medicine from being broken down by the acid in your stomach. It is important not to damage the pellets.

If you take more Nexium Control than you should
If you take more Nexium Control than recommended, talk to your doctor or pharmacist straight away. You may experience symptoms such as diarrhoea, stomach ache, constipation, feeling or being sick and weakness.

If you forget to take Nexium Control
If you forget to take a dose, take it as soon as you remember it, on the same day. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
If you notice any of the following serious side effects, stop taking Nexium Control and contact a doctor immediately:
- Sudden wheezing, swelling of your lips, tongue and throat, rash, fainting, or difficulties in swallowing (severe allergic reaction, seen rarely).
- Reddening of the skin with blisters or peeling. There may also be severe blisters and bleeding in the lips, eyes, mouth, nose, and genitals. This could be 'Stevens-Johnson syndrome' or 'toxic epidermal necrolysis', seen very rarely.
- Yellow skin, dark urine and tiredness, which can be symptoms of liver problems, seen rarely.
- Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome), seen very rarely.

Talk to your doctor as soon as possible if you experience any of the following signs of infection:
This medicine may in very rare cases affect the white blood cells leading to immune deficiency. If you have an infection with symptoms such as fever with a **severely** reduced general condition or fever with symptoms of a local infection such as pain in the neck, throat or mouth, or difficulties in urinating, you must consult your doctor as soon as possible so that a lack of white blood cells (agranulocytosis) can be ruled out by a blood test. It is important for you to give information about your medicine at this time.

Other side effects include:

Common (may affect up to 1 in 10 people)
- Headache.
- Effects on your stomach or gut: diarrhoea, stomach ache, constipation, wind (flatulence).
- Feeling sick (nausea) or being sick (vomiting).
- Benign growths (polyps) in the stomach.

Uncommon (may affect up to 1 in 100 people)

- Swelling of the feet and ankles.
- Disturbed sleep (insomnia), feeling sleepy.
- Dizziness, tingling feelings such as “pins and needles”.
- Spinning feeling (vertigo).
- Dry mouth.
- Increased liver enzymes shown in blood tests that check how the liver is working.
- Skin rash, lumpy rash (hives), and itchy skin.

Rare (may affect up to 1 in 1,000 people)
- Blood problems such as a reduced number of white blood cells or platelets. This can cause weakness, bruising, or make infections more likely.
- Low levels of sodium in the blood. This may cause weakness, being sick (vomiting) and cramps
- Feeling agitated, confused, or depressed.
- Taste changes.
- Eyesight problems such as blurred vision.
- Suddenly feeling wheezy, or short of breath (bronchospasm).
- An inflammation on the inside of the mouth.
- An infection called “thrush” which can affect the gut and is caused by a fungus.
- Hair loss (alopecia).
- Skin rash on exposure to sunshine.
- Joint pain (arthralgia), or muscle pain (myalgia).
- Generally feeling unwell and lacking energy.
- Increased sweating.

Very rare (may affect up to 1 in 10,000 people)
- Low numbers of red blood cells, white blood cells, and platelets (a condition called pancytopenia).
- Aggression.
- Seeing, feeling, or hearing things that are not there (hallucinations).
- Severe liver problems leading to liver failure and inflammation of the brain.
- Muscle weakness.
- Severe kidney problems.
- Enlarged breasts in men.

Not known (frequency cannot be estimated from the available data)
- Low levels of magnesium in the blood. This may cause weakness, being sick (vomiting), cramps, tremor, and changes in heart rhythm (arrhythmias). If you have very low levels of magnesium, you may also have low levels of calcium and/or potassium in your blood.
- Inflammation of the gut (leading to diarrhoea).
- Rash, possibly with pain in the joints.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system: In Ireland, HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie e-mail: medsafety@hpra.ie.
In Malta, ADR Reporting, www.medicinesauthority.gov.mt/adrportal
By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Nexium Control

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the bottle after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

Keep this medicine in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Nexium Control contains

- The active substance is esomeprazole. Each gastro-resistant hard capsule contains 20 mg esomeprazole (as magnesium trihydrate).
- The other ingredients are:
  glycerol monostearate 40-55, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid - ethyl acrylate copolymer (1:1) dispersion 30 per cent, polysorbate 80, sugar spheres (sucrose and maize starch), talc, triethyl citrate, carmine (E120), indigo carmine (E132), titanium dioxide (E171), yellow iron oxide (E172), erythrosine (E127), allura red AC (E129), povidone K-17, propylene glycol, shellac, sodium hydroxide, and gelatin (see section 2, “Nexium Control contains sucrose, sodium and allura red AC (E129)”.)

What Nexium Control looks like and contents of the pack
Nexium Control 20 mg gastro-resistant hard capsules are approximately 11 x 5 mm capsules with a clear body, and an amethyst cap imprinted with “NEXIUM 20 MG” in white. The capsule has a yellow centre band, and contains yellow and purple enteric coated pellets.

Nexium Control is available in high-density polyethylene (HDPE) bottles with an induction seal closure and child resistant closure. The bottle also contains a sealed container with silica gel desiccant.

Each pack contains either 1 or 2 bottles, each with 14 gastro-resistant hard capsules.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
Haleon Ireland Dungarvan Limited, Knockbrack, Dungarvan, Co. Waterford, Ireland

Manufacturer
Haleon Italy Manufacturing S.r.l., Via Nettunense, 90, 04011, Aprilia (LT), Italy.

This leaflet was last revised in January 2025

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

FURTHER HELPFUL INFORMATION

What are the symptoms of heartburn?
The normal symptoms of reflux are a painful sensation in the chest rising up to your throat (heartburn) and a sour taste in the mouth (acid regurgitation).

Why do you get these symptoms?

Heartburn can be a result of eating too much, eating high fat food, eating too quickly and drinking lots of alcohol. You may also notice that when you lie down, that your heartburn gets worse. If you are overweight or smoke you increase the probability of suffering from heartburn.

What can I do to help relieve my symptoms?

- Eat healthier food and try to avoid spicy and fatty foods and large meals late before bedtime.
- Avoid fizzy drinks, coffee, chocolate and alcohol.
- Eat slowly and eat smaller portions.
- Try to lose weight.
- Stop smoking.

When should I seek advice or help?

- You should seek urgent medical advice if you experience chest pain with light-headedness, sweating, dizziness or shoulder pain with shortness of breath.
- If you experience any of the symptoms detailed in Section 2 of this leaflet and it advises you to talk to your doctor or pharmacist.
- If you are suffering from any of the side effects detailed in Section 4 which require medical attention.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for esomeprazole, the scientific conclusions of PRAC are as follows:

In view of available data on Drug reaction with eosinophilia and systemic symptoms (DRESS) from the literature, spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between esomeprazole and DRESS is at least a reasonable possibility. SCARs other than DRESS are already included in 4.8 of the SmPC. Due to the severity of these side effects, they should be included into the proposed warning in 4.4. of the SmPC and the package leaflet accordingly. The PRAC concluded that the product information of products containing esomeprazole should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for esomeprazole the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing esomeprazole is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.