European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

COMMITTEE OF EXPERTS ON THE CLASSIFICATION OF MEDICINES AS REGARDS THEIR SUPPLY (CD-P-PH/PHO)

Report classification/justification of

- Medicines belonging to the ATC group A02BA (H2-receptor antagonists)

- Medicines belonging to the ATC group A02BC (Proton pump inhibitors)

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INTRODUCTION

The legal classification of medicines as regards their supply with or without a medical prescription has implications for patient safety, patient accessibility to medicines and the responsible management of healthcare expenditure.

For many years, the **Council of Europe** (**which is distinct from the European Union**)[1] has been concerned with the supply conditions of medicines for human use and the harmonisation of national legal provisions from the perspective of patient safety and public health protection. An initial Recommendation AP(61)2 was drawn up in 1961 to control a growing tendency of misuse and overuse of sedative and narcotic medicines by empowering the competent authorities to classify new medicines into prescription and non-prescription medicines, taking into consideration the risks associated with the active substance and the conditions of use of the medicines.

On 12 April 2007, the Council of Europe Committee of Ministers adopted Resolution ResAP (2007)1 on the classification of medicines as regards their supply[2]. The resolution is aimed at promoting patient safety and improving patient accessibility to medicines, and is focused on public health. The resolution:

> "*1. Recommends to the governments of the member states of the Partial Agreement in the Social and Public Health Field that they supply information on the national legal classification of medicines as regards their supply on a regular basis;*
>
> *2. Recommends to the same governments that they apply the general provisions and the classification of active substances depending on the supply conditions of the medicines which contain them,* ***as set out in the appendices***."

The text of this Council of Europe resolution comprises a recommendation of the Committee of Ministers (Foreign Affairs Ministers, representing the governments of states participating in an activity) to member states to implement the stipulations of the resolution into national legislation or to adapt national legislation.

Although recommendations are not legally binding, they are legal instruments; they may create soft law and contain a statement of policy. The Committee of Ministers may also invite the member states to report on their efforts to implement a recommendation.

As regards national licences, industry is impacted if national authorities implement the revisions, as applicable.

It has to be borne in mind that the decisions of the Committee of Experts CD-P-PH/PHO as regards the supply of medications, with or without a medical prescription, take into account national assessments and scientific rationale. Revisions are completed and made available following each second annual meeting of the Committee of Experts on the classification of medicines as regards their supply (CD-P-PH/PHO) (Appendices 2011, ResAP (2007)1).

The annually revised appendices of the Council of Europe Resolution ResAP (2007)1 on the classification of medicines as regards their supply provide a key source of reference for the European pharmaceutical industry.

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[1] www.coe.int

[2] CM Council of Europe Resolution ResAP(2007)1

The classification criteria set out in the Council of Europe resolutions have been included in **European Union** legislation, such as Directive 92/26/EC and Directive 2001/83/EC (art. 70-75). In the preamble of Directive 2001/83/EC (see point 32), reference is made to the Council of Europe: "*It is therefore appropriate, as an initial step, to harmonise the basic principles applicable to the classification for the supply of medicinal products in the Community or in the Member State concerned, while taking as a starting point the principles already established on this subject by the Council of Europe*[3]."

To date, the classification of medicines remains a competency of states in Europe. This also holds true for the member states of the European Union.

The Committee of Experts on the classification of medicines as regards their supply (CD-P-PH/PHO), which is co-ordinated by the European Directorate for the Quality of Medicines & HealthCare (EDQM, Council of Europe), does not issue recommendations on the classification of particular medicines, but on **active substances used in a medicine for a specific therapeutic purpose**. The Committee of Experts CD-P-PH/PHO reviews the classification of medicines (INN/ATC[4]) authorised in Europe via national and European marketing authorisation procedures (the latter is applicable to the 47 Council of Europe member states, including the European Union member states) in order to establish recommendations for the classification of medicines (INN/ATC) and their supply conditions (see also Glossary of Terms, page 7), involving:

- Medicines that have not yet been included in Council of Europe recommendations;

- Medicines that qualify to be released from prescription status, i.e. a switch to "over the counter" (OTC) status or vice-versa;

- Revisions of current classifications.

The Committee of Experts CD-P-PH/PHO meets twice annually to finalise the annual review of the recommendations and appendices of ResAP (2007)1. The review is completed at the second of these meetings and is published on the website of the EDQM. These recommendations are an integral part of the Council of Europe's Committee of Ministers Resolution ResAP (2007)1 on the classification of medicines as regards their supply.

The Committee of Experts does not give advice relating to pending marketing authorisation procedures. It uses scientific approaches and methods (taking into account the pharmacological properties of the medicines), and considers issues relating to direct and indirect risks (pharmacovigilance), as well as misuse/abuse and matters of public health concern.

In its work, the CD-P-PH/PHO uses the Anatomical Therapeutic Chemical (ATC) classification maintained by the WHO Collaborating Centre for Drug Statistics Methodology[5]. The Commission of the European Union is entitled to participate in the meetings of the CD-P-PH/PHO.

[3] http://goo.gl/Uy22V1
[4] INN: International non-proprietary name; ATC: Anatomical Therapeutic Chemical (ATC) classification
[5] http://www.whocc.no/atc_ddd_index/

DISCLAIMER

This document is published for information only. The reports included in this document have no legal status and no binding character.

They reflect the conclusions of the reports arising from reviews of scientific classifications of medicines and the rationale and debates on which the recommendations on the classification of medicines as regards their supply, taken by the CD-P-PH/PHO at its 58th meeting on 31 March-1 April 2015 and its 59th meeting on 1-2 December 2015, were based. The document was reviewed and endorsed by the CD-P-PH/PHO at its 60th meeting on 19-20 April 2016.

The reviews carried out do not commit the parent authorities of the experts nor the Council of Europe/EDQM.

GLOSSARY OF TERMS USED IN THIS DOCUMENT

ADR	Adverse drug reaction
ATC	Anatomical Therapeutic Chemical[6]
CIOMS	Council for International Organizations of Medical Sciences
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures - Human
EMA	European Medicines Agency
FDA	Food and Drug Administration
GORD	Gastro-oesophageal reflux disease
HMA	Heads of Medicines Agencies
INR	International Normalised Ratio
IV	Intravenous
MS	Maximal strength
MDD	Maximal daily dose
MQP	Maximal quantity per pack
MRI	Mutual recognition information
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over-the-counter (medicine supplied without prescription)
PDR	Physicians' Desk Reference (www.pdr.net/)
PhVWP	Pharmacovigilance Working Party
PIL	Patient information leaflet
POM	Prescription only medicine
PPI	Proton pump inhibitor
PRAC	Pharmacovigilance Risk Assessment Committee
SCLE	Subacute cutaneous lupus erythematosus
SmPC	Summary of product characteristics

Classification used throughout this document

Following the stipulations of Resolution ResAP (2007)1, the medicine contains one or more active substances classified as **List I** or **List II** to which the following criteria apply:

List I
The supply of a medicine containing one of the substances on this list may only be repeated if the prescriber specifies so on the prescription;

List II
The supply of a medicine containing one of the substances on this list may be repeated without the prescriber having specified so, provided that he/she did not explicitly forbid such repetition and that the amount supplied at renewals (and their frequency) be consistent with medical and pharmaceutical data (such as the prescribed daily dose, the duration of treatment, the degree of medical supervision required by the condition, etc.);

Exemptions from Lists I and II
- For certain substances, exemptions from the "prescription only" requirement may appear in Lists I and II:

[6] WHO Collaborating Centre for Drug Statistics Methodology - http://www.whocc.no/atc_ddd_index/

- In respect of a low dosage or concentration of the active substances and/or therapeutic indications of the medicines in which they are contained;
- According to the route of administration and the composition of the medicine;
- According to the total content of the medicine per container.

- Active substances classified according to the conditions of supply of the medicines which contain them as supplied without prescription, i.e. over-the-counter (OTC) medicines.

Medicines not subject to prescription (OTC medicines)
Active substances of medicines that are classified as not subject to prescription according to the criteria given in item 4 of the General Provisions of ResAP (2007)1 are classified in the list "Medicines not subject to prescription (OTC medicines)".

For the purpose of this resolution, OTC medicines are understood to be those also having a valid marketing authorisation issued by a competent authority.

It is possible that a given active substance can be contained in both an OTC medicine and a medicine subject to prescription of the same ATC (Anatomical Therapeutic Chemical Classification) because of the particular conditions of use of the medicines in question.

General criteria for classification in the lists:

a. List I
1. Active substances of medicines indicated for conditions calling for short-term treatment and/or for which continuous medical supervision is necessary, either because of potential undesirable effects or to check the efficacy of treatment;
2. Active substances of medicines administered for diagnostic purposes;
3. Active substances with a new pharmacological mechanism of action.

b. List II
Active substances of medicines indicated for conditions for which the patient may continue regular or intermittent treatment without new medical advice, and for which well-known undesirable effects do not call for frequent clinical examinations.

c. List of OTC medicines
(see above).

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Cimetidine

1.2 ATC Code: A02BA01 - H2-receptor antagonists

1.3 Therapeutic indications:

Adults: duodenal and benign gastric ulceration, including that associated with nonsteroidal anti-inflammatory drugs (NSAIDs), recurrent and stomal ulceration, oesophageal reflux disease. Other conditions where reduction of gastric acid has been shown to be beneficial: persistent dyspeptic symptoms with or without ulceration, meal-related upper abdominal pain, symptoms associated with NSAIDs. Prophylaxis of gastrointestinal haemorrhage from stress ulceration: before general anaesthesia in patients at risk of acid aspiration (Mendelson's Syndrome); obstetric patients during labour; to reduce malabsorption and fluid loss in the short bowel syndrome; in pancreatic insufficiency to reduce degradation of enzyme supplements; Zollinger-Ellison syndrome.

Paediatric use: as for adults.

OTC indications: for the short-term symptomatic relief of heartburn, dyspepsia, indigestion, acid indigestion and hyperacidity, reflux symptoms and for the prophylaxis of meal-induced heartburn.

1.4 Posology and duration of treatment

Adults:

Duodenal or benign gastric ulceration: 400 mg twice a day with breakfast and at bedtime or single dose of 800 mg at bedtime. Regimes of 200 mg thrice daily with meals and 400 mg *nocte* or, if inadequate, 400 mg four times a day with meals and at bedtime may also be used.
Treatment should be given initially for at least 4 weeks (6 weeks in the case of benign gastric ulcer).
Oesophageal reflux: 400 mg four times a day with meals and at bedtime for 4 to 8 weeks.
Zollinger-Ellison syndrome: it may be necessary to increase the dose to 400 mg four times a day or higher.
Reduction of gastric secretion or to prevent relapse in patients with benign peptic ulceration: 400 mg at bedtime, or in the morning and at bedtime. Patients on prolonged treatment (particularly those treated for more than one year) should be kept under regular surveillance. Antacids may be used concurrently if required.
Prophylaxis of haemorrhage from stress ulceration: doses up to 2.4 g daily may be given in divided doses. 200 –400 mg doses can be given every 4 to 6 hours.
In the prophylaxis of acid aspiration (Mendelson's syndrome): a single dose of 400 mg may be given 90 – 120 minutes before induction of general anaesthesia or, in obstetric patients, at the start of labour. While such a risk persists, a dose of up to 400 mg may be repeated (parenterally if appropriate) at 4 hourly intervals as required, up to the usual maximum of 2.4 g/day.
Pancreatic insufficiency – for protection of pancreatic enzyme supplements: 800 – 1,600 mg/day may be given according to response in four divided doses, one to one and half hours before meals.

Dosage should be reduced in patients with impaired renal function when creatinine clearance is below 50 ml/minute.
Creatinine clearance daily dosage:
30 – 50 ml/minute; 200 mg q.d.s.
15 – 30 ml/minute; 200 mg t.d.s.
0 –15 ml/minute; 200 mg b.d.
Cimetidine is removed by haemodialysis, but not to any significant extent by peritoneal dialysis.

Elderly: the normal adult dosage may be used unless renal function is markedly impaired.

Paediatric: experience in children is less than that in adults. In children more than 2 years old, cimetidine 25-30 mg/kg body weight per day in divided doses may be administered by either the oral or parenteral routes.

The use of cimetidine in children less than 2 years of age is not fully evaluated: 20 mg/kg body weight per day in divided doses has been used.

OTC Indication: maximum dose: 200 mg for two weeks.

1.5 Pharmaceutical forms:

Tablets: 200 mg, 400 mg and 800 mg
Oral solution: 200 mg/5 ml

1.6 Contraindications: hypersensitivity to the active substance or to any of the excipients.

1.7 Relevant warnings: confusional states, mood and behavioural changes and insomnia may occur especially in the elderly or very ill patients or those with renal failure. Those on high dosage are particularly at risk. These states are usually reversible.
Before initiation of cimetidine therapy for any gastric ulceration, malignancy should be excluded by endoscopy, and biopsy if possible. Treatment with cimetidine can mask symptoms and assist transient healing of gastric cancer. The consequences of a potential delay in diagnosis should be kept in mind, particularly in patients of middle age or over or with new or recently changed dyspeptic symptoms.
Patients on prolonged cimetidine therapy (particularly those treated for more than one year) should be kept under regular surveillance with particular attention to the pathology of the gastrointestinal tract.
In patients on drug treatment or with illnesses which could cause falls in blood cell counts, the possibility that H2 receptor antagonism could potentiate this effect should be borne in mind.
Care should be taken that patients with a history of peptic ulcer, particularly the elderly, being treated with cimetidine and a non-steroidal anti-inflammatory agent, are observed regularly.
Close monitoring of prothrombin time is recommended when cimetidine is concurrently used with anticoagulants.
Co-administration of therapeutic agents with a narrow therapeutic index, such as phenytoin or theophylline, may require dosage adjustment when starting or stopping concomitantly administered cimetidine.
In patients such as the elderly, persons with chronic lung disease, diabetes or the immunocompromised, there may be an increased risk of developing community-acquired pneumonia. A large epidemiological study showed an increased risk of developing community-acquired pneumonia in current users of H2 receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk increase of 1.63 (95% CI, 1.07–2.48).

OTC Indication: the maximum treatment period is 2 weeks. If symptoms persist after 2 weeks treatment or recur regularly following self-treatment, consult your doctor.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (Pharmacovigilance)

Council for International Organizations of Medical Sciences (CIOMS) frequencies: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10000, <1/1000), very rare (<1/10000).

Blood and lymphatic system disorders
Uncommon: leucopenia
Rare: thrombocytopenia, aplastic anaemia
Very rare: pancytopenia, agranulocytosis

Immune system disorders
Very rare: anaphylaxis reaction is usually cleared on withdrawal of the drug.

Psychiatric disorders
Uncommon: depression, hallucination. Confusional state, reversible within a few days of withdrawing cimetidine, has been reported, usually in elderly or ill patients.

Nervous system disorders
Common: headache, dizziness.

Cardiac disorders
Uncommon: tachycardia;
Rare: sinus bradycardia;
Very rare: heart block.

Gastrointestinal disorders
Common: diarrhoea;
Very rare: pancreatitis. Pancreatitis cleared on withdrawal of the drug.

Hepatobiliary disorders
Uncommon: hepatitis;
Rare: increased serum transaminase levels. Hepatitis and increased serum transaminase levels cleared on withdrawal of the drug.

Skin and subcutaneous tissue disorders
Common: rash;
Very rare: alopecia and hypersensitivity vasculitis. Hypersensitivity vasculitis usually cleared on withdrawal of the drug.

Musculoskeletal and connective tissue disorders
Common: myalgia;
Very rare: arthralgia.

Renal and urinary disorders
Uncommon: blood creatinine increased;
Rare: interstitial nephritis. Interstitial nephritis cleared on withdrawal of the drug. Small increases in blood creatinine have been reported, unassociated with changes in glomerular filtration rate. The increases do not progress with continued therapy and disappear at the end of therapy.

Reproductive system and breast disorders
Uncommon: gynaecomastia and reversible impotence. Gynaecomastia is usually reversible upon discontinuation of cimetidine therapy. Reversible impotence has been reported particularly in patients receiving high doses (e.g. in Zollinger-Ellison syndrome). However, at regular dosage, the incidence is similar to that in the general population.
Very rare: galactorrhoea

General disorders and administration site conditions
Common: fatigue;
Very rare: fever. Fever cleared on withdrawal of the drug.

2.1.1 Recent cases at European level: none

Interactions with cimetidine are described in the product information. An EMA SmPC training presentation on Section 4.5 (link below) cites cimetidine as an example of where precautions including dose adjustment may need to be considered e.g. ‘Cationic medicinal products that are eliminated by renal tubular secretion (e.g. cimetidine) may interact with active substance X by competing for common renal tubular transport systems’

2.2 Indirect risks (incorrect use): overdosage of up to 20g has been reported with no significant ill-effects. Induction of vomiting and/or gastric lavage may be employed together with symptomatic and supportive therapy.

2.2.1 Recent cases at European level: none

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription status	Additional information / Exemptions				
		Routes of administration	Comments	MS	MDD	MQP
Melclass database*	List II + Exemption Annex III	Oral		200 mg		
Austria (AT)	List II + Exemption Annex III	Oral	POM: children under 18 years	OTC: 200 mg	OTC: 800 mg	
Belgium (BE)	POM	Oral		800 mg	1.6 g	180 g
Switzerland (CH)	Currently not available					
Czech Republic (CZ)	Currently not available					
Germany (DE)	List II	Oral				
Spain (ES)	Currently not available					
France (FR)	List II + Exemption Annex III	Oral		200 mg	400 mg	2 g
Croatia (HR)	-					
Hungary (HU)	Currently not available					
Italy (IT)	List II	Oral		800 mg	800 mg	
Ireland (IE)	List II	Oral				
Lithuania (LT)	Currently not available					
Republic of Macedonia (MK)	Currently not available					
Poland (PL)	Currently not available					
Portugal (PT)	List II	Oral		800 mg	12 g	22.4 g
Romania (RO)	POM	Oral		200 mg	2 g	6 g
United Kingdom (UK)	OTC	Oral			800 mg	

* Melclass database - Available at: http://www.edqm.eu/melclass/

No data is available from other countries.

3.2 Member states' authorities' past or ongoing evaluation of the risk profile of the active ingredient for this therapeutic indication(s) (ATC code); abuse/misuse; efficiency:

Risk/benefit evaluation: Romania: risk/benefit evaluation but no impact on classification.

3.3 Social dimension of classification:

3.3.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Recommendation: cimetidine is a histamine H2-receptor antagonist which rapidly inhibits both basal and stimulated gastric secretion of acid and reduces pepsin output. It is a reversible, competitive antagonist. Cimetidine is used for the treatment of active peptic ulceration, for gastroesophageal reflux disease. It is also indicated for the prophylaxis of peptic ulceration and for conditions where acid reduction is beneficial. Cimetidine is subject to prescription when used in these indications.

Cimetidine is indicated for use in adults and children.

Cimetidine is available in some countries without prescription/ 'over the counter' (OTC) for the short-term (2 weeks) symptomatic relief of heartburn, dyspepsia, indigestion, acid indigestion and hyperacidity, reflux symptoms and for the prophylaxis of meal-induced heartburn.

Cimetidine is classified under List II in Appendix 1 of Resolution ResAP (2007)1. The exemption that applies for OTC use in accordance with Annex III of Resolution ResAP (2007)1 is oral treatment with a maximum strength of 200 mg. The conditions applicable to cimetidine across countries are consistent with this information.

In conclusion, the current classification is **List II with an exemption for oral use under the following circumstances: maximum strength of 200 mg and a maximum period of treatment of two weeks**.

No change in the classification is proposed.

3.3.2 Paediatric use: N.A.

3.3.3 Social dimension: N.A.

4. COMMENTS/REFERENCES

References:

1. SmPC (Ireland and UK) - http://goo.gl/o93L2J
2 .HMA MRI Product Index - http://mri.medagencies.org/Human/
3. EMA: Section 4.5: Interaction with other medicinal products and other forms of interaction – SmPC Training Presentation, SmPC Advisory Group, EMA - http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/01/WC500137018.pdf

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Ranitidine

1.2 ATC Code: A02BA02 - H2-receptor antagonists

1.3 Therapeutic indications:

Adults: treatment of duodenal ulcer and benign gastric ulcer including that associated with non-steroidal anti-inflammatory agents.
Prevention of non-steroidal anti-inflammatory drug-(including aspirin) associated duodenal ulcers, especially in patients with a history of peptic ulcer disease.
Treatment of post-operative ulcer, reflux oesophagitis, Zollinger-Ellison syndrome and other conditions where reduction of gastric acid secretion is likely to be beneficial.

Children (3 to 18 years): short term treatment of peptic ulcer; treatment of gastro-oesophageal reflux, including reflux oesophagitis and symptomatic relief of gastro-oesophageal reflux disease.

OTC indication: adults over 16 years: short-term symptomatic relief of heartburn, indigestion, acid indigestion and hyperacidity.

1.4 Posology and duration of treatment:

Adults (including the elderly) / Adolescents (12 years and over)

Duodenal and benign gastric ulcer: 150 mg twice daily or 300 mg at night. Increased to ranitidine 300 mg twice daily without an increased incidence of unwanted effects. Maintenance dose of 150 mg at night may be used.
Smoking is associated with a higher rate of ulcer relapse, and such patients should be advised to stop smoking. In those who fail to comply with such advice, a dose of 300 mg at night provides additional therapeutic benefit over the standard dose.
In most cases of duodenal ulcer, benign gastric ulcer and post-operative ulcer, healing occurs within 4 weeks. Healing usually occurs after a further 4 weeks in those not fully healed after the initial 4 weeks.
Ulcers following nonsteroidal anti-inflammatory drug therapy: 8 - 12 weeks treatment with 150 mg twice daily or 300 mg at night.
For the prevention of non-steroidal anti-inflammatory drug associated duodenal ulcers, ranitidine 150 mg twice daily may be given concomitantly with non-steroidal anti-inflammatory drug therapy.
Reflux oesophagitis: 150 mg twice daily or 300 mg at night administered for 8-12 weeks. In patients with moderate to severe oesophagitis the dosage may be increased to 150 mg four times daily, alternatively 300 mg twice a day, if necessary.
For the long-term management of reflux oesophagitis, the recommended adult oral dose is 150 mg twice daily for the prevention of relapse in patients with reflux oesophagitis. Zantac Tablets 150 mg are not indicated in patients with complications of reflux oesophagitis e.g. severe oesophegeal stricture or Barratt's oesophagus.
Prophylaxis of haemorrhage from stress ulceration in seriously ill patients or the prophylaxis of recurrent haemorrhage in patients bleeding from peptic ulceration: 150 mg twice daily may be substituted for ranitidine injection once oral feeding commences in patients considered to be still at risk from these conditions.
Zollinger-Ellison syndrome: 150 mg thrice daily, increased as necessary up to a maximum of 6 g daily.
Obstetric patients: 150 mg may be given at commencement of labour, followed by 150 mg at 6 hourly intervals.

Children from 3 to 11 years and over 30 kg of weight

Peptic ulcer acute treatment: 4 mg/kg/day to 8 mg/kg/day administered as two divided doses to a maximum of 300 mg ranitidine per day for a duration of 4 weeks. For those patients with incomplete healing, another 4 weeks of therapy is indicated, as healing usually occurs after eight weeks of treatment.

Gastro-oesophageal reflux: 5 mg/kg/day to 10 mg/kg/day administered as two divided doses to a maximum dose of 600 mg (the maximum dose is likely to apply to heavier children or adolescents with severe symptoms).
Safety and efficacy in new-born patients has not been established.

Patients with renal impairment
Accumulation of ranitidine with resulting elevated plasma concentrations will occur in patients with renal impairment (creatinine clearance less than 50 ml/min). It is recommended that the daily dose of ranitidine in such patients should be 150 mg.

OTC indication:
Maximum strength: 75 mg
Maximum dose: 2 tablets (150 mg) daily for two weeks

1.5 Pharmaceutical forms:

Film-coated tablets: 75 mg, 150 mg and 300 mg
Syrup: 75 mg/5 ml
Injection: 25 mg/ml

1.6 Contraindications: hypersensitivity to the active substance or to any of the excipients.

1.7 Relevant warnings: in keeping with the recommended clinical practice, it is advisable that patients on long-term maintenance therapy receive regular routine assessments by their practitioners. Rare clinical reports suggest that ranitidine may precipitate acute porphyric attacks. Ranitidine should, therefore, be avoided in patients with a history of acute porphyria. The possibility of malignancy should be excluded before commencement of therapy in patients with gastric ulcer as treatment with ranitidine may mask symptoms of gastric carcinoma. Ranitidine is excreted via the kidney and so plasma levels of the drug are increased in patients with renal impairment. The dosage should be adjusted. In patients such as the elderly, persons with chronic lung disease, diabetes or the immunocompromised, there may be an increased risk of developing community-acquired pneumonia. A large epidemiological study showed an increased risk of developing community-acquired pneumonia in current users of ranitidine alone versus those who had stopped treatment, with an observed adjusted relative risk increase of 1.82 (95% CI 1.26 – 2.64). Regular supervision of patients who are taking non-steroidal anti-inflammatory drugs concomitantly with ranitidine is recommended, especially in the elderly and in those with a history of peptic ulcer.

OTC indication: the maximum treatment period is 2 weeks. If symptoms persist after 2 weeks' treatment or recur regularly following self-treatment, consult your doctor.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (Pharmacovigilance):

CIOMS frequencies: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (1/10,000). Adverse event frequencies have been estimated from spontaneous reports from post-marketing data.

Blood and Lymphatic System Disorders
Very Rare: blood count changes (leucopenia, thrombocytopenia); these are usually reversible. Agranulocytosis or pancytopenia, sometimes with marrow hypoplasia or marrow aplasia.

Immune System Disorders
Rare: hypersensitivity reactions (urticaria, angioneurotic oedema, fever, bronchospasm, hypotension and chest pain).
Very Rare: anaphylactic shock.
Unknown: dyspnoea.
These events have been reported after a single dose.

Psychiatric Disorders
Very rare: reversible mental confusion, depression and hallucinations. These have been reported predominantly in severely ill, in elderly and nephropathic patients.

Nervous System Disorders
Very rare: headache (sometimes severe), dizziness and reversible involuntary movement disorders.

Eye Disorders
Very rare: reversible blurred vision.
There have been reports of blurred vision, which is suggestive of a change in accommodation.

Cardiac Disorders
Very rare: as with other H2 receptor antagonists bradycardia, A-V Block and tachycardia.

Vascular Disorders
Very rare: vasculitis.

Gastrointestinal Disorders
Very rare: acute pancreatitis, diarrhoea.
Uncommon: abdominal pain, constipation, nausea (these symptoms mostly improved during continued treatment).

Hepatobiliary Disorders
Rare: transient and reversible changes in liver function tests.
Very rare: hepatitis (hepatocellular, hepatocanalicular or mixed) with or without jaundice, these were usually reversible.

Skin and Subcutaneous Tissue Disorders
Rare: skin rash.
Very rare: erythema multiforme, alopecia.

Musculoskeletal and Connective Tissue Disorders
Very rare: musculoskeletal symptoms such as arthralgia and myalgia.

Renal and Urinary Disorders
Very rare: acute interstitial nephritis.
Rare: elevation of plasma creatinine (usually slight; normalised during continued treatment).

Reproductive System and Breast Disorders
Very rare: reversible impotence, breast symptoms and breast conditions (such as gynaecomastia and galactorrhoea).

Paediatric population
The safety of ranitidine has been assessed in children aged 0 to 16 years with acid-related disease and was generally well tolerated with an adverse event profile resembling that in adults. There are limited long term safety data available, in particular regarding growth and development.

2.1.1 Recent cases at European level: none

2.2 Indirect risks (incorrect use): ranitidine is very specific in action and no particular problems are expected following overdosage with the drug.

2.2.1 Recent cases at European level: none

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription status	Additional information / Exemptions				
		Routes of administration	Comments	MS	MDD	MQP
Melclass database*	List II + Exemption Annex III	Oral	MPT: two weeks	75 mg		
AT	List II + Exemption Annex III	Oral		75 mg		
BE	List II + Exemption Annex III	Oral	OTC: 75mg POM: other strengths:	300 mg	300 mg	150 g
Bosnia-Herzegovina (BA)	OTC	Oral		75 mg	900 mg	750 mg
CH	List II + Exemption Annex III	Oral		OTC: 75 mg POM: 300mg	600 mg	OTC: 900 mg POM: 180 g
CZ	List I + Exemption Annex III	Oral		75 mg	150 mg	750 mg
DE	List II + Exemption Annex III	Oral		75 mg		
ES	List I + Exemption Annex III	Oral		75 mg	150 mg	1.5 g
FR	List II + Exemption Annex III	Oral		75 mg		900 mg
Finland (FI)	List I + Exemption Annex III	Oral		300 mg		1.5 g
HR	List II + Exemption Annex III	Oral		150 mg/150 mg	150 mg/300 mg	1500 mg
HU	POM	Oral		300 mg	600 mg	180 g
IE	List II + Exemption Annex III	Oral		OTC: 75 mg	OTC: 150 mg	OTC: 1.8g (24 tablets)
LT	List I + Exemption Annex III	Oral		POM: 300 mg	POM: 300 mg	100 tablets
MK	List I + Exemption Annex III	Oral		OTC: 75 mg	As per indication	6 g
PL	List I + Exemption Annex III	Oral		OTC: 150 mg; Rx: PO: 300mg IV: 5%	OTC: 300 mg Rx: 300mg; ZE Syndrome: 900 mg)	OTC: 3g; Rx: PO: 30 g IV: 250 mg
PT	POM					
RO	List II + Exemption Annex III	Oral		OTC: 75 mg POM: 150 mg, 300 mg, 25 mg/ml	300 mg	750 mg
UK	List I + Exemption Annex III	Oral			OTC: 300 mg POM: 600mg	14 days supply

* Melclass database - Available at: http://www.edqm.eu/melclass/

No data available from other countries.

3.2 Member states' authorities' past or ongoing evaluation of the risk profile of the active ingredient for this therapeutic indication(s) (ATC code); abuse/misuse; efficiency:

Risk/benefit evaluation: Italy: Risk/benefit evaluation but no impact on classification.

3.3 Social dimension of classification:

3.3.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Recommendation: ranitidine is a specific rapidly acting histamine H2-receptor antagonist. It inhibits basal and stimulated secretion of gastric acid, reducing both the volume and the acid and pepsin content of the secretion. Ranitidine is indicated for the treatment of active peptic ulceration, for gastroesophageal reflux disease. It is also indicated for the prophylaxis of peptic ulceration and for conditions where acid reduction is beneficial. Ranitidine is subject to prescription when used in these conditions.
Ranitidine is indicated for use in adults and children.
Ranitidine is available in some countries without prescription/OTC for the short-term (2 weeks) symptomatic relief of heartburn, indigestion, acid indigestion and hyperacidity.
Ranitidine is classified under List II in Appendix 1 of Resolution ResAP (2007)1. The exemption that applies for OTC use, in accordance with Annex III of Resolution ResAP (2007)1, is oral treatment at a maximum strength of 75 mg. The conditions applicable to ranitidine across countries are consistent with this information.

In conclusion, the current classification is **List II with an exemption for oral use under the following circumstances: maximum strength of 75 mg and a maximum period of treatment of two weeks.**

No change in the classification is proposed.

3.3.2 Paediatric use: N.A.

3.3.3 Social dimension: N.A.

4. COMMENTS/REFERENCES

References:

1. SmPC (Ireland) - http://goo.gl/GEqIzF
2. HMA MRI Product Index - http://mri.medagencies.org/Human/
3. EMA - http://www.ema.europa.eu/ema/

1. THERAPEUTIC PROFILE

1.1 Active ingredient: famotidine

1.2 ATC Code: A02BA03 - H2-receptor antagonists

1.3 Therapeutic indications:

POM Indications (famotidine 20 mg and 40 mg)
Duodenal ulcers;
Prevention of relapses of duodenal ulceration;
Benign gastric ulcers;
Zollinger-Ellison syndrome;
Symptomatic treatment of mild reflux oesophagitis.

OTC Indications (famotidine 10 mg)
The short-term symptomatic relief of heartburn, indigestion (dyspepsia) and excess acid. Prevention of these symptoms when associated with meals, including nocturnal symptoms.

1.4 Posology and duration of treatment:

Posology for POM Indications (famotidine 20 mg and 40 mg)

Adults:
Duodenal ulcers: the initial recommended dose is 40 mg of famotidine to be taken at night. Healing generally occurs in most patients within 4 weeks.
This period, however, may be shortened if an endoscopic examination reveals that the ulcer has healed. However, in those patients whose ulcers have not healed within this 4 week period, treatment should continue for a further 4 weeks.
Prevention of relapses of duodenal ulceration: to prevent ulcers from reoccurring, the recommended dose is 20 mg of famotidine to be taken at night.
Benign gastric ulcers: the recommended dose of 40 mg of famotidine to be taken at night. Treatment should continue for between 4-8 weeks unless earlier healing is revealed by endoscopy.
Zollinger-Ellison syndrome: patients who are not receiving any anti-secretory therapy should be started on a dose of 20 mg of famotidine every 6 hours. The dosage should then be adjusted to individual response. If the desired inhibition of acid secretion cannot be attained with a daily dosage of 800 mg, alternative treatment should be considered to regulate acid secretion, since no long term experience with dosages of more than 800 mg of famotidine/day have been recorded.
Treatment should be continued for as long as necessary. Patients who have been receiving other H2 receptor antagonist treatment can begin famotidine treatment at a higher dosage than the initial dosage that is usually recommended. The starting dosage will depend on the severity of the disease and the dosage of the last dose of H2-antagonist previously used.
Symptomatic treatment of mild reflux oesophagitis: recommended dosage is 20 mg twice daily. Generally, treatment should be conducted for 6 weeks, if necessary for 12 weeks.

Posology for OTC indications (famotidine 10 mg)
Adults and children 16 years of age or older: 1 tablet (10 mg);
Dosage interval: 1 tablet (10 mg) for symptomatic relief of heartburn, indigestion (dyspepsia) and excess acid.
Alternatively, 1 tablet (10 mg) taken 15 minutes prior to meals to prevent these symptoms.
Maximum intake in 24 hours: 2 tablets (20 mg).
The maximum treatment period is 2 weeks.
No dosage adjustment is necessary for the elderly.

1.5 Pharmaceutical forms:
Tablets - 20 mg and 40 mg (POM) 10 mg (OTC)

1.6 Contraindications: hypersensitivity to the active substance or to other H2-receptor antagonists.
Cross sensitivity to this class of compounds has been observed. Therefore, famotidine should not be administered to patients with a history of hypersensitivity to other H2- receptor antagonists.

1.7 Relevant warnings:

Gastric neoplasm
The presence of gastric malignancy should be excluded prior to the use of famotidine tablets for the treatment of gastric ulcers. Symptomatic responses of gastric ulcers following treatment with famotidine do not preclude the presence of gastric malignancy.

Renal dysfunction
As famotidine is excreted primarily via the kidneys, caution should be exercised when treating patients who are suffering from impaired renal function. A reduction in daily dosage should be considered if creatinine clearance falls below 10 ml/min. For dosage regimes refer to the posology section.

Paediatric use / Use in the elderly
The safety and efficacy for the use of famotidine tablets in children has not been established.
When famotidine was administered to elderly patients in clinical trials, no increase in the incidence or change in the type of drug-related side effects was observed. No dosage adjustment is required based on age alone.

General
In the case of long-term treatment with high dosage, monitoring of blood count and liver function is recommended. In the case of long-standing ulcer disease, abrupt withdrawal after symptom relief should be avoided. This medicine contains lactose: patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.
In clinical trials, patients with other underlying acid related gastro-intestinal diseases (e.g. duodenal ulcer, gastric ulcer) did not experience complications; in general, they did not exhibit a clinically significant deterioration in their condition.
If patients have difficulty swallowing, or abdominal discomfort persists they should seek medical advice.

Pregnancy
Famotidine tablets are not recommended for use in pregnancy, and should be prescribed only if clearly needed. Before a decision is made to use famotidine tablets during pregnancy, the physician should weigh the potential benefits from the drug against the possible risks involved.

Breast-feeding
Famotidine is secreted in human breast milk. Therefore breast feeding mothers should either stop taking famotidine or stop breast feeding.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (Pharmacovigilance):
CIOMS frequencies: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (≥ 1/10,000, < 1/1000), very rare (< 1/10,000), including isolated cases. Not known (cannot be estimated from the available data).

Blood and Lymphatic system disorders
Very rare: thrombocytopenia, leucopoenia, agranulocytosis, pancytopenia, neutropenia.

Immune system disorders
Very rare: hypersensitivity reactions (anaphylaxis, angioneurotic oedema, bronchospasm).

Psychiatric disorders
Very rare: reversible psychological disturbances including hallucinations, disorientation, confusion, anxiety disorders, agitation, depression, insomnia, reduced libido.

Nervous system disorders
Common: headache, dizziness.
Uncommon: fatigue, taste disorder

Very rare: paraesthesia, drowsiness, convulsions, grand mal seizures (particularly in patients with impaired renal function).

Metabolism and nutrition disorders
Uncommon: anorexia.

Gastrointestinal disorders
Common: constipation, diarrhoea;
Uncommon: dry mouth, nausea and/or vomiting, anorexia, flatulence, abdominal discomfort or distension.

Hepatobiliary disorders
Very rare: liver enzyme abnormalities, hepatitis, cholestatic jaundice. Isolated cases of worsening of existing hepatic disease.

Skin and subcutaneous tissue disorders
Uncommon: rash, pruritus, urticaria;
Very rare: alopecia, Stevens-Johnson syndrome/toxic epidermal necrolysis, sometimes fatal.

Musculoskeletal, connective tissue and bone disorders
Very rare: arthralgia, muscle cramps.

Reproductive system and breast disorders
Very rare: impotence.

Cardiac disorders
Very rare: atrioventricular block with H2- receptor antagonists administered intravenously, arrhythmias, chest tightness.

Respiratory, thoracic and mediastinal disorders
Very rare: interstitial pneumonia, sometimes fatal.

Investigations
Rare: increase in laboratory values (transaminases, gamma GT, alkaline phosphatase, bilirubin).
Very rare: QT Prolongation.

Adverse Effects – Casual Relationship Unknown
Rare cases of gynaecomastia have been reported; however, in controlled clinical trials the incidences were not greater that those seen with placebo.

2.1.1 Recent cases at European level: none

2.2 Indirect risks (incorrect use): there is no experience to date with overdosage. The usual measures to remove unabsorbed material from the gastro-intestinal tract, clinical monitoring and supportive therapy should be employed. Patients suffering from Zollinger-Ellison syndrome have tolerated doses of up to 800 mg/day. These patients have been treated for more than a year without the development of any significant adverse effects.

2.2.1 Recent cases at European level: none

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription status	Additional information / Exemptions				
		Routes of administration	Comments	MS	MDD	MQP
Melclass database*	List II+Exemption Annex III	Oral		10 mg		
AT	List II					
BE	not authorised					
CH	not authorised					
FR	List II + Exemption Annex III	Oral				
IT	List II					
IRL	List II+Exemption Annex III	Oral				
LT	POM					
MK	List II+Exemption Annex III	Oral				
PL	List II+Exemption Annex III	Oral				
PT	POM + Exemption Annex III	Oral				
RO	List II (oral); List I (IV)					
UK	POM + Exemption Annex III	Oral				

* Melclass database - Available at: http://www.edqm.eu/melclass/

No data available from other member states.

3.2 Member states' authorities' past or ongoing evaluation of the risk profile of the active ingredient for this therapeutic indication(s) (ATC code); abuse/misuse; efficiency: N.A.

3.3 Social dimension of classification: no comments

Recommandation: List II + Exemption Annex III

Exemptions:

- Indication: for adults and children of 16 years of age or older
- Administration route: oral use;
- MS: 10 mg;
- MDD: 20 mg;
- Maximum treatment duration: 2 weeks.

Criteria: famotidine is indicated for use in adults and children 16 years of age or older. Famotidine is available in some countries without prescription/ 'over the counter' (OTC) for the short-term (2 weeks) symptomatic relief of heartburn, indigestion (dyspepsia) and excess acid and prevention of these symptoms when associated with meals including nocturnal symptoms. The conditions applicable to famotidine across countries are consistent with this information.

3.3.2 Paediatric use: -

3.3.3 Social dimension: -

4. COMMENTS/REFERENCES

References:

1. SmPC (Ireland, Portugal and United Kingdom) - http://goo.gl/GEqIzF

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Nizatidine

1.2 ATC Code: A02BA04 - H2-receptor antagonists

1.3 Therapeutic indications:

POM Indications (Nizatidine 150 mg and 300 mg)
Duodenal ulcer,
Benign gastric ulcer,
Prevention of duodenal or benign gastric ulcer recurrence,
Gastric and/or duodenal ulcer associated with concomitant use of non-steroidal anti-inflammatory drugs.
GORD (including erosions, ulcerations and associated heartburn).

OTC indications (Nizatidine 75 mg)
The short-term symptomatic relief of heartburn, indigestion (dyspepsia) and excess acid.

1.4 Posology and duration of treatment:

Posology for POM indications (Nizatidine 150 mg and 300 mg)

Adults:

Duodenal ulcer: the recommended daily dose is 300 mg in the evening. Treatment should continue for four weeks, although this period may be reduced if healing is confirmed earlier by endoscopy. Most ulcers will heal within four weeks, but if complete ulcer healing has not occurred after four weeks therapy, patients should continue therapy for a further four weeks.

Benign gastric ulcer: the recommended daily dose is 300 mg in the evening for four or, if necessary, eight weeks. Prior to treatment with nizatidine, care should be taken to exclude the possibility of gastric cancer. If preferred, the 300 mg daily dose for the treatment of duodenal or benign gastric ulcer may be given as two divided doses of 150 mg in the morning and evening.

Prevention of duodenal and/or benign gastric ulcer recurrence (prophylactic maintenance therapy): the recommended daily dose is 150 mg in the evening. Patients should be kept under regular surveillance. Treatment should not be for more than one year without medical review to determine the need for continued treatment.

Gastric and/or duodenal ulcer associated with concomitant use of non-steroidal anti-inflammatory drugs: the recommended daily dose is 300 mg daily (either 300mg at bedtime or 150 mg twice daily, in the morning and in the evening) for up to 8 weeks. In most patients, the ulcers will heal within 4 weeks. During treatment, the use of non-steroidal anti-inflammatory drugs may continue.

Gastric oesophageal reflux disease: the recommended dosage is from 150 mg twice daily, up to 300 mg twice daily. Therapy for up to 12 weeks is indicated for erosions and ulcerations, and associated heartburn.

Elderly: age does not significantly influence efficacy or safety. Normally dosage modification is not required except in patients who have moderate to severe renal impairment (creatinine clearance less than 50ml/min).

Children: not recommended, as safety and efficacy have not been established.

Patients with impaired renal function: nizatidine is principally excreted via the kidneys.
For patients who have moderate renal impairment (creatinine clearance less than 50 ml/min) or patients who have severe renal impairment (creatinine clearance less than 20 ml/min), the dosage should be reduced as follows:

Posology for OTC indications (Nizatidine 75 mg)
Adults and children 16 years of age or older: 1 tablet (75 mg)
Dosage interval: 1 tablet (75 mg) for symptomatic relief of heartburn, indigestion (dyspepsia) and excess acid.
Alternatively, 1 tablet (75 mg) taken 30 minutes or 1 hour prior to meals to prevent these symptoms.
Maximum intake in 24 hours: 4 tablets (300 mg)
The maximum treatment period is 14 days

1.5 Pharmaceutical forms:

Tablets, capsules
150 mg and 300 mg (POM)
75 mg (OTC)

1.6 Contraindications: hypersensitivity to the active substance, any other H2-receptor antagonists.

1.7 Relevant warnings: as nizatidine is partially metabolised by the liver and principally excreted by the kidneys, patients with impaired liver or kidney function should be treated with caution. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy. Patients receiving prophylactic maintenance therapy should be kept under regular surveillance by the prescribing physician. Treatment should not be for more than one year without medical review to determine the need for continued treatment.

Pregnancy: the safety of nizatidine for use during pregnancy has not been established.

Breast-feeding: studies conducted in lactating women have shown that 0.1% of the administered oral dose of nizatidine is secreted in human milk in proportion to plasma concentrations. Because of the growth depression in pups reared by lactating rats treated with nizatidine, it should be administered to nursing mothers only if considered absolutely necessary.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (Pharmacovigilance): in large scale clinical trials, sweating and urticaria were significantly more common in nizatidine-treated patients when compared with placebo. In these trials, 1.9% of treated patients experienced somnolence, compared to 1.6% of placebo patients (non-significant). In the same trials, patients treated with both nizatidine and placebo had mild, transient, asymptomatic elevations of transaminases or alkaline phosphatase; rare instances of marked elevations (> 500 iu/l) occurred in nizatidine-treated patients. The overall rate of occurrences of elevated liver enzymes and elevations to 3 times the upper limit of normal, however, did not differ significantly from placebo. All abnormalities were reversible after discontinuation of nizatidine. Hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have also been reported, with reversal of the abnormalities after discontinuation. The following effects have also been rarely reported: thrombocytopenic purpura, fatal thrombocytopenia, leucopoenia, agranulocytosis, anaemia, exfoliative dermatitis, vasculitis, arthralgia, myalgia, gynaecomastia, impotence, hyperuricaemia, fever, nausea and reversible mental confusion.
Rare episodes of hypersensitivity reactions (e.g. bronchospasm, laryngeal oedema, rash, pruritus and eosinophilia), serum sickness and anaphylaxis have been reported.

2.1.1 Recent cases at European level: N.A.

2.2 Indirect risks (incorrect use):

There is little experience of overdose in humans.
Tested at very high doses in animals, nizatidine has been shown to be relatively non-toxic. Animal studies suggest that cholinergic-type effects, including lacrimation, salivation, emesis, miosis and diarrhoea, may occur following very large oral doses. Symptomatic and supportive therapy is recommended. Activated charcoal, emesis or lavage may reduce nizatidine absorption. The ability of haemodialysis to remove nizatidine from the body has not been conclusively demonstrated.

However, this method is not expected to be efficient, since nizatidine has a large volume of distribution.

2.2.1 Recent cases at European level: N.A.

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription status	Additional information / Exemptions				
		Routes of administration	Comments	MS	MDD	MQP
Melclass database*	List II					
AT	Not authorised					
BE	Not authorised					
CH	Not authorised					
FR	List II					
HU	Not authorised					
IE	List II					
IT	List II					
LT	Not authorised					
MK	Not authorised					
PL	Not authorised					
PT	OTC (75 mg)		Authorised but not marketed			
RO	List II					
UK	POM + Exemption Annex III	Oral		75 mg	150 mg	

* Melclass database - Available at: http://www.edqm.eu/melclass/

No data available from other member states.

3.2 Member states' authorities' past or ongoing evaluation of the risk profile of the active ingredient for this therapeutic indication(s) (ATC code); abuse/misuse; efficiency: N.A.

3.3 Social dimension of classification

3.3.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Recommendation: List II

Criteria: nizatidine is classified under List II in France, Italy, Ireland and Romania

3.3.2 Paediatric use: N.A.

3.3.3 Social dimension: N.A.

4. COMMENTS/REFERENCES

References:

1. SmPC (Ireland, Portugal and United Kingdom) - http://goo.gl/GEqIzF

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Niperotidine

1.2 ATC Code: A02BA05 - H2-receptor antagonists

Sections 1.3-1.7: no information available.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

Sections 2.1-2.2: no information available.

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

This substance is not available in the 13 countries that have responded to the C1 questionnaires as regards national information, in particular supply conditions and requirements for prescription medicines containing specified active ingredients (March 2015): BE, CH, CZ, FR, HU, IE, IT, LT, MK, PL, PT, RO, UK.

There is no information on this substance on the Melclass Database.

No information is available from other countries.

3.2 Member states' authorities' past or ongoing evaluation of the risk profile of the active ingredient for this therapeutic indication(s) (ATC code); abuse/misuse; efficiency: none

3.3 Social dimension of classification:

3.3.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Recommendation: not to classify

Niperotidine is a specific rapidly acting histamine H2-receptor antagonist.

The literature reports cases of acute hepatitis associated with treatment with niperotidine. Wikipedia reports that the substance was trialled as treatment for excessive gastric acidity but withdrawn after human trials showed liver damage.

This substance is not authorised in the countries that responded to the C1 survey questionnaire.

There is no information on this substance on the Melclass Database.

3.3.2 Paediatric use: N.A.

3.3.3 Social dimension: N.A.

4. COMMENTS/REFERENCES

References:

1. Wikipedia - https://www.wikipedia.org/
2. Gasbarrini G et al. Acute liver injury related to the use of niperotidine. J Hepatol. 1997;27(3):583-6.

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Roxatidine

1.2 ATC Code: A02BA06 - H2-receptor antagonists

1.3 Therapeutic indications: pathologies of the upper gastrointestinal tract associated with gastric acid hypersecretion, such as duodenal ulcer, benign gastric ulcer; reflux oesophagitis; prophylaxis of recurrent ulcer events.

1.4 Posology and duration of treatment:

Adults

Initial treatment in active phase: 150 mg, in a single administration in the evening, or divided into two doses of 75 mg each, morning and evening. If the intake of the drug is regular, ulcer healing occurs in most cases within four weeks and oesophagitis in 6 weeks. The pain symptoms usually disappear within a few days of starting therapy. If needed, treatment may be extended to another 2-4 weeks.

Prophylaxis: the adult daily dose is 75 mg in the evening.

Patients with renal impairment: in patients with creatinine clearance between 20 and 50 ml / min, the daily dose should be reduced to 75 mg, administered in the evening, in the initial therapy (every two days in the prophylaxis of recurrences); if creatinine clearance is less than 20 ml / min the dose should be 75 mg every 2 days, administered in the evening, in the initial therapy (2 times a week in the prophylaxis of recurrences).

Elderly patients who have a creatinine clearance less than 50 ml / min, the dose should not exceed 75 mg. Roxatidine acetate should not be administered in cases of anuria.

Paediatric population: due to the absence of adequate experience to date, the use of roxatidine is contraindicated.

1.5 Pharmaceutical forms: 75 mg and 150 mg extended-release tablets.

1.6 Contraindications:
Hypersensitivity to the active substance or to any of the excipients
Anuria
Severe hepatic impairment
Paediatric use

1.7 Relevant warnings: before initiation of therapy of gastric ulcer with roxatidine acetate it must exclude any malignancy. Since roxatidine acetate and its metabolites are excreted almost completely (90-99%) by the kidneys, in case of renal impairment, the dose will be changed. Since about 30% of roxatidine acetate is metabolised in the liver and there are still insufficient experiences of use in patients with severe hepatic impairment, it is not recommended to use in these patients.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (Pharmacovigilance):

CIOMS frequencies: very common (≥ 1/10), common (≥ 1/100, <1/10), uncommon (≥ 1/1000, <1/100), rare (≥ 1/10000, <1/1000), very rare (<1/10000).

Blood and lymphatic system:
Rare: eosinophilia.
Very rare: reduction in the number of leukocytes and platelets, agranulocytosis, pancytopenia.

Immune system disorders:

Very rare: skin rash, hives, itching and, probably as a hypersensitivity reaction, muscle and joint pain.

Endocrine disorders:
Very rare: disturbances of libido, gynaecomastia.

Nervous system disorders:
Uncommon: headache;
Very rare: dizziness, sleep disturbances, restlessness, drowsiness, visual disturbances, hallucinations, confusion.

Cardiac disorders:
Very rare: alteration in heart rate (increase or decrease).

Gastrointestinal disorders:
Rare: gastrointestinal disorders such as diarrhoea, constipation, nausea, vomiting.

Hepatobiliary disorders
Very rare: increase in liver enzymes.

2.1.1 Recent cases at European level: none

2.2 Indirect risks (incorrect use): to date there are no known cases of acute intoxication.

2.2.1 Recent cases at European level: none

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions

Country	Prescription status	Additional information / Exemptions				
		Routes of administration	Comments	MS	MDD	MQP
Melclass database*	List II					
IT	List II			150 mg	150 mg	2100 mg

* Melclass database - Available at: http://www.edqm.eu/melclass/

This substance is not authorised in the countries that responded to the C1 questionnaire.

3.2 Member states' authorities' past or ongoing evaluation of the risk profile of the active ingredient for this therapeutic indication(s) (ATC code); abuse/misuse; efficiency:

Risk/benefit evaluation
Italy: periodic review at time of renewal.

3.3 Social dimension of classification:

3.3.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Recommendation: not to classify.

Roxatidine is a specific and competitive histamine H2-receptor antagonist. It is indicated for the treatment of duodenal ulcers, benign gastric ulcer and reflux oesophagitis and also used for prophylaxis. It is only indicated for treatment of adults. Roxatidine is subject to prescription.

It is recommended that roxatidine is **not classified**, as a medicine containing this substance is not authorised in at least three member states.

3.3.2 Paediatric use: N.A.

3.3.3 Social dimension: N.A.

4. COMMENTS/REFERENCES

References:

1. SmPC - https://goo.gl/Pe2NUl

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Ranitidine bismuth citrate

1.2 ATC Code: A02BA07 - H2-receptor antagonists

Sections 1.3-1.7: no information available.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

Sections 2.1-2.2: no information available.

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

This substance is not authorised in the countries that responded to the C1 questionnaire (March 2015).
The substance is listed on the Melclass Database as 'currently not available' in 15 countries (BE, CH, CZ, ES, FR, FI, HU, IE, IT, LT, MK, PL, PT, RO, UK).

No information is available from other countries.

3.2 Member states' authorities' past or ongoing evaluation of the risk profile of the active ingredient for this therapeutic indication(s) (ATC code); abuse/misuse; efficiency: N.A.

3.3 Social dimension of classification:

3.3.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Recommendation: not to classify

Ranitidine bismuth citrate is recommended as part of triple therapy for the eradication of *Helicobacter pylori* infection (Maastricht II Consensus Meeting, 2000) or a proton pump inhibitor in combination with clarithromycin and amoxicillin or metronidazole. Bismuth-based quadruple therapy was recommended as a second choice treatment; however it was acknowledged that bismuth is not available in many countries (Maastricht III Consensus Meeting, 2005).

This substance is not authorised in the countries that responded to the C1 questionnaire. The substance is listed on the Melclass Database as 'currently not available' in 15 countries.

It is recommended that **roxatidine is not classified**, as a medicine containing this substance is not authorised in at least three member states.

3.3.2 Paediatric use: N.A.

3.3.3 Social dimension: N.A.

4. COMMENTS/REFERENCES

References:

1. EMA - http://www.ema.europa.eu/ema/
2. HMA MRI Product Index, The European Helicobacter pylori Study Group - Maastricht Consensus Meetings 2000 and 2005.

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Lafutidine

1.2 ATC Code: A02BA08 - H2-receptor antagonists

1.3 Therapeutic indications: gastric ulcers, duodenal ulcers and stomal ulcers. Gastric mucosal lesions (erosion, haemorrhage, redness or oedema) associated with acute gastritis and acute exacerbation of chronic gastritis. Pre-anaesthetic medication.

1.4 Posology and duration of treatment:

Gastric ulcers, duodenal ulcers and stomal ulcers: for adults, the usual dosage is 10 mg as lafutidine orally administered twice a day, once after breakfast and once after the evening meal or before sleeping. The dose may be adjusted according to the patient's age and symptoms.

Gastric mucosal lesions (erosion, haemorrhage, redness or oedema) associated with acute gastritis and acute exacerbation of chronic gastritis: for adults, the usual dosage is 10 mg as lafutidine orally administered once a day, once after the evening meal or before sleeping. The dose may be adjusted according to the patient's age and symptoms.

Pre-anaesthetic medication: for adults, the usual dosage is 10 mg as lafutidine orally administered twice, once before sleeping on the day before operation and once 2 hours before introduction of anaesthetic on the day of operation.

Precautions related to dosage and administration: in dialytic patients (not during dialysis), it is reported that their maximum blood concentration of lafutidine increases to twice as high as that of normal adults. Therefore, the administration should be started carefully with lower dosage.

1.5 Pharmaceutical forms: tablets - 5 mg and 10 mg

1.6 Contraindications:

Pregnancy: the safety of lafutidine in pregnant women has not been established. Therefore, the administration of lafutidine to pregnant women or women who may possibly be pregnant should be strictly limited to occasions where the therapeutic benefits outweigh the possible risks associated with the treatment.

Breast-feeding: animal studies (in rats) have shown that lafutidine is excreted in breast milk. Therefore, mothers should be advised to discontinue breast feeding during treatment.

Paediatric use: the safety of this drug in children has not been established (no clinical experience).

1.7 Relevant warnings:

Patients with a history of drug hypersensitivity

Patients with impaired hepatic function: symptoms may be exacerbated;

Patients with impaired renal function: symptoms may be exacerbated;

Patients on dialysis: increase in blood concentration of lafutidine is reported;

Elderly: patients should be carefully observed during treatment, and the minimum required dose should be used according to symptoms. If response is not evident, other treatments should be implemented. Careful observation should be made for any changes in haematological, hepatic or renal parameters, and for changes in other factors

Since treatment with this product may mask the symptoms of gastric cancer, administration should be made after confirming the tumour is not malignant.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (Pharmacovigilance): adverse reactions (including abnormal changes in laboratory tests) were observed in 32 (2.5%) of the 1,287 patients evaluated at the time of approval. The main adverse reactions were constipation in 3 patients (0.2%). Abnormal changes in laboratory tests were observed in 22 patients.

Clinically Significant Adverse Reactions

Shock, anaphylactic reactions: shock and anaphylactic reactions may appear, therefore patients should be carefully observed. If any abnormality such as facial pallor, decreased blood pressure, generalised redness, or breathing difficulty is seen, this drug should be discontinued and appropriate measures should be taken.

Hepatic function disorder: jaundice (unknown frequency). Hepatic function disorder involving increased AST(GOT), ALT(GPT) or gamma-GTP, or jaundice may appear. Therefore patients should be carefully observed. If any abnormality is seen, this drug should be discontinued, and appropriate measures should be taken.

Agranulocytosis (unknown frequency), thrombocytopenia (unknown frequency): Agranulocytosis (initial symptom: sore throat, general malaise, fever, etc.) or thrombocytopenia may occur. If any abnormality is observed, this drug should be discontinued and appropriate measures should be taken.

Clinically significant adverse reactions: it has been reported that pancytopenia, aplastic anaemia, interstitial nephritis, oculo-muco-cutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell's syndrome), rhabdomyolysis, heart block (atrioventricular block etc.), and asystolia may occur with other H2-receptor antagonists.

2.1.1 Recent cases at European level: N.A.

2.2 Indirect risks (incorrect use): N.A.

2.2.1 Recent cases at European level: N.A.

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions

Country	Prescription status	Additional information / Exemptions				
		Routes of administration	Comments	MS	MDD	MQP
Melclass database*	-					
AT	Not authorised					
BE	Not authorised					
CH	Not authorised					
FR	Not authorised					
HU	Not authorised					
IE	Not authorised					
IT	Not authorised					
LT	Not authorised					
MK	Not authorised					
PL	Not authorised					
PT	Not authorised					
RO	Not authorised					
UK	Not authorised					

* Melclass database - Available at: http://www.edqm.eu/melclass/

No data available from other member states.

3.2 Member states' authorities' past or ongoing evaluation of the risk profile of the active ingredient for this therapeutic indication(s) (ATC code); abuse/misuse; efficiency: N.A.

3.3 Social dimension of classification:

3.3.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

Recommendation: not to classify

Criteria: lafutidine (INN) is a second generation histamine H2 receptor antagonist having multimodal mechanism of action and used to treat gastrointestinal disorders. Lafutidine is not authorised in Europe, it is authorised and marketed in Japan and India only.

3.3.2 Paediatric use: N.A.

3.3.3 Social dimension: N.A.

4. COMMENTS/REFERENCES

References:

1. SmPC (Japan)
2. Martindale - https://www.medicinescomplete.com/mc/

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Cimetidine, combinations

1.2 ATC Code: A02BA51 - H2-receptor antagonists

1.3 Therapeutic indications: -

1.4 Posology and duration of treatment: -

1.5 Pharmaceutical forms: -

1.6 Contraindications: -

1.7 Relevant warnings: -

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (Pharmacovigilance): -

2.1.1 Recent cases at European level: -

2.2 Indirect risks (incorrect use): -

2.2.1 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription status	Additional information / Exemptions				
		Routes of administration	Comments	MS	MDD	MQP
Melclass database*	No information available					
AT	Not authorised					
BE	Not authorised					
CH	Not authorised					
CZ	Not authorised					
FR	Not authorised					
HR	Not authorised					
IE	Not authorised					
IT	Not authorised					
LT	Not authorised					
MK	Not authorised					
PL	Not authorised					
PT	Not authorised					
RO	Not authorised					
UK	Not authorised					

* Melclass database - Available at: http://www.edqm.eu/melclass/

No data available from other member states.

3.2 Member states' authorities' past or ongoing evaluation of the risk profile of the active ingredient for this therapeutic indication(s) (ATC code); abuse/misuse; efficiency: -

3.3 Social dimension of classification:

3.3.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable)

Recommendation: not to classify

Criteria
No information is available.
Cimetidine, combinations is not authorised in Europe.

3.3.2 Paediatric use: -

3.3.3 Social dimension: -

4. COMMENTS/REFERENCES

References: no references found

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Famotidine, combinations

1.2 ATC Code: A02BA53 - H2-receptor antagonists

1.3 Therapeutic indications: OTC indications (10 mg famotidine, 165 mg magnesium hydroxide, 800 mg calcium carbonate): Short-term symptomatic treatment of heartburn or acid regurgitations in adults and adolescents from 16 years old.

1.4 Posology and duration of treatment:

Posology for OTC indications (10 mg famotidine, 165 mg magnesium hydroxide, 800 mg calcium carbonate): for adults and adolescents (from 16 years old). Chew one tablet thoroughly when symptoms occur, and swallow preferably with a glass of water. Do not exceed 2 tablets per day. Treatment duration is limited to 2 weeks.

1.5 Pharmaceutical forms: tablets - 10 mg famotidine, 165 mg magnesium hydroxide, 800 mg calcium carbonate

1.6 Contraindications: hypersensitivity to the active substances or any of the excipients; severe renal failure

1.7 Relevant warnings:

It is recommended to patients to seek medical advice in case of:
- symptoms associated with weight loss,
- difficulty swallowing or persistent abdominal discomfort,
- digestive troubles occurring for the first time or if these symptoms have recently changed,
- known hypercalcaemia, as this product contains calcium,
- known hypophosphataemia, as this product may worsen this condition,
- known hypercalciuria, or a history of renal calculi or nephrocalcinosis.

In case of renal failure this product should only be taken under medical supervision and monitoring of serum magnesium and calcium should be undertaken.

The product should be used with caution in case of hepatic or renal impairment.

In the case of long term use, especially during concomitant treatment with other calcium products and/or Vitamin D products, there is a risk of hypercalcaemia with subsequent kidney function impairment.

Precautions for use: if symptoms persist after 15 days of continuous treatment or get worse, an aetiological survey must be done and the conduct of the treatment should be re-evaluated.

Pregnancy: data on a limited number of exposed pregnancies indicate no adverse effects of famotidine on pregnancy or on the health of the foetus/new-born child. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects of famotidine with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Lactation: famotidine is secreted via breast milk. There is a possibility of famotidine affecting the infant's gastric acid secretion. Magnesium salts may enter breast milk and cause diarrhoea in breast-fed infants. To be avoided during breast-feeding.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (Pharmacovigilance): in clinical trials the most common effects were headaches followed by nausea and diarrhoea. Other symptoms noted included abdominal distension, abdominal pain, dizziness, dry mouth, dyspepsia, eructation, flatulence, nervousness, paraesthesia, taste perversion and thirst.

Other side effects reported for famotidine alone, often when given at higher doses, include anaphylaxis, angioedema, anorexia, arthralgia, cholestatic jaundice, constipation, fatigue, leucopoenia, liver enzyme abnormalities, pancytopenia, pruritus, rash, urticaria, vomiting, and, in isolated cases, worsening of existing hepatic disease. Gynaecomastia has been reported rarely. In most cases that were followed up, it was reversible on discontinuing treatment.
Antacids containing calcium and magnesium salts can cause bloating, changes in stool frequency and consistency, and fullness.

2.1.1 Recent cases at European level: -

2.2 Indirect risks (incorrect use): there is no experience to date with overdosage. The usual measures to remove unabsorbed material from the gastro-intestinal tract, clinical monitoring and supportive therapy should be employed. Patients with Zollinger-Ellison syndrome have tolerated doses up to 800 mg/day of famotidine for more than a year without development of significant adverse effects.

2.2.1 Recent cases at European level: -

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription status	Additional information / Exemptions				
		Routes of administration	Comments	MS	MDD	MQP
Melclass database*	No information					
AT	Not authorised					
BE	Not authorised					
CH	Not authorised					
CZ	Not authorised					
FR	Authorised but not marketed					
FI	OTC (oral use; MS: 10 mg famotidine, 165 mg magnesium hydroxide, 800 mg calcium carbonate)			10 mg		
HU	Not authorised					
IE	OTC (oral use; MS: 10 mg famotidine, 165 mg magnesium hydroxide, 800 mg calcium carbonate)			10 mg		
IT	OTC (oral use; MS: 10 mg famotidine, 165 mg magnesium hydroxide, 800 mg calcium carbonate; adults and children ≥ 16 years)			10 mg		
MK	Not authorised					
PL	Not authorised					
PT	Not authorised					
RO	Not authorised					
UK	OTC (oral use; MS: 10 mg famotidine, 165 mg magnesium hydroxide, 800 mg calcium carbonate)			10 mg		

* Melclass database - Available at: http://www.edqm.eu/melclass/

No data available from other member states.

3.2 Member states' authorities' past or ongoing evaluation of the risk profile of the active ingredient for this therapeutic indication(s) (ATC code); abuse/misuse; efficiency: N.A.

3.3 Social dimension of classification

3.3.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Recommendation: OTC, see Annex III

Conditions for supply as OTC product:

- Oral use;
- For adults and children of 16 years of age or older;
- MS: 10 mg famotidine, 165 mg magnesium hydroxide, 800 mg calcium carbonate;
- MDD:2 tablets/day;
- Maximum treatment duration: 2 weeks; adults and children of 16 years of age or older.

Criteria: famotidine, combinations (INN) is available in Ireland, Finland, Italy and United Kingdom without prescription/ 'over the counter' (OTC), for the short-term (2 weeks) symptomatic relief of heartburn, indigestion (dyspepsia) and excess acid and prevention of these symptoms when associated with meals including nocturnal symptoms. In these countries the combination available is famotidine (10 mg), magnesium hydroxide (165 mg) and calcium carbonate (800 mg).

3.3.2 Paediatric use: N.A.

3.3.3 Social dimension: N.A.

4. COMMENTS/REFERENCES

References:

1. SmPC (Ireland and United Kingdom) - http://goo.gl/o93L2J

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Omeprazole

1.2 ATC Code: A02BC01 - Proton pump inhibitors

1.3 Therapeutic indications:

Adults

Treatment of duodenal ulcers;
Prevention of relapse of duodenal ulcers;
Treatment of gastric ulcers;
Prevention of relapse of gastric ulcers;
In combination with appropriate antibiotics, *Helicobacter pylori* (*H. pylori*) eradication in peptic ulcer disease;
Treatment of NSAID-associated gastric and duodenal ulcers;
Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk;
Treatment of reflux oesophagitis;
Long-term management of patients with healed reflux oesophagitis;
Treatment of symptomatic gastro-oesophageal reflux disease;
Treatment of Zollinger-Ellison syndrome.

Paediatric use
Children over 1 year of age and ≥ 10 kg:
Treatment of reflux oesophagitis;
Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease.

Children and adolescents over 4 years of age:
In combination with antibiotics in treatment of duodenal ulcer caused by *H. pylori.*

OTC indication
Treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.

1.4 Posology and duration of treatment:

Adults:

Treatment of duodenal ulcers: the recommended dose in patients with an active ulcer is 20 mg once daily. In most patients healing occurs within 2 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 2 weeks treatment period. In patients with poorly responsive duodenal ulcer, 40 mg once daily is recommended and healing is usually achieved within 4 weeks.

Prevention of relapse of duodenal ulcers: in *H. pylori* negative patients or when *H. pylori* eradication is not possible, the recommended dose is 20 mg once daily. In some patients 10 mg may be sufficient. In case of therapy failure, the dose can be increased to 40 mg.

Treatment of gastric ulcers: the recommended dose is 20 mg once daily. In most patients healing occurs within 4 weeks. For those patients who may not be fully healed after the initial course, healing usually occurs during a further 4 weeks treatment period. In patients with poorly responsive gastric ulcer 40 mg once daily is recommended and healing is usually achieved within 8 weeks.

Prevention of relapse of gastric ulcers: for the prevention of relapse in patients with poorly responsive gastric ulcer the recommended dose is 20 mg once daily. If needed, the dose can be increased to 40 mg once daily.

In combination with appropriate antibiotics, *Helicobacter pylori* eradication in peptic ulcer disease:

- selection of antibiotics should consider the individual patient's drug tolerance, and should be undertaken in accordance with national, regional and local resistance patterns and treatment guidelines.
- omeprazole 20 mg + clarithromycin 500mg + amoxicillin 1000mg, each twice daily for 1 week
or:
- omeprazole 20 mg + clarithromycin 250 mg (alternatively 500 mg) + metronidazole 400 mg (or 500 mg or tinidazole 500 mg), each twice daily for 1 week
or:
- omeprazole 40 mg + amoxicillin 500mg + metronidazole 400 mg (or 500 mg or tinidazole 500 mg), each 3 times a day for 1 week

In each regimen, if patient is still *H. pylori* positive, therapy may be repeated.

Treatment of NSAID – associated gastric and duodenal ulcers: recommended dose is 20 mg once daily. In most patients healing occurs within 4 weeks. For those patients, who may not be fully healed after the initial course, healing usually occurs during further 4 weeks of treatment.

Prevention of NSAID – associated gastric and duodenal ulcers in patient at risk: for the prevention of NSAID-associated gastric ulcers or duodenal ulcers in patients at risk (age> 60, previous history of gastric and duodenal ulcers, previous history of upper GI bleeding) the recommended dose is omeprazole 20 mg once daily.

Treatment of reflux oesophagitis: 20 mg once daily. In most patients healing occurs within 4 weeks. For those patients, who may not be fully healed after the initial course, healing usually occurs during further 4 weeks of treatment. In patients with severe oesophagitis 40 mg once daily is recommended and healing is usually achieved within 8 weeks.

Long term management of patients with healed reflux oesophagitis: the recommended dose is 10 mg once daily. If needed, the dose can be increased to 20 – 40 mg once daily.

Treatment of GORD: the recommended dose is 20 mg daily. Patients may respond adequately to 10 mg daily, therefore individual dose adjustment should be considered. If symptoms' control has not been achieved after 4 weeks treatment of 20 mg daily, further investigation is recommended.

Treatment of Zollinger-Ellison syndrome: in patients with Zollinger-Ellison syndrome the dose should be individually adjusted and treatment continued as long as clinically indicated. The recommended initial dose is omeprazole 60 mg daily. All patients with severe disease and inadequate response to other therapies have been effectively controlled and more than 90% of the patients maintained on doses of omeprazole 20–120 mg daily. When the dose exceeds 80 mg daily, the dose should be divided and given twice daily.

Paediatric population:

Children >1 year and ≥ 10 kg:

Treatment of reflux oesophagitis

Symptomatic treatment of heartburn and acid regurgitation in GORD:
≥ 1 year of age 10-20 kg 10 mg once daily. The dosage can be increased to 20 mg once daily if needed.
≥ 2 years of age > 20 kg 20 mg once daily. The dosage can be increased to 40 mg once daily if needed.

Reflux oesophagitis: The treatment time is 4 – 8 weeks.
Symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease:
The treatment time is 2–4 weeks. If symptom control has not been achieved after 2–4 weeks the patient should be investigated further.
Children and adolescents over 4 years of age.

Treatment of duodenal ulcer caused by *H. pylori*: when selecting appropriate combination therapy, consideration should be given to official national, regional and local guidance regarding bacterial resistance, duration of treatment (most commonly 7 days but sometimes up to 14 days), and appropriate use of antibacterial agents. The treatment should be supervised by a specialist.
Weight Dosage:
15-≤30 kg: combination with two antibiotics: omeprazole 10 mg, amoxicillin 25 mg/kg body weight and clarithromycin 7.5 mg/kg body weight are all administrated together 2 times daily for 1 week.
30-≤40 kg: combination with two antibiotics: omeprazole 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administrated 2 times daily for 1 week.
>40 kg: combination with two antibiotics: omeprazole 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administrated 2 times daily for 1 week.

Some children with chronic illnesses may require long-term treatment although it is not recommended.

Food and Drug Administration (FDA) paediatric population:
GORD and maintenance of healing of reflux oesophagitis, 1-16 years of age:
5 - < 10 kg: 5 mg once daily
10 - < 20 kg 10 mg once daily
≥20 kg 20 mg once daily

OTC treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults only.

Posology - Adults only
The recommended dose is 20 mg once daily for 14 days.
Self-treatment should be limited to a maximum period of 14 days, and the patient should be instructed to consult a doctor if symptoms persist.
It might be necessary to take the capsules for 2–3 consecutive days to achieve improvement of symptoms.
The majority of patients achieve complete relief of heartburn within 7 days. Once complete relief of symptoms has occurred, treatment should be discontinued.
Patients with impaired hepatic function should be advised by a doctor before taking omeprazole.
Patients with long-term recurrent symptoms of indigestion or heartburn should see their doctor at regular intervals. Especially, patients over 55 years taking any 'over-the-counter' (OTC, non-prescription) indigestion or heartburn remedy on a daily basis should inform their pharmacist or doctor.

Patients should be instructed to consult a doctor if:
- they have had previous gastric ulcer or gastrointestinal surgery.;
- they are 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 should not take omeprazole as a preventative medication.

Special populations

Impaired renal function
Dose adjustment is not needed in patients with impaired renal function.

Impaired hepatic function
Daily dose of 10–20 mg may be sufficient.

Elderly (> 65 years old)
Dose adjustment is not needed in the elderly.

Pregnancy
Results from three prospective epidemiological studies (more than 1000 exposed outcomes) indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/new-born child. Omeprazole can be used during pregnancy.

Breastfeeding

Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used.

IV formulations - indication and dosage: IV formulations as alternatives to oral therapy in adult patients where the use of oral medicinal products is inappropriate. For most indications, a 40 mg daily dose is recommended, although in patients with Zollinger-Ellison syndrome the recommended initial dose is 60 mg daily.

1.5 Pharmaceutical forms:

Film coated tablets 10, 20 and 40 mg;
Gastroresistant tablets 10, 20, 40 mg;
MUPS (multiple unit pellet system) tablets;
Hard capsules 10, 20 and 40 mg;
Gastroresistant capsules, hard 10, 20 and 40 mg;
Powder for solution for infusion and powder for solution for injection - 40 mg.

1.6 Contraindications: hypersensitivity to the active substance, substituted benzimidazoles; concomitant administration of omeprazole with nelfinavir.

1.7 Relevant warnings: in the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment may alleviate symptoms and delay diagnosis.
Co-administration of atazanavir with proton pump inhibitors is not recommended. If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir; omeprazole 20 mg should not be exceeded.
Omeprazole, as all acid-blocking medicines, may reduce the absorption of Vitamin B12 (cyanocobalamin) due to hypo- or achlorchydria. This should be considered in patients with reduced body stores or risk factors for reduced Vit. B12 absorption on long-term therapy.
Omeprazole is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, the potential for interactions with drugs metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and omeprazole. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of omeprazole and clopidogrel should be discouraged.
Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.
Severe hypomagnesaemia has been reported in patients treated with proton pump inhibitors (PPIs) for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.
For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.
As in all long-term treatments, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.
Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

SCLE
Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping omeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors (Pharmacovigilance Risk Assessment Committee (PRAC) recommendation - July 2015).

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

FDA Warnings:
Acute interstitial nephritis
Clostridium difficile associated diarrhoea: PPI therapy may be associated with increased risk of *Clostridium difficile* associated diarrhoea

Interaction with other medicinal products and other forms of interaction: The decreased intragastric acidity during treatment with omeprazole might increase or decrease the absorption of active substances with a gastric pH dependent absorption.

Concomitant administration of omeprazole with nelfinavir is contraindicated.

Concomitant administration of omeprazole with atazanavir is not recommended.

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

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

Other active substances
The absorption of posaconazole, erlotinib, ketoconazol and itraconazol is significantly reduced and thus clinical efficacy may be impaired. For posaconazol and erlotinib concomitant use should be avoided.

Active substances metabolised by CYP2C19
Omeprazole is a moderate inhibitor of CYP2C19, the major omeprazole metabolising enzyme. Thus, the metabolism of concomitant active substances also metabolised by CYP2C19, may be decreased and the systemic exposure to these substances increased. Examples of such drugs are R-warfarin and other vitamin K antagonists, cilostazol, diazepam and phenytoin.

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

Phenytoin
Monitoring phenytoin plasma concentration is recommended during the first two weeks after initiating omeprazole treatment and, if a phenytoin dose adjustment is made, monitoring and a further dose adjustment should occur upon ending omeprazole treatment.

Unknown mechanism
Saquinavir
Concomitant administration of omeprazole with saquinavir/ritonavir resulted in increased plasma levels up to approximately 70% for saquinavir associated with good tolerability in HIV-infected patients.

Tacrolimus
Concomitant administration of omeprazole 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.

Methotrexate

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

Effects of other active substances on the pharmacokinetics of omeprazole

Inhibitors CYP2C19 and/or CYP3A4
Since omeprazole is metabolised by CYP2C19 and CYP3A4, active substances known to inhibit CYP2C19 or CYP3A4 (such as clarithromycin and voriconazole) may lead to increased omeprazole serum levels by decreasing omeprazole's rate of metabolism. Concomitant voriconazole treatment may result in more than doubling of the omeprazole exposure. As high doses of omeprazole have been well-tolerated, adjustment of the omeprazole dose is not generally required. However, dose adjustment should be considered in patients with severe hepatic impairment and if long-term treatment is indicated.

Inducers of CYP2C19 and/or CYP3A4
Active substances known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St John's wort) may lead to decreased omeprazole serum levels by increasing omeprazole's rate of metabolism.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (Pharmacovigilance):

Undesirable effects

The most common side effects (1-10% of patients) are headache, abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting.

The following adverse drug reactions have been identified or suspected in the clinical trials programme for omeprazole and post-marketing. None was found to be dose-related:

Blood and lymphatic system disorders:
Rare: leukopenia, thrombocytopenia;
Very rare: agranulocytosis, pancytopenia.

Immune system disorders:
Rare: hypersensitivity reactions, e.g. fever, angioedema and anaphylactic reaction/shock.

Metabolism and nutrition disorders:
Rare: hyponatraemia;
Not known: hypomagnesaemia – severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.

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;
Rare: dry mouth, stomatitis, gastrointestinal candidiasis;
Not known: microscopic colitis.

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, urticarial;
Rare: alopecia, photosensitivity;
Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN);
Not known: subacute cutaneous lupus erythematosus (PRAC recommendation - July 2015).

Musculoskeletal and connective tissue disorders:
Uncommon: fracture of the hip, wrist or spine;
Rare: arthralgia, myalgia;
Very rare: muscular weakness.

Renal and urinary disorders:
Rare: interstitial nephritis.

Reproductive system and breast disorders:
Very rare: gynaecomastia.

General disorders and administration site conditions:
Uncommon: malaise, peripheral oedema;
Rare: increased sweating.

<u>*Paediatric population:</u>
The safety of omeprazole has been assessed in a total of 310 children aged 0 to 16 years with acid-related disease. There are limited long term safety data from 46 children who received maintenance therapy of omeprazole during a clinical study for severe erosive oesophagitis for up to 749 days. The adverse event profile was generally the same as for adults in short- as well as in long-term treatment. There are no long term data regarding the effects of omeprazole treatment on puberty and growth.

2.1.1 Recent cases at European level:

PhVWP March 2011 – final SmPC and PIL wording agreed for class effect of PPIs (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, rabeprazole, pantoprazole) on magnesium blood levels in long term users.

PhVWP March 2012 – final SmPC and PIL wording agreed for prescription only PPIs (omeprazole, esomeprazole/naproxen, omeprazole/ketoprofen, esomeprazole, lansoprazole, pantoprazole, rabeprazole) and risk of fractures of the hip, wrist and spine.

PRAC recommendations on signals adopted at the PRAC meeting of 6-9 July 2015: recommendations for update of the product information (SmPC (both prescription and non-prescription)): dexlansoprazole; esomeprazole; lansoprazole; omeprazole; pantoprazole; rabeprazole – subacute cutaneous lupus erythematosus.

2.1.2 Indirect risks (incorrect use):

There is limited information available on the effects of overdoses of omeprazole in humans. In the

literature, doses of up to 560 mg have been described, and occasional reports have been received when single oral doses have reached up to 2,400 mg omeprazole (120 times the usual recommended clinical dose). Nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache have been reported. Also apathy, depression and confusion have been described in single cases.
The symptoms described have been transient, and no serious outcome has been reported. The rate of elimination was unchanged (first order kinetics) with increased doses. Treatment, if needed, is symptomatic.

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

Omeprazole is a substituted benzimidazole belonging to the therapeutic group of PPIs. It is administered as a prodrug and specifically and dose-proportionally inhibits the gastric H+/K+-ATPase (proton pump) and thereby inhibits H+ ion transfer into the gastric lumen, which is responsible for acid secretion in the parietal cells of the stomach. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once daily dosing. All pharmacodynamic effects observed can be explained by the effect of omeprazole on acid secretion. As a consequence of reduced acid secretion and intragastric acidity, omeprazole dose-dependently reduces/normalises acid exposure of the oesophagus in patients with gastro-oesophageal reflux disease. No tachyphylaxis has been observed during treatment with omeprazole.

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	**Prescription status**	**Additional information / Exemptions**				
		Routes of administration	Comments	MS	MDD	MQP
Melclass database*	I (1)					
AT	II					
BE	I + Exemption Annex III (Ex.: MS: 20 mg)			40 mg	40 mg	20 g
CH	II + Exemption Annex III	oral	OTC: 20 mg	40 mg	40 mg	
CZ	I + Exemption Annex III (Ex.: MS: 20 mg/14-day use)	oral		20 mg		
FR	II + Exemption Annex III			20 mg		
HR	I + Exemption Annex III (Ex. MS: 10 mg) OTC authorised but not marketed	oral		10 mg	20 mg	280 mg (14 tablets)
IE	II OTC authorised but not marketed	oral	Treatment of reflux symptoms	OTC: 20 mg	OTC: 20 mg	280 mg (14 tablets)
IT	II I.V. form restricted for hospital use only			40 mg	40 mg IV 20 mg – oral	80 mg
MK	POM			20 mg	It depends on indic.	280 mg
PL	I (POM) + Exemption Annex III	oral	OTC: Reflux symptoms	Rp 40 mg OTC 20mg IV 40mg	Rp 40 mg OTC: 20 mg IV 80 mg	OTC 280 mg Rp: 3600 mg iv 200 mg
PT	I + Exemption Annex III	oral	OTC: Reflux like symptoms	POM 40 mg OTC 280 mg	40 mg	4 g
RO	II					
UK	I + Exemption Annex III	oral	Reflux like symptoms	POM 40 mg OTC 20 mg	POM 40 mg OTC 20 mg	OTC 280 mg

* Melclass database - Available at: http://www.edqm.eu/melclass/

No data available from other member states.

3.2 Member states' authorities' past or ongoing evaluation of the risk profile of the active ingredient for this therapeutic indication(s) (ATC code); abuse/misuse; efficiency: N.A.

3.3 Social dimension of classification:

3.3.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Recommendation: List II + Exemption Annex III

Exemptions:

- Treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults
- No longer than 14 days
- MS 20 mg
- MDD 20 mg
- MQP 280 mg

For more information > see OTC Treatment

Justification:
- According to EMA recommendations;
- Omeprazole is classified under List II + Exemption Annex III in most member states.

3.3.2 Paediatric use: POM only

3.3.3 Social dimension: N.A.

4. COMMENTS/REFERENCES

References:

1. Martindale 36 Edition
2. E-Medicines Compendium - https://www.medicines.org.uk/emc/
3. FDA approved medicines (Prilosec label information Dec.2014)
4. Paediatric Public Assessment Report, EU Worksharing Project Losec/Losec MUPS (omeprazole)
5. Prescription only proton pump inhibitors (omeprazole, esomeprazole/naproxen, omeprazole/ketoprofen, esomeprazole, lansoprazole, pantoprazole, rabeprazole) and risk of fractures of the hip, wrist and spine - Final SmPC and PIL wording agreed by PhVWP March 2012 - https://goo.gl/7PeJwD
5. Class effects of proton-pump inhibitors (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, rabeprazole, pantoprazole) on magnesium blood levels in long-term users - Final SmPC and PIL wording agreed by PhVWP December 2011
6. EMEA/H/A-0/1001Article 30 referrals: Losec and associated names (omeprazole) Annex II Scientific conclusions and grounds for amendment of the summary of Product Characteristics, Labelling and Package leaflet presented by the EMEA; 19.09.2011
7. PRAC recommendations on signals adopted at the PRAC meeting of 6-9 July 2015: recommendations for update of the product information (SmPC (both prescription and non-prescription)): dexlansoprazole; esomeprazole; lansoprazole; omeprazole; pantoprazole; rabeprazole – subacute cutaneous lupus erythematosus.

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Pantoprazole

1.2 ATC Code: A02BC02 - Proton pump inhibitors

1.3 Therapeutic indications:

Adults and adolescents 12 years of age and above: reflux oesophagitis

Adults
Eradication of *Helicobacter pylori* (*H. pylori*) in combination with appropriate antibiotic therapy in patients with *H. pylori* associated ulcers;
Gastric and duodenal ulcer;
Zollinger-Ellison syndrome and other pathological hypersecretory conditions.

IV indications and posology
Reflux oesophagitis;
Gastric and duodenal ulcer;
Zollinger-Ellison syndrome and other pathological hypersecretory conditions.

Intravenous administration of pantoprazole is recommended only if oral administration is not appropriate.

OTC pantoprazole: is indicated for short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults.

1.4 Posology and duration of treatment:

Oral forms:

Adults and adolescents 12 years of age and above

Reflux oesophagitis: 40 mg per day. In individual cases the dose may be doubled (increase to 2 x 40 mg daily) especially when there has been no response to other treatment. A 4-week period is usually required for the treatment of reflux oesophagitis. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

Adults:

Eradication of H. pylori in combination with two appropriate antibiotics
In *H. pylori* positive patients with gastric and duodenal ulcers, eradication by a combination therapy should be achieved. Considerations should be given to official local guidance (e.g. national recommendations) regarding bacterial resistance and the appropriate use and prescription of antibacterial agents. Depending upon the resistance pattern, the following combinations can be recommended for the eradication of *H. pylori*:

a) 40 mg twice daily + twice daily 1000 mg amoxicillin + twice daily 500 mg clarithromycin;

b) 40 mg twice daily + twice daily 400-500 mg metronidazole (or 500 mg tinidazole) + twice daily 250-500 mg clarithromycin;

c) 40 mg twice daily + twice daily 1000 mg amoxicillin + twice daily 400-500 mg metronidazole (or 500 mg tinidazole).

In combination therapy for eradication of *H. pylori* infection, the second dose 40 mg should be taken 1 hour before the evening meal. The combination therapy is implemented for 7 days in general and can be prolonged for a further 7 days to a total duration of up to two weeks. If, to ensure healing of the ulcers, further treatment with pantoprazole is indicated, the dose recommendations for duodenal and gastric ulcers should be considered.

Treatment of gastric ulcer: 40 mg once a day. In individual cases the dose may be doubled (increase to 2 x 40 mg daily) especially when there has been no response to other treatment. A 4-week period is usually required for the treatment of gastric ulcers. If this is not sufficient, healing will usually be achieved within a further 4 weeks.

Treatment of duodenal ulcer: 40 mg once a day. In individual cases the dose may be doubled (increase to 2 x 40 mg) especially when there has been no response to other treatment. A duodenal ulcer generally heals within 2 weeks. If a 2-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further 2 weeks.

Zollinger-Ellison syndrome and other pathological hypersecretory conditions: for the long-term management of Zollinger-Ellison syndrome and other pathological hypersecretory conditions, patients should start their treatment with a daily dose of 80 mg. Thereafter, the dose can be titrated up or down as needed using measurements of gastric acid secretion to guide. With doses above 80 mg daily, the dose should be divided and given twice daily. A temporary increase of the dose above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control.

*Treatment duration in Zollinger-Ellison syndrome and other pathological hypersecretory conditions is not limited and should be adapted according to clinical needs.

Prevention of gastroduodenal ulcers caused by non-steroid anti-inflammatory drugs (NSAIDs) in patients at increased risk, requiring long-term use of NSAIDs: 20 mg once a day.

Special populations

Paediatric population: Pantoprazole is not recommended for use in children below 12 years of age due to limited data on safety and efficacy in this age group.

FDA paediatric use:
Children 5 years and older: Short term treatment of erosive oesophagitis associated with GORD:
≥ 15 kg to < 40 kg: 20 mg once daily for up to 8 weeks;
≥40 kg: 40 mg once daily for up to 8 weeks.

Hepatic impairment
A daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver impairment. Pantoprazole must not be used in combination treatment for eradication of *H. pylori* in patients with moderate to severe hepatic dysfunction since currently no data are available on the efficacy and safety of pantoprazole in combination treatment of these patients.

Renal impairment
No dose adjustment is necessary in patients with impaired renal function. Pantoprazole must not be used in combination treatment for eradication of *H. pylori* in patients with impaired renal function since currently no data are available on the efficacy and safety of pantoprazole in combination treatment for these patients.

Elderly
No dose adjustment is necessary in elderly patients.

Pregnancy
Pantoprazole should not be used during pregnancy unless clearly necessary.

Breast-feeding
Decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with pantoprazole should be made taking into account the benefit of breast-feeding to the child and the benefit of pantoprazole therapy to women.

IV Forms:

Adults: data are available on intravenous use for up to 7 days. Therefore, as soon as oral therapy is possible, treatment IV should be discontinued and 40 mg pantoprazole PO should be administered instead.

Recommended dose

Gastric and duodenal ulcer, reflux oesophagitis: the recommended intravenous dose is one vial (40 mg pantoprazole) per day.

Zollinger-Ellison syndrome and other pathological hypersecretory conditions: for the long-term management of Zollinger-Ellison syndrome and other pathological hypersecretory conditions, patients should start their treatment with a daily dose of 80 mg. Thereafter, the dose can be titrated up or down as needed using measurements of gastric acid secretion to guide. With doses above 80 mg daily, the dose should be divided and given twice daily. A temporary increase of the dose above 160 mg pantoprazole is possible but should not be applied longer than required for adequate acid control. If a rapid acid control is required, a starting dose of 2 x 80 mg is sufficient to manage a decrease of acid output into the target range (< 10 mEq/h) within one hour in the majority of patients.

Children:
The experience in children is limited. Therefore, pantoprazole IV is not recommended for use in patients below 18 years of age until further data become available.

OTC Posology (oral)
The recommended dose is 20 mg pantoprazole (one tablet) per day. It might be necessary to take the tablets for 2–3 consecutive days to achieve improvement of symptoms. Once complete relief of symptoms has occurred, treatment should be discontinued.
The treatment should not exceed 4 weeks without consulting a doctor. If no symptom relief is obtained within 2 weeks of continuous treatment, the patient should be instructed to consult a doctor.

Patients should be instructed to consult a doctor if:

- they have unintentional weight loss, anaemia, gastrointestinal bleeding, dysphagia, persistent vomiting or vomiting with blood, since it may alleviate symptoms and delay diagnosis of a severe condition. In these cases, malignancy should be excluded;

- they have had previous gastric ulcer or gastrointestinal surgery;

- they are on continuous symptomatic treatment of indigestion or heartburn for 4 or more weeks;

- they have jaundice, hepatic impairment, or liver disease;

- they have any other serious disease affecting general well-being;

- 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 another proton pump inhibitor or H2 antagonist concomitantly.

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

Patients should be advised that the tablets are not intended to provide immediate relief.

Patients may start to experience symptomatic relief after approximately one day of treatment with pantoprazole, but it might be necessary to take it for 7 days to achieve complete heartburn control.
Patients should not take pantoprazole as a preventive medicinal product.

1.5 Pharmaceutical forms:

Gastro-resistant tablets 20, 40 mg
Powder for solution for injection/and infusion 40 mg

1.6 Contraindications:

Hypersensitivity to the active substance, substituted benzimidazoles

1.7 Relevant warnings:

Hepatic impairment
In patients with severe liver impairment, the liver enzymes should be monitored regularly during treatment with pantoprazole, particularly on long-term use. In the case of a rise of the liver enzymes, the treatment should be discontinued.

Combination therapy
In the case of combination therapy, the summaries of product characteristics of the respective medicinal products should be observed.

In presence of alarm symptoms
In the presence of any alarm symptom (e. g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis, anaemia or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with pantoprazole may alleviate symptoms and delay diagnosis.
*Further investigation is to be considered if symptoms persist despite adequate treatment.

Co-administration with atazanavir
Co-administration of atazanavir with proton pump inhibitors is not recommended. If the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended in combination with an increase in the dose of atazanavir to 400 mg with 100 mg of ritonavir. A pantoprazole dose of 20 mg per day should not be exceeded.

Influence on vitamin B12 absorption
In patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions requiring long-term treatment, pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy or if respective clinical symptoms are observed.

Long term treatment
In long-term treatment, especially when exceeding a treatment period of 1 year, patients should be kept under regular surveillance.

Bone fractures
Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in the presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Hypomagnesaemia
Severe hypomagnesaemia has been reported in patients treated with PPIs like pantoprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.
For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Gastrointestinal infections caused by bacteria

Pantoprazole, like all PPIs, might be expected to increase the counts of bacteria normally present in the upper gastrointestinal tract. Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella, Campylobacter* and *C. difficile*.

SCLE
Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping pantoprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors (PRAC recommendation - July 2015).

FDA Warnings: Acute interstitial nephritis

Effect of pantoprazole on the absorption of other medicinal products
Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may reduce the absorption of drugs with a gastric pH dependent bioavailability, e.g. some azole antifungals such as ketoconazole, itraconazole, posaconazole and other medicine such as erlotinib.

HIV medications (atazanavir)
Co-administration of atazanavir and other HIV medications whose absorption is pH-dependent with proton-pump inhibitors might result in a substantial reduction in the bioavailability of these HIV medications and might impact the efficacy of these medicines. Therefore, the co-administration of proton pump inhibitors with atazanavir is not recommended.

Coumarin anticoagulants (phenprocoumon or warfarin)
Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in International Normalised Ratio (INR) have been reported during concomitant treatment in the post-marketing period. Therefore, in patients treated with coumarin anticoagulants (e.g. phenprocoumon or warfarin), monitoring of prothrombin time / INR is recommended after initiation, termination or during irregular use of pantoprazole.

Methotrexate
Concomitant use of high dose methotrexate (e.g. 300 mg) and proton-pump inhibitors has been reported to increase methotrexate levels in some patients. Therefore in settings where high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of pantoprazole may need to be considered.

Other interactions studies
Pantoprazole is extensively metabolised in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4.
Interaction studies with drugs also metabolised with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, and an oral contraceptive containing levonorgestrel and ethinyl oestradiol did not reveal clinically significant interactions.
Results from a range of interaction studies demonstrate that pantoprazole does not affect the metabolism of active substances metabolised by CYP1A2 (such as caffeine, theophylline), CYP2C9 (such as piroxicam, diclofenac, naproxen), CYP2D6 (such as metoprolol), CYP2E1 (such as ethanol) or does not interfere with p-glycoprotein related absorption of digoxin.

There were no interactions with concomitantly administered antacids.

Interaction studies have also been performed by concomitantly administering pantoprazole with the respective antibiotics (clarithromycin, metronidazole, amoxicillin). No clinically relevant interactions were found.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (Pharmacovigilance):

Undesirable effects

Approximately 5% of patients can be expected to experience adverse drug reactions (ADRs). The most commonly reported ADRs are diarrhoea and headache, both occurring in approximately 1% of patients.

Adverse reactions reported with pantoprazole, ranked under the following frequency classification:

Blood and lymphatic system disorders:
Rare: agranulocytosis;
Very rare: thrombocytopenia, leukopenia, pancytopenia.

Immune system disorders:
Rare: hypersensitivity reactions (including anaphylactic reactions and anaphylactic shock).

Metabolism and nutrition disorders:
Rare: hyperlipidaemias and lipid increases, weight changes;
Not known: hyponatremia, hypomagnesaemia; hypocalcaemia associated with hypomagnesemia, hypokalaemia.

Psychiatric disorders:
Uncommon: sleep disorders;
Rare: depression and all aggravations;
Very rare: disorientation and all aggravations;
Not known: hallucination, confusion (especially in predisposed patients as well as aggravation of the symptoms in case of pre-existence)

Nervous system disorders:
Uncommon: headache, dizziness;
Rare: taste disorders;
Very rare: paraesthesia.

Eye disorders:
Rare: blurred vision.

Gastrointestinal disorders:
Uncommon: diarrhoea, nausea/vomiting, abdominal distension and bloating, constipation, dry mouth, abdominal pain and discomfort.

Hepatobiliary disorders:
Uncommon: increased liver enzymes;
Rare: bilirubin increased;
Not known: hepatocellular injury, jaundice; hepatocellular failure.

Skin and subcutaneous tissue disorders:
Uncommon: rash, exantema, eruptions, pruritus;
Rare: urticaria, angioedema;
Not known: Stevens-Johnson syndrome, Lyell syndrome, erythema multiforme, photosensitivity, subacute cutaneous lupus erythematosus (PRAC recommendation - July 2015).

Musculoskeletal and connective tissue disorders:
Uncommon: fracture of the hip, wrist or spine;
Rare: arthralgia, myalgia;
Not known: muscle spasm as a consequence of electrolyte disturbances.

Renal and urinary disorders:
Not known: interstitial nephritis with possible progression to renal failure

Reproductive system and breast disorders:
Rare: gynaecomastia

General disorders and administration site conditions:
Uncommon: asthenia, fatigue and malaise;
Rare: body temperature increased, peripheral oedema

2.1.1 Recent cases at European level:

PhVWP March 2011 – final SmPC and PIL wording agreed for class effect of PPIs (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, rabeprazole, pantoprazole) on magnesium blood levels in long term users.

PhVWP March 2012 – final SmPC and PIL wording agreed for prescription only PPIs (omeprazole, esomeprazole/naproxen, omeprazole/ketoprofen, esomeprazole, lansoprazole, pantoprazole, rabeprazole) and risk of fractures of the hip, wrist and spine.

PRAC recommendations on signals adopted at the PRAC meeting of 6-9 July 2015: recommendations for update of the product information (SmPC (both prescription and non-prescription)): dexlansoprazole; esomeprazole; lansoprazole; omeprazole; pantoprazole; rabeprazole – subacute cutaneous lupus erythematosus.

2.1.2 Indirect risks (incorrect use): there are no known symptoms of overdose in man. Systemic exposures with up to 240 mg administered intravenously over 2 minutes were well tolerated. As pantoprazole is extensively protein bound, it is not readily dialyzable. In the case of overdose with clinical signs of intoxication, apart from symptomatic and supportive treatment, no specific therapeutic recommendations can be made.

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific blockade of the proton pumps of the parietal cells. Pantoprazole is converted to its active form in the acidic environment in the parietal cells where it inhibits the H+, K+-ATPase enzyme, i.e. the final stage in the production of hydrochloric acid in the stomach. The inhibition is dose-dependent and affects both basal and stimulated acid secretion. In most patients, freedom from symptoms is achieved within 2 weeks. As with other proton pump inhibitors and H2 receptor inhibitors, treatment with pantoprazole reduces acidity in the stomach and thereby increases gastrin in proportion to the reduction in acidity. The increase in gastrin is reversible. Since pantoprazole binds to the enzyme distal to the cell receptor level, it can inhibit hydrochloric acid secretion independently of stimulation by other substances (acetylcholine, histamine, gastrin). The effect is the same whether the product is given orally or intravenously.

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription status	Additional information / Exemptions				
		Routes of administration	Comments	MS	MDD	MQP
Melclass database*	I (1)					
AT	II + Exemption Annex III (Ex.: MS: 20 mg)		OTC: short term treatment of reflux symptoms in adults (max 14 days)		20 mg	-
BE	I (POM)+ Exemption Annex III (Ex.: MS: 20 mg)		OTC: short term treatment of reflux symptoms in adults	40 mg	40 mg	28 g (POM)
CH	II + Exemption Annex III (Ex.: MS: 20 mg)					
CZ	I (POM) + Exemption Annex III (Ex.: MS: 20 mg)		OTC: short term treatment of reflux symptoms in	20 mg		

			adults / 14 days			
FR	II + Exemption Annex III			40 mg	80 mg	2000 mg
HR	I + Exemption Annex III (Ex.: MS: 20 mg)					
IE	II + Exemption Annex III		OTC: short term treatment of reflux symptoms in adults, no longer than 4 weeks	20 mg	20 mg	280 mg (14 tablets)
IT	II + Exemption Annex III (Ex.: MS: 20 mg)					
MK	I (POM) + Exemption Annex III (Ex.: MS: 20 mg)		OTC: short term treatment of reflux symptoms in adults, 14 tablets	40 mg OTC: 20 mg	40 mg OTC 20 mg	1200 mg OTC 280 mg
PL	I (POM) + Exemption Annex III (Ex.: MS: 20 mg)		OTC: short term treatment of reflux symptoms in adults, no longer than 14 days	Rp 40 mg OTC 20 mg	Rp 40 mg OTC 20 mg	Rp 4 g OTC 280 mg
PT	I (POM) + Exemption Annex III (Ex.: MS: 20 mg)		OTC: Reflux like symptoms	40 mg	80 mg	4 g
RO	I: IV II: for oral forms + Exemption Annex III (Ex.: MS: 20 mg)		OTC: short term treatment of reflux symptoms in adults	20 mg	20 mg	280 mg
UK	I (POM) + Exemption Annex III (Ex.: MS: 20 mg)		OTC: short term treatment of reflux symptoms in adults	20 mg	20 mg	280 mg

* Melclass database - Available at: http://www.edqm.eu/melclass/

No data available from other member states.

3.2 Member states' authorities' past or ongoing evaluation of the risk profile of the active ingredient for this therapeutic indication(s) (ATC code); abuse/misuse; efficiency: no

3.3 Social dimension of classification:

3.3.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Recommendation: List II + Exemption Annex III

Exemptions:

- Short term treatment of reflux symptoms in adults only
- No longer than 14 days
- MS: 20 mg
- MDD: 20 mg
- MQP: 280 mg

For more details > see OTC Pantoprazole

Justification:
- According to EMA recommendations;
- Pantoprazole is classified under list II + Exemption Annex III in most member states.

3.3.2 Paediatric use: Pantoprazole is not recommended for use in children below 12 years of age due to limited data on safety and efficacy in this age group.

Children ≥12 years: POM only.

3.3.3 Social dimension: N.A.

4. COMMENTS/REFERENCES

References:

1. Martindale 36 Edition
2. E-Medicines Compendium - https://www.medicines.org.uk/emc/
3. FDA approved drugs (Protonix- pantoprazole sodium, label information, March 2012) - https://goo.gl/7PeJwD
4. EPARs (12.06.2009) for: Controloc Control, updated 19.03.2014; Pantecta Control and Pantoloc Control, updated 03.05.2013; Pantozol Control and Somac Control, updated 02.05.2013
5. Pantoprazole, EMEA/H/A-30/1002, Art. 30 referrals; European Commission final decision (17/12/2009); SmPC
6. Prescription only proton pump inhibitors (omeprazole, esomeprazole/naproxen, meprazole/ketoprofen, esomeprazole, lansoprazole, pantoprazole, rabeprazole) and risk of fractures of the hip, wrist and spine - Final SmPC and PIL wording agreed by PhVWP March 2012
7. Class effects of proton-pump inhibitors (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, rabeprazole, pantoprazole) on magnesium blood levels in long-term users - Final SmPC and PIL wording agreed by PhVWP December 2011
8. PRAC recommendations on signals adopted at the PRAC meeting of 6-9 July 2015: recommendations for update of the product information (SmPC (both prescription and non-prescription)): dexlansoprazole; esomeprazole; lansoprazole; omeprazole; pantoprazole; rabeprazole – subacute cutaneous lupus erythematosus.

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Lansoprazole

1.2 ATC Code: A02BC03 - Proton pump inhibitors

1.3 Therapeutic indications:

Adults:
Treatment of duodenal and gastric ulcer;
Treatment and prophylaxis of reflux oesophagitis;
Eradication of *Helicobacter pylori* concurrently given with appropriate antibiotic therapy and prevention of relapse of peptic ulcers in patients with *H. pylori* associated ulcers;
Treatment of NSAID-associated benign gastric and duodenal ulcers in patients requiring continued NSAID treatment;
Prophylaxis of NSAID-associated gastric ulcers and duodenal ulcers in patients at risk requiring continued therapy;
Symptomatic gastroesophageal reflux disease;
Zollinger-Ellison syndrome.

1.4 Posology and duration of treatment:

Adults:
For optimal effect, lansoprazole should be taken once daily in the morning, except when used for *H. pylori* eradication when treatment should be twice a day, once in the morning and once in the evening. Lansoprazole should be taken at least 30 minutes before food.

The orodispersible tablets can be dispersed in a small amount of water and administered via a nasogastric tube or oral syringe.

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

Treatment of gastric ulcer: the recommended dose is 30 mg once daily for 4 weeks. The ulcer usually heals within 4 weeks, but in patients not fully healed within this time, the medication may be continued at the same dose for another 4 weeks.

Reflux oesophagitis: the recommended dose is 30 mg once daily for 4 weeks. In patients not fully healed within this time, the treatment may be continued at the same dose for another 4 weeks.

Prophylaxis of reflux oesophagitis: 15 mg once daily. The dose may be increased up to 30 mg daily as necessary.

Eradication of *Helicobacter pylori:*
When selecting appropriate combination therapy consideration should be given to official local guidance regarding bacterial resistance, duration of treatment (most commonly 7 days but sometimes up to 14 days), and appropriate use of antibacterial agents.
The recommended dose is 30 mg twice daily for 7 days in combination with one of the following:
clarithromycin 250-500 mg twice daily + amoxicillin 1 g twice daily;
clarithromycin 250 mg twice daily + metronidazole 400-500 mg twice daily.

H. pylori eradication rates of up to 90% are obtained when clarithromycin is combined with lanzoprasole and amoxicillin or metronidazole.
Six months after successful eradication treatment, the risk of re-infection is low and relapse is therefore unlikely.
Use of a regimen including lansoprazole 30 mg twice daily, amoxicillin 1 g twice daily and metronidazole 400–500 mg twice daily has also been examined. Lower eradication rates were seen using this combination than in regimens involving clarithromycin. It may be suitable for those who are unable to take clarithromycin as part of an eradication therapy, when local resistance rates to metronidazole are low.

Treatment of NSAID associated benign gastric and duodenal ulcers in patients requiring continued NSAID treatment: 30 mg once daily for 4 weeks. In patients not fully healed the treatment may be continued for another 4 weeks. For patients at risk or with ulcers that are difficult to heal, a longer course of treatment and/or a higher dose should be considered.

Prophylaxis of NSAID associated gastric and duodenal ulcers in patients at risk (such as age > 65 or history of gastric or duodenal ulcer) requiring prolonged NSAID treatment: 15 mg once daily. If the treatment fails the dose 30 mg once daily should be used.

Symptomatic gastro-oesophageal reflux disease: the recommended dose is 15 mg or 30 mg daily. Relief of symptoms is obtained rapidly. Individual adjustment of dosage should be considered. If the symptoms are not relieved within 4 weeks with a daily dose of 30 mg, further examinations are recommended.

Zollinger-Ellison syndrome: the recommended initial dose is 60 mg once daily. The dose should be individually adjusted and the treatment should be continued for as long as necessary. Daily doses of up to 180 mg have been used. If the required daily dose exceeds 120 mg, it should be given in two divided doses.

Special populations

Impaired hepatic or renal function: there is no need for a dose adjustment in patients with impaired renal function. Patients with moderate or severe liver disease should be kept under regular supervision and a 50% reduction of the daily dose is recommended.

Elderly: due to reduced clearance of lansoprazole in the elderly an adjustment of dose may be necessary based on individual requirements. A daily dose of 30 mg should not be exceeded in the elderly unless there are compelling clinical indications.

Children: the use of lansoprazole is not recommended in children as clinical data are limited. Treatment of small children below 1 year of age should be avoided as available data have not shown beneficial effects in the treatment of gastro-oesophageal reflux disease.

FDA paediatric use: the safety and effectiveness of lansoprazole have been established in paediatric patients 1-17 years of age for: short-term treatment of symptomatic GORD and erosive oesophagitis.
1-11 years of age:
≤30 kg: 15 mg once daily up to 12 weeks;
>30 kg: 30 mg once daily up to 12 weeks.
12-17 years of age:
For short-term treatment of symptomatic GORD: 15 mg once daily for up to 8 weeks;
For erosive oesophagitis: 30 mg once daily for up to 8 weeks.
Lansoprazole was not effective in patients with symptomatic GORD in 1 month - < 1 year of age, in a multi-centre, double blind, placebo controlled study.

Pregnancy: the use of lansoprazole during pregnancy is not recommended.

Breast feeding: a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with lansoprazole should be made taking into account the benefit of breastfeeding to the child and the benefit of lansoprazole therapy to the woman.

FDA OTC indication: adults only, for frequent heartburn 15 mg once daily for up to14 days, it can be repeated every 4 months.

1.5 Pharmaceutical forms:

Orodispersible tablets 15 and 30 mg;
Capsules 15 and 30 mg;
Gastro-resistant granules for oral suspension 30 mg.

1.6 Contraindications:

Hypersensitivity to the active substance;
Lansoprazole should not be administered with atazanavir.

1.7 Relevant warnings: in common with other anti-ulcer therapies, the possibility of malignant gastric tumour should be excluded when treating a gastric ulcer with lansoprazole because lansoprazole can mask the symptoms and delay the diagnosis.
Lansoprazole should be used with caution in patients with moderate and severe hepatic dysfunction.
Decreased gastric acidity due to lansoprazole might be expected to increase gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with lansoprazole may lead to a slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.
Severe hypomagnesaemia has been reported in patients treated with PPIs for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.
For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.
In patients suffering from gastro-duodenal ulcers, the possibility of *H. pylori* infection as an aetiological factor should be considered.
Because of limited safety data for patients on maintenance treatment for longer than 1 year, regular review of the treatment and a thorough risk/benefit assessment should regularly be performed in these patients.
Very rarely cases of colitis have been reported in patients taking lansoprazole. Therefore, in the case of severe and/or persistent diarrhoea, discontinuation of therapy should be considered.
The treatment for the prevention of peptic ulceration of patients in need of continuous NSAID treatment should be restricted to high risk patients (e.g. previous gastrointestinal bleeding, perforation or ulcer, advanced age, concomitant use of medication known to increase the likelihood of upper GI adverse events [e.g. corticosteroids or anticoagulants], the presence of a serious co-morbidity factor or the prolonged use of NSAID maximum recommended doses).
Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

SCLE:
Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping lansoprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors (PRAC recommendation - July 2015).

FDA Warnings:
Acute interstitial nephritis;
Cyanocobalamin (vit. B12) deficiency: daily long term use (e.g. longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin;
Clostridium difficile associated diarrhoea: PPI therapy may be associated with increased risk of *Clostridium difficile* associated diarrhoea.

Interactions:

Effects of lansoprazole on other drugs:
Medicinal products with pH dependent absorption.

Lansoprazole may interfere with the absorption of drugs where gastric pH is critical to bioavailability (e.g. ampicillin esters, digoxin, iron salts, erlotinib, ketoconazole, atazanavir and mycophenolate mofetil).

Atazanavir: lansoprazole should not be co-administered with atazanavir.

Ketoconazole and itraconazole:
The absorption of ketoconazole and itraconazole from the gastrointestinal tract is enhanced by the presence of gastric acid. Administration of lansoprazole may result in sub-therapeutic concentrations of ketoconazole and itraconazole and the combination should be avoided.

Digoxin:
Co-administration of lansoprazole and digoxin may lead to increased digoxin plasma levels. The plasma levels of digoxin should therefore be monitored and the dose of digoxin adjusted if necessary when initiating and ending lansoprazole treatment.

Medicinal products metabolised by P450 enzymes
Lansoprazole may increase plasma concentrations of drugs that are metabolised by CYP3A4. Caution is advised when combining lansoprazole with drugs which are metabolised by this enzyme and have a narrow therapeutic window.

Theophylline:
Lansoprazole reduces the plasma concentration of theophylline, which may decrease the expected clinical effect at the dose. Caution is advised when combining the two drugs.

Tacrolimus:
Co-administration of lansoprazole increases the plasma concentrations of tacrolimus (a CYP3A and Pgp substrate). Lansoprazole exposure increased the mean exposure of tacrolimus by up to 81%. Monitoring of tacrolimus plasma concentrations is advised when concomitant treatment with lanzoprazole is initiated or ended.

Medicinal products transported by P-glycoprotein
Lansoprazole has been observed to inhibit the transport protein, P-glycoprotein (P-gp) *in vitro*. The clinical relevance of this is unknown.

Effects of other drugs on lansoprazole

Drugs which inhibit CYP2C19
Fluvoxamine:
A dose reduction may be considered when combining lansoprazole with the CYP2C19 inhibitor fluvoxamine. The plasma concentrations of lansoprazole increase up to 4-fold.

Drugs which induce CYP2C19 and CYP3A4
Enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin, and St John´s wort (*Hypericum perforatum*) can markedly reduce the plasma concentrations of lansoprazole.

Others:
Sucralfate/Antacids may decrease the bioavailability of lansoprazole. Therefore lansoprazole should be taken at least 1 hour after taking these drugs.

No clinically significant interactions of lansoprazole with nonsteroidal anti-inflammatory drugs have been demonstrated, although no formal interactions studies have been performed.

FDA interactions: warfarin: there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly (in such patients monitoring of INR and prothrombin time may be needed).

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (Pharmacovigilance):

Undesirable effects
The most common side effects (1-10% of patients) are headache, dizziness, abdominal pain,

constipation, diarrhoea, flatulence, nausea/vomiting, urticaria, itching, rash, fatigue and dry mouth or throat.

The following adverse drug reactions have been identified:

Blood and lymphatic system disorders:
Uncommon: leukopenia, thrombocytopenia eosinophilia;
Rare: anaemia;
Very rare: agranulocytosis, pancytopenia.

Immune system disorders:
Very rare: anaphylactic shock.

Metabolism and nutrition disorders:
Rare: hypomagnesaemia.

Psychiatric disorders:
Uncommon: depression;
Rare: hallucination, confusion, insomnia.

Nervous system disorders:
Common: headache, dizziness;
Rare: somnolence, vertigo, paraesthesia, restlessness, tremor.

Eye disorders:
Rare: visual disturbances.

Gastrointestinal disorders:
Common: nausea, diarrhoea, stomach ache, constipation vomiting, flatulence; dry mouth or throat;
Rare: pancreatitis, candidiasis of oesophagus, taste disturbances and glossitis;
Very rare: colitis, stomatitis

Hepatobiliary disorders:
Uncommon: increased liver enzymes;
Rare: hepatitis, jaundice

Skin and subcutaneous tissue disorders:
Common: urticaria, itching, rash;
Rare: erythema multiforme, petechiae, hair loss, photosensitivity and purpura;
Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN);
Not known: subacute cutaneous lupus erythematosus.

Musculoskeletal and connective tissue disorders:
Uncommon: arthralgia, myalgia, fracture of the hip, wrist or spine.

Renal and urinary disorders:
Rare: interstitial nephritis.

Reproductive system and breast disorders:
Rare: gynaecomastia.

General disorders and administration site conditions:
Common: fatigue;
Uncommon: oedema;
Rare: angioedema, impotence, hyperhidrosis, anorexia and fever.

Investigations:
Very rare: increase in cholesterol and triglyceride levels, hyponatremia.

2.1.1 Recent cases at European level:

PhVWP March 2011 – final SmPC and PIL wording agreed for class effect of PPIs (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, rabeprazole, pantoprazole) on magnesium blood levels in long term users.

PhVWP March 2012 – final SmPC and PIL wording agreed for prescription only PPIs (omeprazole, esomeprazole/naproxen, omeprazole/ketoprofen, esomeprazole, lansoprazole, pantoprazole, rabeprazole) and risk of fractures of the hip, wrist and spine.

PRAC recommendations on signals adopted at the PRAC meeting of 6-9 July 2015: recommendations for update of the product information (SmPC (both prescription and non-prescription)): dexlansoprazole; esomeprazole; lansoprazole; omeprazole; pantoprazole; rabeprazole – subacute cutaneous lupus erythematosus.

2.1.2 Indirect risks (incorrect use): the effects of overdose on lansoprazole in humans are not known (although the acute toxicity is likely to be low) and, consequently, instruction for treatment cannot be given. However, daily doses of up to 180 mg of lansoprazole orally and up to 90 mg of lansoprazole intravenously have been administered in trials without significant undesirable effects. In the case of suspected overdose the patient should be monitored. Lansoprazole is not significantly eliminated by haemodialysis. If necessary, gastric emptying, charcoal and symptomatic therapy is recommended.

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

Lansoprazole is a gastric proton pump inhibitor. It inhibits the final stage of gastric acid formation by inhibiting the activity of H+/K+ ATPase of the parietal cells in the stomach. The inhibition is dose dependent and reversible, and the effect applies to both basal and stimulated secretion of gastric acid. Lansoprazole is concentrated in the parietal cells and becomes active in their acidic environment, whereupon it reacts with the sulphydryl group of H+/K+ATPase causing inhibition of the enzyme activity.
Lansoprazole is a racemate of two active enantiomers that are biotransformed into the active form in the acidic environment of the parietal cells. As lansoprazole is rapidly inactivated by gastric acid, it is administered orally in enteric-coated form(s) for systemic absorption.

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription status	Additional information / Exemptions				
		Routes of administration	Comments	MS	MDD	MQP
Melclass database*	I (1)					
AT	II					
BE	I (POM)			30 mg	30 mg	15 g
CH	II			30 mg	30 mg / or 60 mg	1680 mg
CZ	I (POM)				60 mg	1680 mg
FR	II					
HR	I			30 mg	60 mg	1680 mg
IE	II					
IT	II			30 mg	30 mg	420 mg
MK	I (POM)			30 mg	It depends on indication	840 mg
Norway (NO)	II					
PL	I + Exemption Annex III (15mg)		Exemption: 15mg Short-term treatment symptoms of reflux oesophagitis, 14 days, adults only	OTC: 15 mg Rp: 30 mg	OTC: 15 mg Rp: 60 mg Z.E. syndr.: 180 mg	OTC: 210 mg Rp: 840 mg
PT	I (POM) + Exemption			60 mg	60 mg	3.6 g

	Annex III					
RO	II					
UK	I (POM)			30 mg	30 mg	840 mg

* Melclass database - Available at: http://www.edqm.eu/melclass/

No data available from other member states.

3.2 Member states' authorities' past or ongoing evaluation of the risk profile of the active ingredient for this therapeutic indication(s) (ATC code); abuse/misuse; efficiency: no

3.3 Social dimension of classification:

3.3.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Recommendation: List II

Justification:
Lansoprazole is classified as POM (list I or II) in the majority of the member states.

3.3.2 Paediatric use: the use of lansoprazole is not recommended in children as clinical data are limited. Treatment of small children below 1 year of age should be avoided as available data have not shown beneficial effects in the treatment of GORD.

3.3.3 Social dimension: N.A.

4. COMMENTS/REFERENCES

References:

1. Martindale 36 Edition
2. E-Medicines Compendium - https://www.medicines.org.uk/emc/
3. FDA approved drugs: Prevacid Dec.2014; and Prevacid 24hr (lansoprazole delayed release capsules 15 mg, acid reducer OTC - https://goo.gl/7PeJwD
4. EMEA: CHMP Summary Information on Referral Opinion Pursuant to Art.30 of Council Directive 2001/83/EC for Agopton and associated names (lansoprazole) 13. Dec.2006
5. Agopton orodispersible tablet, 30 mg SMPC adopted 23.10.2015, DE/H/1699/004/MR
6. Prescription only proton pump inhibitors (omeprazole, esomeprazole/naproxen, omeprazole/ketoprofen, esomeprazole, lansoprazole, pantoprazole, rabeprazole) and risk of fractures of the hip, wrist and spine - Final SmPC and PIL wording agreed by PhVWP March 2012
7. Class effects of proton-pump inhibitors (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, rabeprazole, pantoprazole) on magnesium blood levels in long-term users - Final SmPC and PIL wording agreed by PhVWP December 2011
8. PRAC recommendations on signals adopted at the PRAC meeting of 6-9 July 2015: recommendations for update of the product information (SmPC (both prescription and non-prescription)): dexlansoprazole; esomeprazole; lansoprazole; omeprazole; pantoprazole; rabeprazole – Subacute cutaneous lupus erythematosus.

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Rabeprazole

1.2 ATC Code: A02BC04 - Proton pump inhibitors

1.3 Therapeutic indications:

Adults:
Rabeprazole is indicated for the treatment of:

Active duodenal ulcer
Active benign gastric ulcer
Symptomatic erosive or ulcerative gastro-oesophageal reflux disease (GORD)
Gastro-oesophageal reflux disease long-term management (GORD Maintenance)
Symptomatic treatment of moderate to very severe gastro-oesophageal reflux disease (symptomatic GORD)
Zollinger-Ellison syndrome
In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* in patients with peptic ulcer disease.

1.4 Posology and duration of treatment:

Adults/elderly:

Active duodenal ulcer: the recommended oral dose for active duodenal ulcer is 20 mg to be taken once daily in the morning. Most patients with active duodenal ulcer heal within four weeks. However a few patients may require an additional four weeks of therapy to achieve healing.

Active benign gastric ulcer: the recommended oral dose for active benign gastric ulcer is 20 mg to be taken once daily in the morning. Most patients with active benign gastric ulcer heal within six weeks. However again a few patients may require an additional six weeks of therapy to achieve healing.

Erosive or ulcerative gastro-oesophageal reflux disease (GORD): the recommended oral dose for this condition is 20 mg to be taken once daily for four to eight weeks.

Gastro-oesophageal reflux disease long-term management (GORD Maintenance): for long-term management, a maintenance dose 20 mg or 10 mg once daily can be used depending upon patient response.

Symptomatic treatment of moderate to very severe gastro-oesophageal reflux disease (symptomatic GORD): 10 mg once daily in patients without oesophagitis. If symptom control has not been achieved during four weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using an on-demand regimen taking 10 mg once daily when needed.

Zollinger-Ellison syndrome: the recommended adult starting dose is 60 mg once a day. The dose may be titrated upwards to 120 mg/day based on individual patient needs. Single daily doses up to 100 mg/day may be given. 120 mg dose may require divided doses, 60 mg twice daily. Treatment should continue for as long as clinically indicated.

Eradication of H. pylori: patients with *H. pylori* infection should be treated with eradication therapy. The following combination given for 7 days is recommended: rabeprazole 20 mg twice daily + clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily.

Special populations:

Renal and hepatic impairment: no dosage adjustment is necessary for patients with renal and mild to moderate hepatic impairment. However, because there are no clinical data on the use of rabeprazole in the treatment of patients with severe hepatic dysfunction, caution is recommended when treatment is first initiated in such patients.

Paediatric population: rabeprazole is not recommended for use in children, as there is no experience of its use in this group.

FDA paediatric use:
Short term treatment of symptomatic GORD in adolescent patients 12 years of age and older: 20 mg once daily up to 8 weeks
- Treatment of GORD in pediatric patients 1-11 years of age:
< 15 kg: 5 mg once daily (with the option to increase to 10 mg once daily)
≥15 kg: 10 mg once daily for up to 12 weeks

1.5 Pharmaceutical forms: gastro-resistant tablets 10 and 20 mg

1.6 Contraindications: contra-indicated in patients with known hypersensitivity; contra-indicated in pregnancy and during breast feeding.

1.7 Relevant warnings: symptomatic response to therapy with rabeprazole sodium does not preclude the presence of gastric or oesophageal malignancy, therefore the possibility of malignancy should be excluded prior to commencing treatment.
Patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.
A risk of cross-hypersensitivity reactions with other proton pump inhibitor or substituted benzimidazoles cannot be excluded.
There have been post marketing reports of blood dyscrasias (thrombocytopaenia and neutropaenia). In the majority of cases where an alternative aetiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole.
Hepatic enzyme abnormalities have been seen in clinical trials and have also been reported since market authorisation. In the majority of cases, where an alternative aetiology cannot be identified, the events were uncomplicated and resolved on discontinuation of rabeprazole. No evidence of significant drug-related safety problems was seen in study of patients with mild to moderate hepatic impairment versus normal age and sex matched controls. However, because there are no clinical data on the use of rabeprazole in the treatment of patients with severe hepatic dysfunction, the prescriber is advised to exercise caution when treatment is first initiated in such patients.
Co-administration with atazanavir is not recommended.
Decreased gastric acidity due to any means, including proton pump inhibitors such as rabeprazole, increases counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may possibly increase the risk of gastrointestinal infections such as *Salmonella, Campylobacter* and *Clostridium difficile*.
Severe hypomagnesaemia has been reported in patients treated with PPIs like rabeprazole sodium for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.
Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

SCLE:
Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping rabeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors (PRAC recommendation - July 2015).

FDA Warnings:

Acute interstitial nephritis;
Cyanocobalamin (vit. B12) deficiency: daily long term use (e.g. longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin.

Interactions: rabeprazole sodium produces a profound and long lasting inhibition of gastric acid secretion. An interaction with compounds whose absorption is pH dependent may occur. Co-administration of rabeprazole sodium with ketoconazole or itraconazole may result in a significant decrease in antifungal plasma levels. Therefore individual patients may need to be monitored to determine if a dosage adjustment is necessary when ketoconazole or itraconazole are taken concomitantly. In clinical trials, antacids were used concomitantly with the administration of rabeprazole and, in a specific drug-drug interaction study, no interaction with liquid antacids was observed.

Co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg once daily) to healthy volunteers resulted in a substantial reduction in atazanavir exposure. The absorption of atazanavir is pH dependent. Although not studied, similar results are expected with other proton pump inhibitors. Therefore PPIs, including rabeprazole, should not be co-administered with atazanavir.

When methotrexate is given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of rabeprazole may need to be considered.

FDA interactions: warfarin: there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly (in such patients monitoring of INR and prothrombin time may be needed).

Pregnancy: there are no data on the safety of rabeprazole in human pregnancy. Rabeprazole is contraindicated during pregnancy.

Breast-feeding: it is not known whether rabeprazole sodium is excreted in human breast milk. No studies in lactating women have been performed. Therefore rabeprazole must not be used during breast feeding.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (Pharmacovigilance):

The most commonly reported adverse drug reactions, during controlled clinical trials with rabeprazole were headache, diarrhoea, abdominal pain, asthenia, flatulence, rash and dry mouth. The majority of adverse events experienced during clinical studies were mild or moderate in severity, and transient in nature.

The following adverse events have been reported from clinical trial and post-marketed experience:

Infections and infestations:
Common: infection.

Blood and the lymphatic system disorders:
Rare: neutropaenia, leucopaenia, thrombocytopenia, leukocytosis.

Immune system disorders:
Rare: hypersensitivity (facial swelling, hypotension and dyspnoea).

Metabolism and nutrition disorders:
Rare: anorexia;
Not known: hyponatremia, hypomagnesaemia.

Psychiatric disorders:

Common: insomnia;
Uncommon: nervousness;
Rare: depression;
Not known: confusion.

Nervous system disorders:
Common: headache, dizziness;
Uncommon: somnolence.

Eye disorders:
Rare: visual disturbance

Vascular disorders:
Not known: peripheral oedema.

Respiratory, thoracic and mediastinal disorders:
Common: cough, pharyngitis, rhinitis;
Uncommon: bronchitis, sinusitis.

Gastrointestinal disorders:
Common: diarrhoea, vomiting, nausea, abdominal pain, constipation, flatulence;
Uncommon: dyspepsia, dry mouth, eructation;
Rare: gastritis, stomatitis, taste disturbance.

Hepatobiliary disorders:
Rare: hepatitis, jaundice, hepatic encephalopathy.

Skin and subcutaneous tissue disorders:
Uncommon: rash, erythema;
Rare: pruritus, sweating, bullous reactions;
Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis;
Not known: subacute cutaneous lupus erythematosus.

Musculoskeletal, connective tissue and bone disorders:
Common: non-specific pain, back pain;
Uncommon: myalgia, leg cramps, arthralgia, fracture of the hip, wrist or spine

Renal and urinary disorders:
Uncommon: urinary tract infection;
Rare: interstitial nephritis.

Reproductive system and breast disorders:
Not known: gynaecomastia.

General disorders and administration site conditions:
Common: asthenia, influenza like illness;
Uncommon: chest pain, chills, pyrexia.

Investigations:
Uncommon: increased hepatic enzymes;
Rare: weight increased.

2.1.1 Recent cases at European level:

PhVWP March 2011 – final SmPC and PIL wording agreed for class effect of PPIs (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, rabeprazole, pantoprazole) on magnesium blood levels in long term users.

PhVWP March 2012 – final SmPC and PIL wording agreed for prescription only PPIs (omeprazole, esomeprazole/naproxen, omeprazole/ketoprofen, esomeprazole, lansoprazole, pantoprazole,

rabeprazole) and risk of fractures of the hip, wrist and spine.

PRAC recommendations on signals adopted at the PRAC meeting of 6-9 July 2015: recommendations for update of the product information (SmPC (both prescription and non-prescription)): dexlansoprazole; esomeprazole; lansoprazole; omeprazole; pantoprazole; rabeprazole – subacute cutaneous lupus erythematosus.

2.1.2 Indirect risks (incorrect use):
Experience to date with deliberate or accidental overdose is limited. The maximum established exposure has not exceeded 60 mg twice daily, or 160 mg once daily. Effects are generally minimal, representative of the known adverse event profile and reversible without further medical intervention. No specific antidote is known. Rabeprazole sodium is extensively protein bound and is, therefore, not dialysable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

Rabeprazole sodium belongs to the class of anti-secretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H2 histamine antagonist properties, but suppress gastric acid secretion by the specific inhibition of the H+/K+-ATPase enzyme (the acid or proton pump). The effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after administration, rabeprazole sodium rapidly disappears from both the plasma and gastric mucosa. As a weak base, rabeprazole is rapidly absorbed following all doses and is concentrated in the acid environment of the parietal cells. Rabeprazole is converted to the active sulphenamide form through protonation and it subsequently reacts with the available cysteines on the proton pump.

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription status	Additional information / Exemptions				
		Routes of administration	Comments	MS	MDD	MQP
Melclass database*	I (1)					
AT	II					
BE	I (POM)			20 mg	20 mg	24 g
CH	II			20 mg	20 mg / ev. 2x20 mg	1120 mg
CZ	I (POM)					
FR	II					
HR	Not authorised					
IE	II					
IT	II			20 mg	20 mg	280 mg
MK	Not authorised					
PL	I (POM)			20 mg	20 mg / 60 mg in Z-Es	1120 mg
PT	I (POM)			20 mg	20 mg	1.2 g
RO	II					
UK	I + Exemption Annex III		Max 14 days	20 mg		

* Melclass database - Available at: http://www.edqm.eu/melclass/

No data available from other member states.

3.2 Member states' authorities' past or ongoing evaluation of the risk profile of the active ingredient for this therapeutic indication(s) (ATC code); abuse/misuse; efficiency: no

3.3 Social dimension of classification

3.3.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Recommendation: List II

Justification:
Rabeprazole is classified under list II or list I (POM) in the majority of member states.

3.3.2 Paediatric use: rabeprazole is not recommended for use in children, as there is no experience of its use in this group.

3.3.3 Social dimension: N.A.

4. COMMENTS/REFERENCES

References:

1. Martindale 36 Edition
2. E-Medicines Compendium - https://www.medicines.org.uk/emc/
3. FDA Aciphex prescribing information, 19.12.2014 - https://goo.gl/vYELU3
4. SmPC for rabeprazole AT/H/0261-0262/001-002/R 001, 05.03.2014 CMS: CZ, FR, HU, NL, PT, SL, ES Rapporteur's Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended UK/W/045/pdWS/001Rabeprazole - Rapporteur: UK [Pariet Aciphex, MAH Eisai, gastro-resistant tablets 10 and 20 mg, published 30.01.2013
5. PRAC recommendations on signals adopted at the PRAC meeting of 6-9 July 2015: recommendations for update of the product information (SmPC (both prescription and non-prescription)): dexlansoprazole; esomeprazole; lansoprazole; omeprazole; pantoprazole; rabeprazole – subacute cutaneous lupus erythematosus.

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Esomeprazole

1.2 ATC Code: A02BC05 - Proton pump inhibitors

1.3 Therapeutic indications:

Adults
Gastro-oesophageal reflux disease (GORD);
- treatment of erosive reflux oesophagitis;
- long-term management of patients with healed oesophagitis to prevent relapse;
- symptomatic treatment of GORD.

In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* and
- healing of *Helicobacter pylori* associated duodenal ulcer;
- 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.

Prolonged treatment after IV induced prevention of re-bleeding of peptic ulcers. Treatment of Zollinger Ellison syndrome.

Paediatric use

Children below the age of 1 year: the experience of treatment with esomeprazole in infants < 1 year is limited and treatment is therefore not recommended.

Children 1-11 years old:
GORD
- treatment of endoscopically proven erosive reflux oesophagitis;
- symptomatic treatment of GORD.

Children over 4 years of age
In combination with antibiotics in treatment of duodenal ulcer caused by *Helicobacter pylori.*

Adolescents from the age of 12 years:
GORD
- treatment of erosive reflux oesophagitis;
- long-term management of patients with healed oesophagitis to prevent relapse;
- symptomatic treatment of GORD.
In combination with antibiotics in treatment of duodenal ulcer caused by *Helicobacter pylori*.

1.4 Posology and duration of treatment:

Adults:

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 GORD: 20 mg once daily in patients without oesophagitis. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily. An on-demand regimen

taking 20 mg once daily, when needed, can be used. In NSAID treated patients at risk of developing gastric and duodenal ulcers, subsequent symptom control using an on-demand regimen is not recommended.

In combination with appropriate antibacterial therapeutic regimens 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 esomeprazole 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.

Prolonged treatment after IV. induced prevention of rebleeding of peptic ulcers: 40 mg once daily for 4 weeks after IV induced prevention of rebleeding of peptic ulcers.

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

Special Populations:

Patients with 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.

Patients with 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 should not be exceeded.

Older people: dose adjustment is not required in the elderly.

Pregnancy: caution should be exercised when prescribing to pregnant women.

Breast-feeding: esomeprazole should not be used during breast-feeding.

Children:

Children 1 – 11 years with a body weight of ≥10 kg

GORD
- Treatment of endoscopically proven erosive reflux oesophagitis
Weight ≥ 10- < 20 kg: 10 mg once daily for 8 weeks.
Weight ≥ 20 kg: 10 mg or 20 mg once daily for 8 weeks.

- Symptomatic treatment of GORD: 10 mg once daily for up to 8 weeks.
Doses over 1 mg/kg/day have not been studied.

Children over 4 years of age

Treatment of duodenal ulcer caused by Helicobacter pylori: when selecting appropriate combination therapy, consideration should be given to official national, regional and local guidance regarding bacterial resistance, duration of treatment (most commonly 7 days but sometimes up to 14 days), and appropriate use of antibacterial agents. The treatment should be supervised by a specialist.

The posology recommendation is:

Weight	Posology
< 30 kg	Combination with two antibiotics: esomeprazole 10 mg, amoxicillin 25 mg/kg body weight and clarithromycin 7.5 mg/kg body weight are all administered together twice daily for one week.
30 – 40 kg	Combination with two antibiotics: esomeprazole 20 mg, amoxicillin 750 mg and clarithromycin 7.5 mg/kg body weight are all administered together twice daily for one week.
> 40 kg	Combination with two antibiotics: esomeprazole 20 mg, amoxicillin 1 g and clarithromycin 500 mg are all administered together twice daily for one week.

Adolescents from the age of 12 years

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 GORD: 20 mg once daily in patients without oesophagitis. If symptom control has not been achieved after 4 weeks, the patient should be further investigated. Once symptoms have resolved, subsequent symptom control can be achieved using 20 mg once daily.

FDA pediatric use:
1 – 11 years of age:
Short term treatment of symptomatic GORD: 10 mg once daily up to 8 weeks
Healing of erosive oesophagitis:
< 20 kg: 10 mg once daily for 8 weeks
≥ 20 kg: 20 mg once daily for 8 weeks
12 – 17 years of age:
Symptomatic GORD: 20 mg once daily for 4 weeks
Healing of erosive oesophagitis: 20 or 40 mg once daily for 4 to 8 weeks

IV use (for injection and infusion):

Adults:

- Gastric antisecretory treatment when the oral route is not possible, such as GORD in patients with oesophagitis and/or severe symptoms of reflux; healing of gastric ulcers associate with NSAID therapy; prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk; prevention of re-bleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

Children and adolescents aged 1-18 years:

- Gastric antisecretory treatment when the oral route is not possible, such as GORD in patients with erosive reflux oesophagitis and/or severe symptoms of reflux.

IV Posology

Adults:

- Gastric antisecretory treatment when the oral route is not possible: patients who cannot take oral medication may be treated parenterally with 20–40 mg once daily. Patients with reflux oesophagitis should be treated with 40 mg once daily. Patients treated symptomatically for reflux disease should be treated with 20 mg once daily.

For healing of gastric ulcers associated with NSAID therapy the usual dose is 20 mg once daily. For prevention of gastric and duodenal ulcers associated with NSAID therapy, patients at risk should be treated with 20 mg once daily.
Usually the intravenous treatment duration is short and transfer to oral treatment should be made as soon as possible.

Prevention of re-bleeding of gastric and duodenal ulcers: following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers, 80 mg should be administered as a bolus infusion over 30 minutes, followed by a continuous intravenous infusion of 8 mg/h given over 3 days (72 hours). The parenteral treatment period should be followed by oral acid suppression therapy.

IV Posology Children and adolescents aged 1-18 years

Gastric antisecretory treatment when the oral route is not possible: patients who cannot take oral medication may be treated parenterally once daily, as a part of a full treatment period for GORD (see doses in table below). Usually the intravenous treatment duration should be short and transfer to oral treatment should be made as soon as possible.

Recommended intravenous doses of esomeprazole in children:

Age group	Treatment of erosive reflux oesophagitis	Symptomatic treatment of GORD
1-11 Years	Weight <20 kg: 10 mg once daily Weight ≥20 kg: 10 mg or 20 mg once daily	10 mg once daily
12-18 Years	40 mg once daily	20 mg once daily

OTC indication and posology
Esomeprazole is indicated for short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitations) **in adults.**

The **recommended dose is 20 mg esomeprazole** (one tablet) per day. It might be necessary to take tablets for 2-3 consecutive days to achieve improvement of symptoms. The duration of treatment is up 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, patient should be instructed to consult a doctor.

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

Patients with long-term recurrent symptoms of indigestion or heartburn should see their doctor at regular intervals. Patients over 55 years taking any non-prescription indigestion or heartburn remedy on a daily basis should inform their pharmacist or doctor.
Patients should not take esomeprazole as a long term preventive medicinal product.

1.5 Pharmaceutical forms:
Gastro-resistant granules for oral suspension, sachet 10 mg
Gastro resistant tablet 20 and 40 mg
Powder for solution for infusion 40 mg

1.6 Contraindications: hypersensitivity to the active substance, to substituted benzimidazoles. Esomeprazole should not be used concomitantly with nelfinavir.

1.7 Relevant warnings: 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 esomeprazole may alleviate symptoms and delay diagnosis.
Long term use: patients on long-term treatment (particularly those treated for more than a year) should be kept under regular surveillance.

On demand treatment: patients on on-demand treatment should be instructed to contact their physician if their symptoms change in character.

Helicobacter pylori eradication: 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.

Gastrointestinal infections: treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Absorption of vitamin B12: esomeprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B12 (cyanocobalamin) due to hypo- or achlorhydria. This should be considered in patients with reduced body stores or risk factors for reduced vitamin B12 absorption on long-term therapy.

Hypomagnesaemia: severe hypomagnesaemia has been reported in patients treated with PPIs like esomeprazole for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.
For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), healthcare professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Risk of fracture: proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

SCLE:
Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping esomeprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors (PRAC recommendation – July 2015).

Combination with other medicinal products

Co-administration of esomeprazole with atazanavir is not recommended. If the combination of atazanavir with a proton pump inhibitor 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 drugs metabolised through CYP2C19 should be considered. An interaction is observed between clopidogrel and esomeprazole. The clinical relevance of this interaction is uncertain. As a precaution, concomitant use of esomeprazole and clopidogrel should be discouraged. When prescribing esomeprazole for on-demand therapy, the implications for interactions with other pharmaceuticals, due to fluctuating plasma concentrations of esomeprazole should be considered.

Interference with laboratory tests: increased Chromogranin A(CgA) level may interfere with investigations for neuroendocrine tumors. To avoid this interference, esomeprazole treatment should be stopped for at least 5 days before CgA measurements.

FDA warning: acute interstitial nephritis.

Effects of esomeprazole on the pharmacokinetics of other drugs:

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 CYP 2C19.
For atazanavir and nelfinavir, 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.

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. As with other medicinal products that decrease intragastric acidity, the absorption of medicinal products such as ketoconazole, itraconazole and erlotinib can decrease 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 drugs metabolised by CYP2C19, 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.

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

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

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

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

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

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 coumarin derivatives.

Clopidogrel
Results from studies in healthy subjects have shown a pharmacokinetic (PK)/(PD) interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg PO.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%.
When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were the same in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups. Inconsistent data on the clinical implications of a PK/PD interaction of esomeprazole in terms of major cardiovascular events have been reported from both observational and clinical studies. As a precaution concomitant use of clopidogrel should be discouraged.

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

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (Pharmacovigilance):

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. The following adverse drug reactions have been identified or suspected in the clinical trials for esomeprazole and post-marketing. None was found to be dose-related.

Blood and lymphatic system disorders:
Rare: leukopenia, thrombocytopenia;
Very rare: agranulocytosis, pancytopenia.

Immune system disorders:
Rare: hypersensitivity reactions e.g. fever, angioedema and anaphylactic reaction/shock.

Metabolism and nutrition disorders:
Uncommon: peripheral oedema;
Rare: hyponatraemia;
Not known: hypomagnesaemia; severe hypomagnesaemia may correlate with hypocalcaemia. Hypomagnesaemia may also be associated with hypokalaemia.

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;
Not known: microscopic colitis.

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, urticarial;
Rare: alopecia, photosensitivity;
Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN);
Not known: subacute cutaneous lupus erythematosus.

Musculoskeletal and connective tissue disorders:
Uncommon: fracture of the hip, wrist or spine;
Rare: arthralgia, myalgia;
Very rare: muscular weakness.

Renal and urinary disorders:
Rare: interstitial nephritis; in some patients renal failure has been reported concomitantly.

Reproductive system and breast disorders:
Very rare: gynaecomastia.

General disorders and administration site conditions:
Rare: malaise, increased sweating.

2.1.1 Recent cases at European level:
PhVWP March 2011 – final SmPC and PIL wording agreed for class effect of PPIs (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, rabeprazole, pantoprazole) on magnesium blood levels in long term users.

PhVWP March 2012 – final SmPC and PIL wording agreed for prescription only PPIs (omeprazole, esomeprazole/naproxen, omeprazole/ketoprofen, esomeprazole, lansoprazole, pantoprazole, rabeprazole) and risk of fractures of the hip, wrist and spine.

PRAC recommendations on signals adopted at the PRAC meeting of 6-9 July 2015: recommendations for update of the product information (SmPC (both prescription and non-prescription)): dexlansoprazole; esomeprazole; lansoprazole; omeprazole; pantoprazole; rabeprazole – subacute cutaneous lupus erythematosus.

2.1.2 Indirect risks (incorrect use): overdose: there is very limited experience to date with deliberate overdose. The symptoms described in connection with 280 mg 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.

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

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. Esomeprazole is acid labile and is administered orally as enteric-coated granules. Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription status	Additional information / Exemptions				
		Routes of administration	Comments	MS	MDD	MQP
Melclass database*	I (1)					
AT	II + Exemption Annex III	Oral use		20 mg	20 mg	
BE	I (POM)			40 mg	40 mg	20 g
CH	II + Exemption Annex III			Ex.: 20 mg 40 mg	Ex.: 20 mg 40 mg, ev. 2x40mg	3920 mg
CZ	I + Exemption Annex III (Ex.: MS: 20 mg)			20 mg		
FR	II					
HR	I + Exemption Annex III (Ex.: MS: 20 mg)					
IE	II + Exemption Annex III	Ex.: short-term treatment of reflux symptoms		20 mg	20 mg	
IT	II			40 mg	40 mg	560 mg
MK	I (POM)			40 mg	It depends on indication	1.2 mg
PL	I + Exemption Annex III (Ex.: MS: 20 mg)	OTC: short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitations) in adults; no longer than 14 days		Rp. 40 mg OTC 20mg	Rp 40 mg/160 mg in Z-E syndrome/80mg IV OTC 20 mg	RP 2240 mg OTC 280mg
PT	I + Exemption Annex III (Ex.: MS: 20 mg)	Restricted prescription for IV use		40 mg	40mg/80 mg/160 mg	2.24 g
RO	II					

* Melclass database - Available at: http://www.edqm.eu/melclass/

No data available from other member states.

3.2 Member states' authorities' past or ongoing evaluation of the risk profile of the active ingredient for this therapeutic indication(s) (ATC code); abuse/misuse; efficiency: no

3.3 Social dimension of classification:

3.3.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Recommendation: List II + Exemption Annex III

Exemptions:

- Adults only
- For short-term treatment of reflux symptoms (e.g. heartburn and acid regurgitations)
- No longer than 14 days
- MS: 20 mg
- MDD: 20 mg

For more information > see OTC treatment

Justification:
- According to EMA recommendations;
- Esomeprazole is classified under list II + Exemption Annex III in the majority of member states.

3.3.2 Paediatric use: Paediatric population POM only.

3.3.3 Social dimension: N.A.

4. COMMENTS/REFERENCES

References:

1. Martindale 36 Edition
2. E-Medicines Compendium (Nexium) - https://www.medicines.org.uk/emc/
3. Prescription only proton pump inhibitors (omeprazole, esomeprazole/naproxen, omeprazole/ketoprofen, esomeprazole, lansoprazole, pantoprazole, rabeprazole) and risk of fractures of the hip, wrist and spine. Final SmPC and PIL wording agreed by PhVWP March 2012
4. Class effects of proton-pump inhibitors (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, rabeprazole, pantoprazole) on magnesium blood levels in long - term users. Final SmPC and PIL wording agreed by PhVWP December 2011
5. FDA – approved drugs (Esomeprazole magnesium, delayed release capsules 20 and 40 mg) label information - https://goo.gl/7PeJwD
6. Nexium SmPC (13.08.2014) MR Number: SE/H/0211/001 - Nexium Control 20 mg gastro-resistant tablet, oral use, EMA: EU/1/13/860/001-002; EPAR: procedure no EMEA/H/C/002618
7. PRAC recommendations on signals adopted at the PRAC meeting of 6-9 July 2015: recommendations for update of the product information (SmPC (both prescription and non-prescription)): dexlansoprazole; esomeprazole; lansoprazole; omeprazole; pantoprazole; rabeprazole – subacute cutaneous lupus erythematosus.

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Dexlansoprazole

1.2 ATC Code: A02BC06 - Proton pump inhibitors

1.3 Therapeutic indications:

Adults:
- treatment of erosive reflux oesophagitis;
- maintenance of healed erosive reflux oesophagitis and maintenance of relief of heartburn;
- short-term treatment of heartburn and acid regurgitation associated with symptomatic non-erosive gastro-oesophageal reflux disease (GORD).

1.4 Posology and duration of treatment:

Adults

Treatment of erosive reflux oesophagitis: the recommended dose is 60 mg once daily for 4 weeks. In patients not fully healed within this time, the treatment may be continued at the same dose for another 4 weeks.

Maintenance of healed erosive reflux oesophagitis and maintenance of relief of heartburn: the recommended dose is 30 mg once daily for up to 6 months in patients where prolonged acid suppression is needed.

Symptomatic non-erosive gastro-oesophageal reflux disease (GORD): the recommended dose is 30 mg once daily for up to 4 weeks.

Special populations

Elderly: due to reduced clearance of dexlansoprazole in the elderly an adjustment of dose may be necessary based on individual requirements. A daily dose of 60 mg should not be exceeded in the elderly unless there are compelling clinical indications.

Renal impairment: no dosage adjustment is necessary for patients with renal impairment.

Hepatic impairment: no dosage adjustment is necessary for patients with mild hepatic impairment. Patients with moderate hepatic impairment should be kept under regular supervision and a maximum daily dose of 30 mg should be considered. No studies have been conducted in patients with severe hepatic impairment, the use of dexlansoprazole is not recommended for these patients.

Paediatric population: the safety and efficacy of dexlansoprazole in children and adolescents under 18 years of age have not been established. No data are available.

Pregnancy: there are no or limited amount of data from the use of dexlansoprazole in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of dexlansoprazole during pregnancy.

Breastfeeding: it is not known whether dexlansoprazole is excreted in human breast milk. Animal studies have shown excretion of lansoprazole in milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

1.5 Pharmaceutical forms: modified release capsules 30 and 60 mg

1.6 Contraindications: hypersensitivity to the dexlansoprazole. Dexlansoprazole should not be administered with atazanavir or nelfinavir.

1.7 Relevant warnings: the possibility of malignant gastric tumor should be excluded when using

dexlansoprazole because dexlansoprazole can mask the symptoms and delay the diagnosis.

Dexlansoprazole should be used with caution in patients with moderate hepatic dysfunction. Dexlansoprazole is not recommended for patients with severe hepatic impairment.

Decreased gastric acidity due to any means, including PPIs such as dexlansoprazole, 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*, *Campylobacter* and *Clostridium difficile*.

Because of limited safety data for patients on treatment for longer than 1 year, regular review of the treatment and a thorough risk/benefit assessment should regularly be performed in these patients.

Severe hypomagnesaemia has been reported in patients treated with PPIs like dexlansoprazole for at least three months, in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI. For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Very rarely cases of colitis have been reported in patients taking lansoprazole. Similar effects could be expected with dexlansoprazole. Therefore, in the case of severe and/or persistent diarrhoea, discontinuation of therapy should be considered.

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

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

SCLE:
Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun-exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the health care professional should consider stopping dexlansoprazole. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors (PRAC recommendation - July 2015).

FDA Warnings:
Acute interstitial nephritis
Cyanocobalamin (vit. B12) deficiency: daily long term use (e.g. longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin.

Interactions:

Interaction studies have only been performed in adults.

Effects of other drugs on dexlansoprazole

CYP2C19 and CYP3A4 have been shown to be involved in the metabolism of dexlansoprazole.

Drugs which inhibit CYP2C19: inhibitors of CYP2C19 (such as fluvoxamine) would likely increase the systemic exposure of dexlansoprazole.

Drugs which induce CYP2C19 and CYP3A4: enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin, and St John´s wort (*Hypericum perforatum*) may reduce the plasma concentrations of dexlansoprazole.

Others:
Sucralfate/Antacids: Sucralfate/Antacids may decrease the bioavailability of dexlansoprazole. Therefore dexlansoprazole should be taken at least 1 hour after taking these drugs.

Effects of dexlansoprazole on other drugs:

Medicinal products with pH dependent absorption: Dexlansoprazole may interfere with the absorption of drugs where gastric pH is critical to bioavailability.

Atazanavir and nelfinavir: A study has shown that co-administration of lansoprazole (60 mg once daily) with atazanavir 400 mg to healthy volunteers resulted in a substantial reduction in atazanavir exposure (approximately 90% decrease in AUC and Cmax). Similar effect would be expected with dexlansoprazole. Dexlansoprazole should not be co-administered with atazanavir.
A study has shown that co-administration of omeprazole (40 mg once daily) with nelfinavir 1250 mg twice daily to healthy volunteers resulted in a significant reduction in nelfinavir exposure (approximately 36% and 37% decrease in AUC and Cmax, respectively). Although interaction studies with dexlansoprazole have not been conducted, reduction of AUC and Cmax of nelfinavir may be expected with dexlansoprazole. Therefore, dexlansoprazole should not be co-administered with nelfinavir.

Ketoconazole, itraconazole and erlotinib: The absorption of ketoconazole, itraconazole and erlotinib from the gastrointestinal tract is enhanced by the presence of gastric acid. Administration of dexlansoprazole may result in sub-therapeutic concentrations of ketoconazole, itraconazole and erlotinib, and the combination should be avoided.

Digoxin: co-administration of dexlansoprazole and digoxin may lead to increased digoxin plasma levels. The plasma levels of digoxin should therefore be monitored and the dose of digoxin adjusted if necessary when initiating and ending dexlansoprazole treatment.

Medicinal products metabolised by P450 enzymes: *in vitro* studies have shown that dexlansoprazole is not likely to inhibit CYP isoforms 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1 or 3A4. As such, no clinically relevant interactions with drugs metabolised by these CYP enzymes would be expected.
Furthermore, *in vivo* studies showed that dexlansoprazole did not have an impact on the pharmacokinetics of coadministered phenytoin (CYP2C9 substrate) or theophylline (CYP1A2 substrate). The subjects' CYP1A2 genotypes in the drug–drug interaction study with theophylline were not determined.
Although *in vitro* studies demonstrated that dexlansoprazole has the potential to inhibit CYP2C19, an *in vivo* drug–drug interaction study in mainly CYP2C19 extensive and intermediate metabolisers has shown that dexlansoprazole does not affect the pharmacokinetics of diazepam (CYP2C19 substrate).

Tacrolimus: co-administration of dexlansoprazole may increase the plasma concentrations of tacrolimus (a CYP3A and P-glycoprotein [P-gp] substrate), especially in transplant patients who are intermediate or poor metabolisers of CYP2C19. Monitoring of tacrolimus plasma concentrations is advised when concomitant treatment with dexlansoprazole is initiated or ended.

Warfarin: in a study, co-administration of dexlansoprazole and warfarin did not result in any significant differences in the pharmacokinetics of warfarin or INR compared to administration of warfarin with placebo. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Clopidogrel: a study has shown that concomitant administration of dexlansoprazole (60 mg once daily) and clopidogrel 75 mg to healthy volunteers resulted in a reduction in the exposure to the active metabolite of clopidogrel (approximately 9% decrease in AUC and 27% decrease in C_{max}). Co-administration of dexlansoprazole had no clinically meaningful effect on pharmacodynamics of clopidogrel. No dose adjustment of clopidogrel is necessary when administered with an approved dose of dexlansoprazole.

Methotrexate: case reports, published population pharmacokinetic studies, and retrospective analyses

suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of high-dose methotrexate with PPIs have been conducted.

Medicinal products transported by P-glycoprotein: lansoprazole has been observed to inhibit the transport protein, P-gp *in vitro.* Similar effects could be expected with dexlansoprazole. The clinical relevance of this is unknown.
Others: no clinically significant interactions of dexlansoprazole with nonsteroidal anti-inflammatory drugs have been demonstrated, although no formal interactions studies have been performed.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (Pharmacovigilance):

Dexlansoprazole at doses of 30, 60, or 90 mg has been evaluated for safety in clinical studies in patients treated for up to 1 year. In these clinical studies, adverse reactions associated with treatment with dexlansoprazole were mostly mild or moderate, with an overall incidence similar to placebo and lansoprazole. The most commonly reported adverse reactions were diarrhoea, abdominal pain, headache, nausea, abdominal discomfort, flatulence and constipation. The incidence of these adverse reactions was not affected by gender, age, or race.

Adverse reactions reported for dexlanzoprazole (30 mg, 60 mg or 90 mg) in clinical studies and post-marketing experience are listed below:

Blood and lymphatic system disorders:
Not known: autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura.

Immune system disorders:
Not known: anaphylactic reaction, hypersensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), anaphylactic shock.

Metabolism and nutrition disorders:
Not known: hypomagnesaemia.

Musculoskeletal and connective tissue disorders:
Uncommon: fracture of the hip, wrist or spine.

Psychiatric disorders:
Uncommon: insomnia, depression;
Rare: auditory hallucinations.

Nervous system disorders:
Common: headache;
Uncommon: dizziness, altered taste;
Rare: convulsion, paraesthesia.

Eye disorders:
Rare: visual disturbances;
Not known: blurred vision.

Ear and labyrinth disorders:
Rare: vertigo;
Not known: deafness.

Gastrointestinal disorders:
Common: diarrhoea, abdominal pain, nausea, abdominal discomfort, flatulence, constipation;
Uncommon: vomiting, dry mouth.
Rare: candidiasis.

Hepatobiliary disorders:
Uncommon: liver function tests abnormal;
Not known: hepatitis drug induced.

Skin and subcutaneous tissue disorders:
Uncommon: urticaria, pruritus, rash;
Not known: subacute cutaneous lupus erythematosus.

Renal and urinary disorders:
Rare: interstitial nephritis.

Respiratory, thoracic and mediastinal disorders:
Uncommon: cough.

Vascular disorders:
Uncommon: hypertension, hot flushes.

General disorders and administration site conditions:
Uncommon: asthenia, appetite changes.

Description of selected adverse reactions

Diarrhoea and abdominal pain: in Phase 3 clinical studies, the most commonly reported adverse reaction was diarrhoea (excluding infective diarrhoea), the majority of which were non-serious. Overall, few subjects (2.4%) prematurely discontinued due to an adverse reaction while receiving dexlansoprazole therapy. The most common (≥ 0.5%) adverse reactions leading to premature discontinuation were diarrhoea, gastrointestinal and abdominal pains. Initial onset of diarrhoea and abdominal pain was independent of the duration of exposure, and the majority of these events were mild to moderate in severity. There were no apparent dose-related trends observed across dexlansoprazole doses for the incidence of these events.

Hypersensitivity: there have been post-marketing cases reporting serious hypersensitivity reactions. Hypersensitivity reactions were more frequently reported in females (74%). The majority of the serious cases were managed with steroids and/or antihistamines and withdrawal of the medicinal product. Severe reactions of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) were reported in few patients.

Haemolytic anaemia: there have been few serious post-marketing reports of haemolytic anaemia after approximately four to seven months on dexlansoprazole 60 mg therapy.

2.1.1 Recent cases at European level:

PhVWP March 2011 – final SmPC and PIL wording agreed for class effect of PPIs (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, rabeprazole, pantoprazole) on magnesium blood levels in long term users.

PhVWP March 2012 – final SmPC and PIL wording agreed for prescription only PPIs (omeprazole, esomeprazole/naproxen, omeprazole/ketoprofen, esomeprazole, lansoprazole, pantoprazole, rabeprazole) and risk of fractures of the hip, wrist and spine.

PRAC recommendations on signals adopted at the PRAC meeting of 6-9 July 2015: recommendations for update of the product information (SmPC (both prescription and non-prescription)): dexlansoprazole; esomeprazole; lansoprazole; omeprazole; pantoprazole; rabeprazole – subacute cutaneous lupus erythematosus.

2.1.2 Indirect risks (incorrect use): the effects of overdose of dexlansoprazole in humans are not known (although the acute toxicity is likely to be low) and, consequently, instruction for treatment cannot be given. There have been no reports of significant overdose of dexlansoprazole. Multiple doses of dexlansoprazole 120 mg and a single dose of dexlansoprazole 300 mg did not result in death or other severe adverse events. Serious adverse reactions of hypertension have been reported in

association with twice daily doses of dexlansoprazole 60 mg. Non-serious adverse reactions observed with twice daily doses of dexlansoprazole 60 mg include hot flushes, contusion, oropharyngeal pain, and weight loss. In the case of suspected overdose the patient should be monitored. Dexlansoprazole is not significantly eliminated by haemodialysis. If necessary, gastric emptying, charcoal and symptomatic therapy is recommended.

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

Dexlansoprazole is the R-enantiomer of lansoprazole. It is a gastric PPI. It inhibits the final stage of gastric acid formation by inhibiting the activity of H+/K+ ATPase of the parietal cells in the stomach. The inhibition is dose-dependent and reversible, and the effect applies to both basal and stimulated secretion of gastric acid. Dexlansoprazole is concentrated in the parietal cells and becomes active in their acidic environment, whereupon it reacts with the sulphydryl group of H+/K+ATPase causing inhibition of the enzyme activity.

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription status	Additional information / Exemptions				
		Routes of administration	Comments	MS	MDD	MQP
Melclass database*	I (1)					
AT	Not authorised					
BE	I (POM)			60 mg	60 mg	1.68 g
CH	II			60 mg	60 mg	3360 mg
CZ	Not authorised					
FR	Not authorised					
HR	Not authorised					
HU	POM					
IE	Not authorised					
IT	II	Approved, but not marketed		30 mg	60 mg	420 mg
MK	Not authorised					
PL	I			60 mg	60 mg	1680 mg
PT	POM	Approved but not marketed				
UK	POM					

* Melclass database - Available at: http://www.edqm.eu/melclass/

No data available from other member states.

3.2 Member states' authorities' past or ongoing evaluation of the risk profile of the active ingredient for this therapeutic indication(s) (ATC code); abuse/misuse; efficiency: no

3.3 Social dimension of classification:

3.3.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Recommendation: List I

Justification: in most member states dexlansoprazole is not marketed or classified under list I (POM). No changes in the classification is proposed.

3.3.2 Paediatric use: the safety and efficacy of dexlansoprazole in children and adolescents under 18 years of age have not been established. No data are available.

3.3.3 Social dimension: N.A.

4. COMMENTS/REFERENCES

References:

1. SmPC for Dexilant (10.09.2013) MPA - SE DC(PT/H/0858/001-002) CMS: AT, BE, FR, DE, GR, HU, IR, IT, LV, LT, PL, RO, SK, ES, SE
2. PhVWPMarch 2011 – final SmPC and PIL wording agreed for class effect of PPIs (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, rabeprazole, pantoprazole) on magnesium blood levels in long term users
3. PhVWP March 2012 – final SmPC and PIL wording agreed for prescription only PPIs (omeprazole, esomeprazole/naproxen, omeprazole/ketoprofen, esomeprazole, lansoprazole, pantoprazole, rabeprazole) and risk of fractures of the hip, wrist and spine
4. FDA approved drugs Dexilant 30 and 60 mg delayed release capsules – prescribing information - https://goo.gl/7PeJwD
5. PRAC recommendations on signals adopted at the PRAC meeting of 6-9 July 2015: recommendations for update of the product information (SmPC (both prescription and non-prescription)): dexlansoprazole; esomeprazole; lansoprazole; omeprazole; pantoprazole; rabeprazole – subacute cutaneous lupus erythematosus.

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Dexrabeprazole

1.2 ATC Code: A02BC07 - Proton pump inhibitors

1.3 Therapeutic indications: gastro-oesophageal reflux disease, gastric and duodenal ulcers.

1.4 Posology and duration of treatment:

Dose (adults): 10 mg once daily for 4–8 weeks depending upon condition and response.

Maintenance: 5 –10 mg once daily.

Special population: no data.

1.5 Pharmaceutical forms: gastro-resistant tablets 10 and 20 mg.

1.6 Contraindications: hypersensitivity.

1.7 Relevant warnings: very limited data.

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (Pharmacovigilance):

Headache, diarrhoea, nervousness, abdominal pain, pharyngitis, nausea, vomiting, and gas (frequency not reported);

It may reduce absorption of ketoconazole and itraconazole and it may prolong the elimination of diazepam, phenytoin and warfarin (no further details available).

2.1.1 Recent cases at European level: no data

2.1.2 Indirect risks (incorrect use): no data

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription status	Additional information / Exemptions				
		Routes of administration	Comments	MS	MDD	MQP
Melclass database*	I (1)					
AT	Not authorised					
BE	Not authorised					
CH	Not authorised					
FR	Not authorised					
HU	Not authorised					
IE	Not authorised					
IT	Not authorised					
LT	Not authorised					
MK	Not authorised					
PL	Not authorised					
PT	Not authorised					
RO	Not authorised					
UK	Not authorised					

* Melclass database - Available at: http://www.edqm.eu/melclass/

No data available from member states.

The only product Dexpure, India, has no SmPC in English available, no other data available.

3.2 Member states' authorities' past or ongoing evaluation of the risk profile of the active ingredient for this therapeutic indication(s) (ATC code); abuse/misuse; efficiency: no

3.3 Social dimension of classification:

3.3.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Recommendation: not to classify (not marketed in any member state and no data available)

3.3.2 Paediatric use: no data available

3.3.3 Social dimension: N.A.

4. COMMENTS/REFERENCES

References:

1. Dexrabeprazole Sodium (Dexpure) Drug Information - Indications, Dosage, Side Effects and Precautions | Medindia

No data in EMA, MRI product index, Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), E-Medicines Compendium, FDA

1. THERAPEUTIC PROFILE

1.1 Active ingredient: lansoprazole, combinations.

1.2 ATC Code: A02BC53 - Proton pump inhibitors

NOTE: no data in EMA, MRI product index, CMDh, E-Medicines Compendium, FDA. The only data available are on Indian websites.

Available combination: lansoprazole and domperidone

1.3 Therapeutic indications: no data

1.4 Posology and duration of treatment: no data

1.5 Pharmaceutical forms: no data

1.6 Contraindications: no data

1.7 Relevant warnings: no data

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (Pharmacovigilance): no data

2.1.1 Recent cases at European level: no data

2.1.2 Indirect risks (incorrect use): no data

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription status	Additional information / Exemptions				
		Routes of administration	Comments	MS	MDD	MQP
Melclass database*	-					
AT	Not authorised					
BE	Not authorised					
CH	Not authorised					
CZ	Not authorised					
FR	Not authorised					
HR	Not authorised					
HU	Not authorised					
IE	Not authorised					
IT	Not authorised					
LT	Not authorised					
MK	Not authorised					
PL	Not authorised					
PT	Not authorised					
RO	Not authorised					
UK	Not authorised					

* Melclass database - Available at: http://www.edqm.eu/melclass/

No data available from member states.

3.2 Member states' authorities' past or ongoing evaluation of the risk profile of the active ingredient for this therapeutic indication(s) (ATC code); abuse/misuse; efficiency: no

3.3 Social dimension of classification

3.3.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Recommendation: not to classify

3.3.2 Paediatric use: no data

3.3.3 Social dimension: no data

4. COMMENTS/REFERENCES

References:

No data in EMA, MRI product index, CMDh, E-Medicines Compendium, FDA. Only limited information on Indian websites.

1. THERAPEUTIC PROFILE

1.1 Active ingredient: Rabeprazole, combinations

1.2 ATC Code: A02BC54 - Proton pump inhibitors

NOTE: no data in EMA, MRI product index, CMDh, E-Medicines Compendium, FDA. Limited data are available on Indian websites only.

Available combinations:

Rabeprazole and domperidone (*Combination no. 1*)

Rabeprazole and itopride (*Combination no. 2)*

1.3 Therapeutic indications:

Combination no. 1

Rivazol: GORD, heartburn and hyperacidity, reflux oesophagitis, regurgitation & flatulence, gastric and peptic ulcer.

Rabezyme-D: dyspepsia, GORD, nausea associated with acid peptic disorders, post-operative nausea and vomiting, chronic gastritis.

Acidom: rabeprazole 10 mg and domperidone 20 mg

Combination no. 2

Gastro-oesophageal reflux disease in adults.

1.4 Posology and duration of treatment: all combinations once daily

1.5 Pharmaceutical forms:

Combination no. 1: hard gelatine capsules rabeprazole 20 mg + domperidone 30 mg

Combination no. 2: capsules rabeprazole 20 mg itopride 150 mg

1.6 Contraindications: hypersensitivity

1.7 Relevant warnings:

Combination no. 1: generally well tolerated.

Combination no. 2: caution should be exercised in patients with history of liver impairment and during pregnancy.

Special precautions: itopride should be used with caution because it enhances the action of acetylcholine.

Interactions:

Combination no. 1:
Rabeprazole: pH dependent interactions with digoxin and ketoconazole.
Domperidone: a) concomitant administration of anticholinergic drugs may decrease the effect of domperidone; b) azole antifungals / macrolide antibiotics increase plasma levels of domperidone.

Combination no. 2: drug Interactions: rabeprazole increase elimination T1/2 of digoxin, decreases effects with aminoglutethimide, carbamazepine, phenytoin and rifampin and reduces absorption of ketoconazole and itraconazole. Anticholinergic agents reduce the action of itopride.

Pregnancy:

Combination no. 1: no data
Combination no. 2: not recommended

Breast-feeding:
Combination no. 1: no data
Combination no. 2: contraindicated

2. LIST DIRECT/INDIRECT RISKS (SAFETY PROFILE)

2.1 Direct risks (Pharmacovigilance):

Combination no. 1: most common side effects are somnolence, dizziness, dry mouth and blurring of vision

Combination no. 2: side effects: headache, diarrhoea, dizziness, rash. Potentially fatal: anaphylaxis, agranulocytosis.

2.1.1 Recent cases at European level: no data

2.1.2 Indirect risks (incorrect use): no data

3. CONCLUSIONS – RECOMMENDATIONS FOR LEGAL CLASSIFICATION

Combination no. 1: rabeprazole inhibits the H+-K+-ATPase enzyme and thereby decreases gastric acid secretion. Domperidone increases lower oesophageal sphincter tone and enhances upper GI motility, thereby preventing reflux of gastric contents into the oesophagus.

Rationale for combination: rabeprazole being the fastest acting PPI gives a quick relief from the hyper acid secretory conditions. A significant percentage of GORD patients have delayed gastric emptying and hypotensive oesophageal sphincter. Domperidone, a prokinetic and anti-emetic improves the LES tone, increases the gastric motility and thus helps in gastric emptying. In GORD patients not responding to Rabeprazole alone, combination of Rabeprazole and Domperidone may be effective.

Combination no. 2: this combination medication contains a proton pump inhibitor and prokinetic agent Rabeprazole is a PPI that suppresses gastric acid secretion by inhibiting the gastric H+/K+ ATPase at the secretory surface of the gastric parietal cell. Itopride increases acetylcholine (ACh) concentrations by inhibiting dopamine D2 receptors and acetylcholinesterase. Higher ACh increases GI peristalsis, increases the lower oesophageal sphincter pressure, stimulates gastric motility, accelerates gastric emptying, and improves gastro-duodenal coordination.

3.1 Member states' legal classification of the active ingredient for these therapeutic indications (ATC codes) and supply conditions:

Country	Prescription status	Additional information / Exemptions				
		Routes of administration	Comments	MS	MDD	MQP
Melclass database*	-					
AT	Not authorised					
BE	Not authorised					
CH	Not authorised					
CZ	Not authorised					
FR	Not authorised					
HR	Not authorised					
HU	Not authorised					
IE	Not authorised					
IT	Not authorised					
LT	Not authorised					
MK	Not authorised					
PL	Not authorised					
PT	Not authorised					
RO	Not authorised					
UK	Not authorised					

* Melclass database - Available at: http://www.edqm.eu/melclass/

No data available from member states.

3.2 Member states' authorities' past or ongoing evaluation of the risk profile of the active ingredient for this therapeutic indication(s) (ATC code); abuse/misuse; efficiency: no data

3.3 Social dimension of classification

3.3.1 Conditions of supply (Indications, Administration Route, MS, MDD, MQP, as applicable):

Recommendation: not to classify

3.3.2 Paediatric use: no data

3.3.3 Social dimension: no data

4. COMMENTS/REFERENCES

References:

No data in EMA, MRI product index, CMDh, E-Medicines Compendium, FDA

Only limited information on Indian websites:

- Rivazol DSR hard capsules (rabeprazole 20 mg and domperidone 30 mg) 100 capsules – DM Pharma (indian website) product information

- Rabezyme D SR (rabeprazole 20 mg + domperidone 30 mg) TAG Health Care

- Aciflux Rabeprazole and Itopride Drug Information - Indications, Dosage, Side Effects and Precautions | Medindia - www.medicineindia.org

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