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2 July 2014

Dear Sir/Madam

CONSULTATION DOCUMENT: ARM 88; NEXIUM CONTROL 20MG GASTRO-RESISTANT TABLETS
REQUEST TO CLASSIFY A PRODUCT AS GSL

The consultation seeks your views on the GSL classification of Nexium Control 20mg Gastro-Resistant Tablets. The Marketing Authorisation Holder's GSL Classification Summary and Patient Information Leaflet are attached.

Following an application through the centralised procedure Nexium Control was approved as a non-prescription medicine by the European Commission on 26 August 2013. A medicine classified through the centralised procedure as non-prescription can be classified as either P or GSL in the UK. The Marketing Authorisation Holder has submitted evidence to seek to demonstrate that the product may be considered to meet the conditions for GSL supply in the UK. The Marketing Authorisation Holder's GSL classification summary and the proposed label and patient leaflet are set out below.

You are invited to comment on the proposal and a form can be found below. Comments should be sent to me either by post to room 3-M, 151 Buckingham Palace Road, London SW1W 9SZ or by email (reclassification@mhra.gsi.gov.uk) to arrive by **23 July 2014.** Contributions received after that date cannot be included in the exercise.

Within the terms of the Freedom of Information Act, the Agency intends to make copies of comments received publicly available. Unless you state otherwise we will assume that you have no objections to your comments being publicly available on the Agency's website.

Yours faithfully

Abiodun Aderogba
Self Medication Unit

REPLY FORM: ARM 88; ; NEXIUM CONTROL 20MG GASTRO-RESISTANT TABLETS

To: Abiodun Aderogba From: _____

MHRA _____
Room 3-M
151 Buckingham Palace Road _____
LONDON SW1W 9SZ

ALL RESPONDENTS MUST TICK ONE OF THE FOLLOWING BOXES

- **My reply may be made freely available** ☐
- **I wish my reply to remain confidential*** ☐
- **I wish parts of my reply to remain confidential*** ☐

*Please use the space below to explain why you feel the information in your reply should be treated as confidential. In line with the Freedom of Information Act 2000, if we receive a request for disclosure of the information we will take full account of your explanation, but we cannot give an assurance that confidentiality can be maintained in all circumstances. Responses to consultation will not normally be released under FOI until the regulatory process is complete

Explanation regarding why your response should remain confidential

_____

_____

_____

_____

_____

_____

Name: **Signature**

Date:

GSL CLASSIFICATION SUMMARY

1. Applicant Details

Name of the applicant:

Pfizer Consumer Healthcare Ltd

2. Product Details

Name:

Nexium Control 20 mg gastro-resistant tablets - EU/1/13/860/001-002

Active:

Esomeprazole (as magnesium trihydrate), 20 mg

Indications:

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

Current Dosage including age limits:

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 SmPC 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 SmPC 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.

Pack size:

Current: 7 or 14 Tablets - Not subject to medicinal prescription

Proposed: 7 or 14 Tablets - General Sales List (GSL)

3. Rationale for GSL classification

Nexium Control was approved as a non-prescription medicine by the European Commission on 26 August 2013. The non-prescription model and circumstances for use in Europe as approved within the centralised procedure are centred on the product information as the key risk minimization tool. No specific intervention of the pharmacist is referenced in the Risk Management Plan (RMP) as a requirement to ensure the appropriate selection and safe usage of Nexium Control.

Pfizer Consumer Healthcare Ltd provided data to support the interpretation of "not subject to medicinal prescription" as GSL within the UK legislative framework. This data demonstrated that the self-selection Over The Counter (OTC) model proposed for Nexium Control, centred on the OTC labelling can ensure appropriate and safe self-selection by consumers without the specific requirement for the intervention of a pharmacist. This is further supported by a detailed benefit/risk analysis using the Brass et al (2011) model. This analysis defined a number of benefits of widening access and availability to Nexium Control and identified the risk minimisation measures included in the RMP that support the low risk associated with expanding access. The model also shows that some of these risks are

inherent to the GSL category and Nexium Control itself does not provide any additional risks when compared to the other GSL products available in the UK.

Heartburn is a well established GSL indication within the UK environment. Currently 95% of the upper GI category (unit sales) in the UK are supplied via General Sale (antacids, alginates & H2RAs) (Internal Market Research 2013). UK consumers suffering from heartburn and acid regurgitation are therefore very familiar with and experienced in self-diagnosis and self-selection of appropriate treatments for this condition, without the intervention of a Pharmacist.

By enabling a new class of medicine to be self selected within the GSL category, it will allow those who are suffering from heartburn wider access and more choice to effectively treat their symptoms.

PPIs have been available in the UK as a Pharmacy Only medicine since January 2004. These have been used safely/without incident within the UK. Pfizer has provided data to show the safe use of omeprazole in a non-pharmacy environment, equivalent to GSL, elsewhere in the world. Esomeprazole is the S-isomer of omeprazole and reduces gastric acid secretion through a specific targeted mechanism of action. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. Esomeprazole has a well established and similar safety profile to omeprazole. This supports the conclusion and provides examples of how PPIs can be safely self-selected and used appropriately without pharmacist intervention.

Pfizer believe that there is no incremental risk associated with addition of Nexium Control as a GSL product when compared to other GSL products available in the UK and that this product can be safely supplied via self selection using the OTC labelling without the intervention of the pharmacist.

Hazard to Health

The safety and tolerability profiles of esomeprazole are well established. The majority of side effects identified or suspected are mild and transient in nature. No dose-related side effects have been identified.

US data provided on omeprazole used in the GSL setting showed a low number of drug interactions and the likelihood of clinical significance was low. The data did not show any specific safety issues relating to misuse or accidental overdose as a result of the sale and supply of the PPI in a GSL environment. Due to the similarity in profiles of the actives, it is likely that Nexium Control will have a similar safety profile to omeprazole if available in a GSL setting.

Given the widespread use of esomeprazole around the world, its safety profile is well established and it is unlikely that allowing wider access via GSL distribution would change the safety profile.

In relation to dosage for particular populations the following has been documented:

Pregnant and Lactation

Esomeprazole with non-prescription status is not intended for use during pregnancy and lactation as clearly stated in the Product Information. The importance of precaution with medication during pregnancy is well known among consumers, but accidental ingestion cannot be ruled out especially in cases where the pregnancy is unknown at the time of ingestion. However accidental ingestion of esomeprazole during conception or early pregnancy has not been associated with any identified risk of severe complications and/or malformations; esomeprazole should not be used during breast-feeding. Information and advice in the Package Leaflet text regarding use during pregnancy is considered to be sufficient as risk mitigation.

Children

Esomeprazole for non-prescription use is not indicated for children less than 18 years of age. However, information from a prescription only esomeprazole clinical development programme (in Europe, the prescription product is approved for children aged from 1 year to adolescence) showed an adverse event pattern similar to that in adults.

The risk of causing harm due to unintentional intake by children is considered to be low. Information and advice in Package Leaflet and outer carton text regarding use in children is considered to be sufficient as risk mitigation.

Hypersensitivity reactions

The hypersensitivity reactions (e.g. angioedema, anaphylactic reactions/shock and bronchospasm) are rare. The Package Leaflet, outer carton text includes clear instructions for the patient not to start self-medication if known hypersensitivity to esomeprazole or other ingredients within this medicine.

Severe Hepatic/Renal impairment

For prescribed esomeprazole, the dose is limited to 20 mg in patients with severe hepatic impairment. A dose adjustment is not needed in patients with impaired renal function. The probability and risk of causing harm due to unintentional intake of non-prescription esomeprazole (20 mg) by patient with Severe Hepatic or Renal impairment is considered to be low. Information and advice in the Package Leaflet text is considered to be sufficient as risk mitigation.

Patients with severe chronic diseases usually have frequent contacts with their doctors and they are also clearly instructed in the PIL to visit a doctor before taking Nexium Control. An intervention by a pharmacist at the point of sale will not significantly affect patient's ability to make this assessment.

The PIL and outer carton provide appropriate information and guidance regarding use and clear recommendations if and when to consult a pharmacist or doctor. Contact with a pharmacist at the point of sale will not significantly affect any residual hazard that may exist.

Therefore the product profile does not pose a significant hazard to public health. The use of the product in particular patient populations has been assessed and the risk has been shown to be mitigated by the risk minimisation measures in place.

Risk of Misuse

Ability to self assess condition and consequences in delay in treating disease

One of the key areas relating to misuse refers to the patient's ability to self assess their condition and what a delay in treating their disease may mean.

Heartburn and acid regurgitation are clearly described in the product information and can easily be assessed by the patients themselves. Furthermore, the product information and consumer education materials which will be made available, describe the symptoms and underlying causes of heartburn. They will also aid the individual in identifying any symptoms/red flags for which they should seek advice. This information will then clearly direct the patient to seek advice from a healthcare professional.

The key concerns relating to a delay or misdiagnosing the problem relate to masking:

- Peptic ulcers
- Barrett's oesophagus
- Malignant oesophageal or gastric disorders.

Signs and symptoms that should initiate a referral by a doctor for investigation, such as alarm symptoms and lack of treatment effect, are also easily recognisable by patients and as such can be acted upon and are detailed on the carton and PIL. Furthermore the treatment period has a maximum of 14 days, after which if symptoms have not improved or worsen then the patient should seek medical advice. As such, any delay in receiving this advice would be for two weeks only. However, it is unlikely that there are underlying causes without any additional alarm symptoms present. Therefore the 14 day period of use, reference to alarm symptoms in the PIL and the likelihood of having an underlying condition without alarm symptoms limits any risks associated with use without pharmacist intervention.

In consideration of this proposed GSL classification The Commission of Human Medicines (CHM) advised that steps should be taken to ensure that patients were not misinterpreting

their symptoms and confusing reflux symptoms with those of ischaemic heart disease. Therefore the following action was taken to address and resolve these concerns.

The warning to talk to a doctor or pharmacist if "You are over 55 and have new or recently changed reflux symptoms." was added to the carton.

Furthermore the warning detailed below was added to section 2 of the Patient Information Leaflet:

"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."

This addition will allow patients who are experiencing any alarm symptoms associated with ischaemic heart disease to correctly identify them and provide them with a course of action to take. There is also an additional section at the end of the Patient Information Leaflet called "Further helpful information" which provides additional information about reflux and again makes reference to these alarm symptoms and what action to take.

In line with NICE guidelines, if the patient goes to a doctor exhibiting reflux symptoms without any alarm symptoms, they will be prescribed a PPI product. Therefore if the patient does need to liaise with a healthcare professional and they have used a PPI prior to any medical interaction, it will provide the doctor or pharmacist with some insight into the issue or cause prior to prescribing medication.

To minimise issues relating to self assessment and ensuring the patient is directed to a doctor or pharmacist, information has been included on the carton and in the PIL.

- Information provided on the outer carton provides clear instructions on use. It also advises the following:

  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.

- Additional Warnings and Advice on the carton include:

  Read the package leaflet before use.

  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.

- Signs and symptoms that should initiate a doctor-driven investigation, such as alarm/red flag symptoms and lack of effect during treatment, are clearly described in the patient information leaflet and also easily recognisable by patients.

As such, there is comprehensive information available at point of sale to help patients to appropriately self select the product and contact health care professionals as appropriate.

Excessive or prolonged use, intentional and accidental overdose

Treatment for Nexium Control is limited to 14 days. The pack sizes of 7 and 14 tablets minimize the risk of people taking the product for longer than required and the product information clearly states that the product should not be taken for more than 14 days without seeking a doctor's advice.

Results from non-clinical studies indicate that esomeprazole, even in high doses, has a low toxicity. Clinical experience of doses in excess of 240 mg/day is limited. The symptoms described in connection with oral ingestion of 280 mg have been gastrointestinal symptoms and weakness. The ingestion of a single dose of 800 mg has been documented but no symptoms were reported. Long-term exposure (up to 1 year) to prescribed esomeprazole has not raised any safety concern.

The pack size restriction would mean the maximum amount that could be taken from one pack is 280 mg and as the SmPC and PIL identifies the symptoms related to this level of overdose for esomeprazole were GI symptoms and weakness.

Esomeprazole does not produce euphoric, stimulant, sedative or other addictive effects most commonly associated with abuse or misuse. No potential for misuse for illegal purposes has been identified.

It is unlikely that an increased incidence of overdose may occur as a result of the product becoming available GSL.

Evidence from PPI use with no pharmacist interaction

Information available for Omeprazole, a similar PPI, has been available in the US without healthcare professional intervention for 10 years. In a study conducted following the FDA approval of Prilosec OTC (OTC omeprazole) in the US, it was demonstrated that consumers were able to appropriately self-select an OTC proton pump inhibitor (PPI) and were compliant with the directions for use, using only the product labelling to guide their actions.

The outcomes measured in the study were self-selection, compliance and duration of use, physician contact and heartburn medication use.

GSL CLASSIFICATION SUMMARY

Based on this study results, the following were demonstrated:

- there is no evidence of misuse
- there is no evidence of significant long-term use
- consumers consulted a physician if they had persistent symptoms
- consumers were compliant with the directions of use, using only the product labelling as guidance

In summary

There is no additional risk based on the active compound esomeprazole when compared to other products in the GSL heartburn category. All products within the category could potentially mask underlying conditions, however the signposting on the carton and PIL, the available education materials and limited duration of use mean that there is no incremental risk of misuse associated with Nexium Control compared to other products on the market.

Special Precautions in Handling

There are no special requirements for precaution in handling of Nexium Control. As such, consumers will be able to safely and effectively handle and store the medicine without the need for advice from a Pharmacist.

Convenience to the Purchaser

Heartburn is a well established GSL indication within the UK environment. Currently 95% of the non prescription upper GI category (unit sales) in the UK is supplied via General Sale (antacids, alginates & H2RAs) (Internal Market Research 2013).

Approximately 35% of the UK's 50.2 million adult population (Forbes 2013) are susceptible to heartburn, and of those 75% suffer more than once a week and 15% suffer nearly every day (Forbes 2013). This amounts to 8.2 million consumers who suffer for 2 or more days a week (Forbes 2013).

Making a PPI available GSL would enable access to this medicine for those for whom "traditional" indigestion remedies do not provide complete relief. By enabling a new class of medicine to be self selected in the GSL category, it will allow those who are suffering wider access and more choice to effectively treat their symptoms.

The dosage regime is also simpler than products currently available GSL, where only one tablet is required to be taken each day, the effect of which then lasts for 24 hours.

Within the indigestion market, 56% of the sales value is through the major multiple grocers, only 37% through chemist (Internal Market Research 2013). This indicates consumers would expect to buy indigestion remedies within the supermarket arena and are used to doing so. In a recent study (2013), when asked where they would expect to buy Nexium Control, 72% of

respondents said they would expect to buy it in a supermarket. 65% of supermarket shoppers like the fact that they can buy indigestion tablets in the same trip as doing their other shopping (Forbes 2013). It may also be convenience of location, an important purchase attribute to over 70 % of heartburn users in deciding where to shop for product (Forbes 2013).

Role of the Pharmacist

The role of the community pharmacist in the UK is wide. They fulfill a number of important roles within the community including dispensing prescriptions, providing advice on ailments and help ensuring that appropriate sale and use of OTC medication. As such a part of the role is to help ensure patient safety by performing when needed some of the activities detailed below:

- Using the WWHAM criteria when discussing ailments and potential medications with a customer
- Recommending appropriate medication or referral to doctor as appropriate
- Explaining how to use the product correctly
- Providing advice on medications already purchased
- Ensuring that Pharmacy Only medicines are given to an appropriate patient

As part of their key activities, the pharmacist is making sure that a patient is not exhibiting any alarm signals which may need referral to a doctor. When recommending or selling medicines, they use their pharmacy knowledge to make certain that a patient is not taking any other medicines that may be contraindicated or interact with the product being bought.

The packaging of the product was developed and approved as the primary tool to assist self selection and this was recognised during the EMA assessment of the licence. There were no further requirements for risk mimimisation established during the centralised marketing authorization application procedure and no requirement for the pharmacist to be present at point of sale.

The carton states when a patient should talk to a doctor or pharmacist and signposts to the patient information to provide detailed advice on the contraindications, special warnings and interactions. It also specifies how to correctly take the product. In Section 2 of the PIL there is a reference to the potential alarm symptoms / red flags that a patient may be having and they are advised to consult their doctor if they are experiencing these. As such, even if a pharmacist is not present at the point of sale, the patient will still be able to access this information themselves and ensure appropriate action is taken.

GSL CLASSIFICATION SUMMARY

Irrespective of the GSL status of the product, a comprehensive training programme for pharmacists will still be provided as it is recognized that some consumers may wish to contact a pharmacist and this gives patients the option to go into the pharmacy to ask for further advice or purchase the product in the pharmacist setting. The types of training will include detail aids, face to face training (where applicable), articles and a dedicated Health Care Professional website.

The packaging and PIL will make it clear that consumers should refer to healthcare professionals for further information and advice if they are experiencing any the following:

- certain alarm symptoms
- a worsening or continuation of symptoms beyond 14 days,

In addition it contains advice about contraindicated medications and actions to be taken, in the event of accidental overdose or the development of possible side effects. As such the product information provides sign posting to pharmacists and doctors in the circumstances a patient may need advice.

4. Specific GSL requirements

Conditions for GSL supply:

For internal use, in the form of gastro-resistant tablets.

For the short term relief of reflux symptoms (e.g. heartburn and acid regurgitation).

For adults aged 18 years and over.

Maximum duration of treatment without consulting a doctor: 2 weeks

Maximum strength: 20mg

Maximum dose: 20mg

Maximum daily dose: 20mg

Maximum pack size: 14 tablets

The label will include:

Read the package leaflet before use.

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.

GSL CLASSIFICATION SUMMARY

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.

The Patient Leaflet will include:

Information about the symptoms of indigestions and how to avoid confusion between reflux symptoms and those of ischaemic heart disease.

5. Safety Profile

Esomeprazole is a proton pump inhibitor (PPI) and is an oral formulation that was first approved in 2000 in Sweden. Nexium as a prescription drug is currently approved in more than 125 countries worldwide for various gastric acid-related disorders.

Esomeprazole is the S-enantiomer of omeprazole, which has been available OTC in the US since 2003 which is an equivalent status to GSL in the UK. Safety data relating to its use in the United States have shown that it can be safely used within this environment. Nexium Control was granted OTC status in the US in 2003; Omeprazole also has OTC status in Mexico which again is equivalent to GSL in the UK.

Safety and tolerability of esomeprazole is well-established and is supported by post marketing experience from approximately 80 million patient-years of oral esomeprazole treatment as of 31st December 2012. It is estimated that, >90000 patients/subjects have been exposed to esomeprazole in clinical trials. The majority of reactions are mild and transient in nature, the most frequent being headache and gastrointestinal disorders, i.e., abdominal pain, diarrhoea, flatulence, nausea/vomiting and constipation.

Within the UK the following has been reported for all single ingredient and combination products containing esomeprazole for all prescription dosage forms during the time period 15th February 2000 to 11th November 2013.

Table 1: Adverse Event Reactions (ADRs) reported between 15th Feb 2000 and 11th Nov 2013 as detailed in the Drug Analysis Print for Esomeprazole from MHRA

Total number of ADR reports:	521
Total number of reactions:	1155
Total number of fatal ADR reports:	0

In UK, the total exposure of oral esomeprazole until 31 December 2012 has been estimated to be approximately 2 208 601 person years. Relative to the large number of patient exposures in the UK, the number of reported events for esomeprazole is low and the majority of these are mild, non-serious and self-limiting in nature. These data, in conjunction with the safety information included in the MAA, support the well-established safety profile of esomeprazole. There is no reason to expect that this would change with the wider distribution that is anticipated where the product to be available GSL.

6. Support for GSL classification

This is a company submission and there is no additional support from other experts or organisations provided.

References:

Brass EP, Lofstedt R, Renn O. Improving the decision making process for nonprescription drugs: a framework for benefit – risk assessment. Clin Pharmacol Ther 2011:doi: 10.1038/clpt.2011.231.Internal Market Research 2013

Fendrick AM, Shaw M, Schachtel B, et al. Self-selection and use patterns of over-the-counter omeprazole for frequent heartburn. Clin Gastroenterol Hepatol 2004;2(1):17–21.

Forbes 2013 – Internal Company Market Research

Drug Analysis Prints for Esomeprazole 15th February 2000 to 11th November 2013

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

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).

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.

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.

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.

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 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
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 in the United Kingdom, Yellow Card Scheme Website www.mhra.gov.uk/yellowcard. In Ireland IMB Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2. Tel: +353 1 6764971 Fax: +353 1 6762517 Website: www.imb.ie e-mail: imbpharmacovigilance@imb.ie.
In Malta, ADR Reporting, The Medicines Authority, Post-Licensing Directorate, 203 Level 3, Rue D'Argens, GŻR-1368 Gżira Website: www.medicinesauthority.gov.mt e-mail: postlicensing.medicinesauthority@gov.mt.
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, 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) 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

Marketing Authorisation Holder: Pfizer Consumer Healthcare Ltd, Ramsgate Road, Sandwich, Kent, CT13 9NJ, UK.

Manufacturer: Wyeth Lederle S.r.l., Via Nettunense, 90, 04011, Aprilia (LT), Italy.

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

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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 medical 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 requires medical attention.

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

CI3185-02

Component Travel Direction

WYA0215


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• One tablet daily
• Lasts 24 hours
7 tablets
Lot
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Nexium CONTROL®
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Do not store above 30°C. Store in the original package in order to protect from moisture. Keep out of the sight and reach of children. Medicinal product not subject to medical prescription.
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W195
WYA0279
CA3274-01
Component Travel Direction
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.
Talk to your pharmacist or doctor if:
• You are taking any medicines listed in the packaged 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.
• The tablets should be swallowed whole. Do not chew or crush the tablets.
• 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.
• Read the package leaflet before use.
Oral use. Each gastro-resistant tablet contains 20 mg esomeprazole (as magnesium trihydrate). Contains sucrose. See package leaflet for further information.
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