IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA1473/001/001
Case No: 2050120

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

McDowell Pharmaceuticals

4 Altona Road, **Lisburn**, **N. Ireland**, **BT27 5QB**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Nexium 20 mg Gastro-Resistant Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **30/01/2009**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nexium 20 mg Gastro-Resistant Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gastro-resistant tablet contains 20mg esomeprazole (as magnesium trihydrate).
Excipients: Sucrose (contained in sugar spheres)
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Gastro-resistant tablet.
Product imported from the UK:
Light Pink, oblong, biconvex, tablet engraved ‘20 mg’ on one side and ‘A/EH’ on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

NEXIUM tablets are indicated for:
Gastro-Oesophageal Reflux Disease (GORD)
treatment of erosive reflux oesophagitis
long-term management of patients with healed oesophagitis to prevent
relapse symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In combination with an appropriate antibacterial therapeutic regimen for the eradication of Helicobacter pylori and
healing of Helicobacter pylori associated duodenal ulcer and
prevention of relapse of peptic ulcers in patients with Helicobacter pylori associated ulcers.

Patients requiring continued NSAID therapy
Healing of gastric ulcers associated with NSAID therapy.
Prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.

Treatment of Zollinger Ellison Syndrome

4.2 Posology and method of administration

The tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed. For patients who have difficulty in swallowing, the tablets can also be dispersed in half a glass of non-carbonated water. No other liquids should be used as the enteric coat may be dissolved. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

For patients who cannot swallow, the tablets can be dispersed in non-carbonated water and administered through a gastric tube. It is important that the appropriateness of the selected syringe and tube is carefully tested for preparation and administration, please see Section 6.6

Adults and adolescents from the age of 12 years.

Gastro-Oesophageal Reflux Disease (GORD)

- treatment of erosive reflux oesophagitis
40 mg once daily for 4 weeks.
An additional 4 weeks treatment is recommended for patients in whom oesophagitis has not healed or who have persistent symptoms.

- long-term management of patients with healed oesophagitis to prevent relapse
20 mg once daily.

- symptomatic treatment of gastro-oesophageal reflux disease (GORD)
20 mg once daily in patients without oesophagitis. If symptom control has not been achieved after four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen taking 20 mg once daily, when needed.

In NSAID treated patients at risk of developing gastric and duodenal ulcers, subsequent symptom control using an on demand regimen is not recommended.

Adults

In combination with an appropriate antibacterial therapeutic regimen for the eradication of Helicobacter pylori and

-healing of Helicobacter pylori associated duodenal ulcer and prevention of relapse of peptic ulcers in patients with Helicobacter pylori associated ulcers.

20 mg NEXIUM with 1 g amoxicillin and 500 mg clarithromycin, all twice daily for 7 days.

Patients requiring continued NSAID therapy
Healing of gastric ulcers associated with NSAID therapy:
The usual dose is 20 mg once daily. The treatment duration is 4-8 weeks.
Prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk:
20 mg once daily.

Treatment of Zollinger Ellison Syndrome
The recommended initial dose is Nexium 40mg twice daily. The dosage should then be individually adjusted and treatment continues as long as clinically indicated. Based on the clinical data available, the majority of patients can be controlled on doses between 80 and 160mg esomeprazole daily. With doses above 80mg daily, the dose should be divided and given twice daily.

Children below the age of 12 years
NEXIUM should not be used in children since no data is available.

Impaired renal function
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).

Impaired hepatic function
Dose adjustment is not required in patients with mild to moderate liver impairment. For patients with severe liver impairment, a maximum dose of 20 mg NEXIUM should not be exceeded, (see section 5.2).

Elderly
Dose adjustment is not required in the elderly.

4.3 Contraindications

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole, like other PPIs, should not be administered with atazanavir (see section 4.5).

4.4 Special warnings and precautions for use

In the presence of any alarm symptom (e.g. 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 NEXIUM may alleviate symptoms and delay diagnosis.

Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

Patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character. When prescribing esomeprazole for on-demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered, see section 4.5.

When prescribing esomeprazole for eradication of Helicobacter pylori possible drug interactions for all components in the triple therapy should be considered. Clarithromycin is a potent inhibitor of CYP3A4 and hence contraindications and interactions for clarithromycin should be considered when the triple therapy is used in patients concurrently taking other drugs metabolised via CYP3A4 such as cisapride.

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

4.5 Interaction with other medicinal products and other forms of interaction

Effects of esomeprazole on the pharmacokinetics of other drugs
Medicinal products with pH dependant absorption
The decreased intragastric acidity during treatment with esomeprazole, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of ketoconazole and itraconazole can decrease during treatment with esomeprazole.
Co-administration of omeprazole (40mg once daily) with atazanvir 300mg/ritonavir 100mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 75% decrease in AUC, Cmax and Cmin). Increasing the atazanavir dose to 400mg did not compensate for the impact of omeprazole on atazanavir exposure. PPIs including esomeprazole should not be co-administered with atazanavir (see section 4.3).

Drugs metabolised by CYP2C19
Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C 19, such as diazepam, citalopram, imipramine, clomipramine, phenytoin etc., the plasma concentrations of these drugs may be increased and a dose reduction could be needed. This should be considered especially when prescribing esomeprazole for on-demand therapy. Concomitant administration of 30 mg esomeprazole resulted in a 45% decrease in clearance of the CYP2C 19 substrate diazepam. 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. Omeprazole (40mg once daily) increased voriconazole (a CYP2C 19 substrate) Cmax and AUC by 15% and 41% respectively.

Concomitant administration of 40mg 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 treatment with warfarin or other coumarine derivatives.

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 (t1/2) 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 (see also section 4.4).

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

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 drugs on the pharmacokinetics of esomeprazole
Esomeprazole is metabolised by CYP2C1 9 and CYP3A4. Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg b.i.d.), resulted in a doubling of the exposure (AUC) to esomeprazole. Concomitant administration of esomeprazole and a combined inhibitor of CYP2C 19 and CYP 3A4 may result in more than doubling of the esomeprazole exposure. The CYP2C19 and CYP3A4 inhibitor voriconazole increased omeprazole AUC by 280%. A dose adjustment of esomeprazole is not required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

4.6 Pregnancy and lactation

For Nexium, clinical data on exposed pregnancies are insufficient. With the racemic mixture omeprazole data on a larger number of exposed pregnancies stemmed from epidemiological studies indicate no malformative nor foetotoxic effects. Animal studies with esomeprazole do not indicate direct or indirect harmful effects with respect to embryonal/fetal development. Animal studies with the racemic mixture do not indicate direct or indirect harmful effects with respect to pregnancy, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

It is not known whether esomeprazole is excreted in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

No effects have been observed

4.8 Undesirable effects

The following adverse drug reactions have been identified or suspected in the clinical trials programme for esomeprazole and post-marketing. None was found to be dose-related. The reactions are classified according to frequency (common >1/100, <1/10; uncommon >1/1000, <1/100; rare >1/10000, <1/1000; very rare <1/10000).

<u>Blood and lymphatic system disorders</u>
Rare: Leukopenia, thrombocytopenia
Very rare: Agranulocytosis, pancytopenia

<u>Immune system disorders</u>
Rare: Hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock

<u>Metabolism and nutrition disorders</u>
Uncommon: Peripheral oedema
Rare: Hyponatraemia

Psychiatric disorders
Uncommon: Insomnia
Rare: Agitation, confusion, depression
Very rare: Aggression, hallucinations

Nervous system disorders
Common: Headache
Uncommon: Dizziness, paraesthesia, somnolence
Rare: Taste disturbance

Eye disorders
Rare: Blurred vision

Ear and labyrinth disorders
Uncommon: Vertigo

Respiratory, thoracic and mediastinal disorders
Rare: Bronchospasm

Gastrointestinal disorders
Common: Abdominal pain, constipation, diarrhoea, flatulence, nausea/vomiting
Uncommon: Dry mouth
Rare: Stomatitis, gastrointestinal candidiasis

Hepatobiliary disorders
Uncommon: Increased liver enzymes
Rare: Hepatitis with or without jaundice
Very rare: Hepatic failure, encephalopathy in patients with pre-existing liver disease

Skin and subcutaneous tissue disorders
Uncommon: Dermatitis, pruritus, rash, urticaria
Rare: Alopecia, photosensitivity
Very rare: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone disorders
Rare: Arthralgia, myalgia
Very rare: Muscular weakness

Renal and urinary disorders
Very rare: Interstitial nephritis

Reproductive system and breast disorders
Very rare: Gynaecomastia

General disorders and administration site conditions
Rare: Malaise, increased sweating

4.9 Overdose

There is very limited experience to date with deliberate overdose. The symptoms described in connection with 280mg 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 dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Proton Pump Inhibitor 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.

Site and 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.

Effect on gastric acid secretion
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 GORD 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.

Therapeutic effects of acid inhibition
Healing of reflux oesophagitis with esomeprazole 40 mg occurs in approximately 78% of patients after four weeks, and in 93% after eight weeks.

One week treatment with esomeprazole 20 mg b.i.d. and appropriate antibiotics, results in successful eradication of H. pylori in approximately 90% of patients.

After eradication treatment for one week there is no need for subsequent monotherapy with antisecretory drugs for effective ulcer healing and symptom resolution in uncomplicated duodenal ulcers.

Other effects related to acid inhibition
During treatment with antisecretory drugs serum gastrin increases in response to the decreased acid secretion.

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.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur at a somewhat increased frequency.

These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear to be reversible.

In two studies with ranitidine as an active comparator, Nexium showed better effect in healing of gastric ulcers in patients using NSAIDs, including COX-2 selective NSAIDs.
In two studies with placebo as comparator, Nexium showed better effect in the prevention of gastric and duodenal ulcers in patients using NSAIDs (aged>60 and/or with previous ulcer), including COX-2 selective NSAIDs.

5.2 Pharmacokinetic properties

Absorption and distribution
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 40mg and increases to 89% after repeated once-daily administration. For 20mg esomeprazole the corresponding values are 50% and 68%, respectively. 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.
Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Metabolism and excretion
Esomeprazole is completely metabolised by the cytochrome P450 system (CYP). The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C 19, 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.
The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C 19 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. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship 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 CYP2C 19 enzyme by esomeprazole and/or its sulphone metabolite. 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.

Special patient populations
Approximately 1-2% of the population lack a functional CYP2C 19 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 increased by about 60%. These findings have no implications for the posology of esomeprazole.
The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years of age).
Following a single dose of 40mg 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.

Impaired organ function
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 20mg 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.
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.

Paediatric
Adolescents 12-18 years:
Following repeated dose administration of 20mg and 40mg esomeprazole, the total exposure (AUC) and the time to reach maximum plasma drug concentrations (t_{max}) in 12 to 18 year olds was similar to that in adults for both esomeprazole doses.

5.3 Preclinical safety data

Preclinical bridging studies reveal no particular hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, and toxicity to reproduction. Carcinogenicity studies in the rat with the racemic mixture have shown gastric ECL-cell hyperplasia and carcinoids. These gastric effects in the rat are the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid and are observed after long-term treatment in the rat with inhibitors of gastric acid secretion.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hyprolose
Glycerol monostearate 40-55
Hypromellose
Iron Oxide (reddish-brown, yellow) (E172)
Magnesium Stearate
Methacrylic acid ethyl acrylate copolymer (1:1) dispersion 30 per cent
Microcrystalline cellulose
Synthetic Paraffin
Macrogol
Polysorbate 80
Crospovidone
Sodium Stearyl Fumarate
Sugar Spheres (sucrose and maize starch)
Talc
Titanium Dioxide (E171)
Triethyl citrate

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C
Store in the original package

6.5 Nature and contents of container

Aluminium blisters in a cardboard carton containing 28 tablets

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Not to be crushed or chewed; swallow whole
Or
Administration through gastric tube

1. Put the tablet into an appropriate syringe and fill the syringe with approximately 25 ml water and approximately 5 ml air. For some tubes, dispersion in 50 ml water is needed to prevent the pellets from clogging the tube.
2. Immediately shake the syringe for approximately 2 minutes to disperse the tablet.
3. Hold the syringe with the tip up and check that the tip has not clogged.
4. Attach the syringe to the tube whilst maintaining the above position.
5. Shake the syringe and position it with the tip pointing down.
   Immediately inject 5 – 10 ml into the tube. Invert the syringe after injection and shake (the syringe must be held with the tip pointing up to avoid clogging of the tip)
6. Turn the syringe with the tip down and immediately inject another 5 – 10 ml into the tube. Repeat this procedure until the syringe is empty.
7. Fill the syringe with 25 ml of water and 5 ml of air and repeat step 5 if necessary to wash down any sediment left in the syringe. For some tubes, 50 ml water is needed.

7 Parallel Product Authorisation Holder

McDowell Pharmaceuticals
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8 Parallel Product Authorisation Number

PPA 1473/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 30th January 2009

10 DATE OF REVISION OF THE TEXT