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 tablet 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 in the indication: “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 esomeprazole, substituted benzimidazoles or to any of the excipients (see 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. Especially, 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 H₂ antagonist concomitantly.

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 medicine.

Interference with laboratory tests
The increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference the esomeprazole treatment should be temporarily stopped five days before CgA measurements.

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, Cₘₐₓ, and Cₘᵲᵢₙ). 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 (qd)) 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 qd without omeprazole 20 mg qd. Co-administration of omeprazole (40 mg qd) reduced mean nelfinavir AUC, Cₘₐₓ, and Cₘᵲᵢₙ by 36–39 % and mean AUC, Cₘₐₓ, and Cₘᵲᵢₙ 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 qd). Treatment with omeprazole 20 mg qd had no effect on the exposure of darunavir (with concomitant ritonavir) and amprenavir (with concomitant ritonavir).
Treatment with esomeprazole 20 mg qd had no effect on the exposure of amprenavir (with and without concomitant ritonavir). Treatment with omeprazole 40 mg qd 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 dosage 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 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 drug 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 trial 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 + ASA 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\text{max} and AUC$_{\tau}$ 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\text{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\text{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$_{\tau}$ 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 300-1000 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.

**Breastfeeding**
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 trials (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 trials 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 ≥1/1000 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).

<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td>leukopenia, thrombocytopenia</td>
<td>agranulocytosis, pancytopenia</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td>hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>peripheral oedema</td>
<td>hyponatraemia</td>
<td>hypomagnesaemia; severe hypomagnesaemia can correlate with hypocalcaemia; hypomagnesaemia may also result in hypokalaemia</td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Very rare</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------------------------------------------</td>
<td>----------------------------</td>
<td>------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td>insomnia</td>
<td>agitation, depression</td>
<td>aggression, hallucinations</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>headache</td>
<td>dizziness, paraesthesia, somnolence</td>
<td>taste disturbance</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td>blurring vision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>vertigo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting</td>
<td>dry mouth</td>
<td>stomatitis, gastrointestinal candidiasis</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td>increased liver enzymes</td>
<td>hepatitis with or without jaundice</td>
<td>hepatic failure, hepatic encephalopathy in patients with pre-existing liver disease</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>dermatitis, pruritus, rash urticaria</td>
<td>alopecia, photosensitivity</td>
<td>erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td>arthralgia, myalgia</td>
<td>muscular weakness</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td>Interstitial nephritis</td>
<td></td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td></td>
<td>gynaecomastia</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site disorders</td>
<td></td>
<td>malaise, increased sweating</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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 national reporting system listed in Appendix V.
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: A02B C05.

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 drugs, serum gastrin increases in response to the decreased acid secretion. CgA also increases due to decreased gastric acidity.

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
In the 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 according to standard methodology. In both studies esomeprazole 20 mg was significantly better compared to placebo for the primary endpoint, complete resolution of heartburn (p<0.001) and for the secondary endpoints such as relief of heartburn, days without heartburn and mean heartburn severity scoring. This applies for all of the time points 1, 2 and 4 weeks of treatment and for both day and night time scoring with increasing treatment effect by time. Furthermore, approximately 78% of the subjects on esomeprazole reported first resolution of heartburn within the first week of treatment.

The median time to first resolution of night-time heartburn was 1 day. About 80% of nights were heartburn free during all time periods and 90% of nights were heartburn free by week 2 of each trial.

Subjects also demonstrated relief of reflux symptoms other than heartburn, including regurgitation (58.5%-63.6% showed relief during week 2 evaluation). Following Overall Treatment Evaluation (OTE) of patients at week 2, 78.0-80.7% of patients, 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 drug 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 area 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. **PHARMAACEUTICAL PARTICULARS**

#### 6.1 List of excipients

Glycerol monostearate 40-55,
hyprolose,
hypromellose,
iron oxide (reddish-brown) (E 172),
iron oxide (yellow) (E 172),
magnesium stearate,  
methacrylic acid ethylacrylate copolymer (I:I) dispersion 30 per cent,  
cellulose microcrystalline,  
synthetic paraffin,  
macrogol 6000,  
polysorbate 80,  
crospovidone (Type A),  
sodium stearyl fumarate,  
sugar spheres (sucrose),  
talc,  
titanium dioxide (E 171),  
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 and 14 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB  
SE-151 85 Södertälje  
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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 AUTHORIZATION

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 manufacturers responsible for batch release

AstraZeneca AB
Gärtunavägen
Södertälje
15185
Sweden

AstraZeneca GmbH
Tinsdaler Weg 183
22880 Wedel
GERMANY

AstraZeneca S. A. France
Parc Industriel Pompelle
Chemin de Vrilly
Box 1050
F-51689 Reims Cedex 2
France

AstraZeneca UK Ltd.
Silk Road Business Park
Macclesfield, Ches SK10 2NA
United Kingdom

Biofabri S.L
A Relva, s/n, O Porriño, 36400 Pontevedra
Spain

Corden Pharma GmbH
Otto-Hahn-Strasse, 68723 Plankstadt
Germany

Recipharm Monts
18, rue de Montbazon, 37260 Monts
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-
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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.
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

#### 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

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product not subject to medical prescription.

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 ingredients of this medicine.

Do not use if you are taking a medicine containing Nelfinavir (used to treat HIV infection).

Please refer to section 2 of the package leaflet if you are taking other medicines.

How to use
Take one tablet once a day. Do not exceed this dose.

If your symptoms worsen or do not improve after taking this medicine for 14 days in a row, contact your doctor.

Relieves Heartburn & Acid Reflux

One tablet daily

16. INFORMATION IN BRAILLE

Nexium Control 20 mg
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blister</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nexium Control 20 mg gastro-resistant tablets</td>
</tr>
<tr>
<td>esomeprazole</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca AB</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. OTHER</th>
</tr>
</thead>
</table>
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

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).

You may experience relief from your acid reflux and heartburn symptoms after the first day of taking this medicine, but it 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).

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 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.

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.

Tell your doctor before taking this medicine, if:
• You are due to have an endoscopy or a urea breath test.
• You are due to have a specific blood test (Chromogranin A)

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 H2 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
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.

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 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.

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).

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.
• Changes 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).

**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 listed in Appendix V. 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 tablet contains 20 mg esomeprazole (as magnesium trihydrate).
- The other ingredient(s) are glycerol monostearate 40-55, hypromellose, iron oxide (reddish-brown) (E 172), iron oxide (yellow) (E 172), magnesium stearate, methacrylic acid ethylacrylate copolymer (I:I) dispersion 30 per cent, cellulose microcrystalline, synthetic
paraffin, macrogol 6000, polysorbate 80, crospovidone (Type A), sodium stearyl fumarate, sugar spheres (sucrose), talc, titanium dioxide (E 171) and triethyl citrate.

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

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

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
AstraZeneca AB
SE-151 85 Södertälje
Sweden

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

**België/Belgique/Belgien**
AstraZeneca S.A./N.V.
Tel: +32 2 370 48 11

**Lietuva**
UAB AstraZeneca Lietuva
Tel: +370 5 2660550

**България**
АстраЗенека България ЕООД
Тел.: +359 2 971 25 33

**Luxembourg/Luxemburg**
AstraZeneca S.A./N.V.
Tél/Tel: +32 2 370 48 11

**Česká republika**
AstraZeneca Czech Republic s.r.o.
Tel: +420 222 807 111

**Magyarország**
AstraZeneca Kft.
Tel.: +36 1 883 6500

**Danmark**
AstraZeneca A/S
Tlf: +45 43 66 64 62

**Malta**
Associated Drug Co. Ltd
Tel: +356 2277 8000

**Deutschland**
AstraZeneca GmbH
Tel: +49 41 03 7080

**Nederland**
AstraZeneca BV
Tel: +31 79 363 2222

**Eesti**
AstraZeneca
Tel: +372 6549 600

**Norge**
AstraZeneca AS
Tlf: +47 21 00 64 00

**Ελλάδα**
AstraZeneca A.E.
Tηλ.: +30 2 106871500

**Österreich**
AstraZeneca Österreich GmbH
Tel: +43 1 711 31 0

**España**
AstraZeneca Farmacéutica Spain, S.A.
Tel: +34 91 301 91 00

**Пolska**
AstraZeneca Pharma Poland Sp. z o.o.
Tel.: +48 22 874 35 00

**Portugal**
AstraZeneca Produtos Farmacêuticos, Lda.
This leaflet was last revised in

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