ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF LOSEC AND ASSOCIATED NAMES (SEE ANNEX I)

Losec (omeprazole) was included in the list of products for SPC harmonisation and a referral was triggered in order to resolve divergences and harmonise the nationally authorised SPCs across Europe. The marketing authorisation holder (MAH) also took the opportunity to harmonise Module 3. The scope of the referral included all licences, whether prescription only (POM/Rx) or non-prescription (over-the-counter or OTC). There are currently 4 separate formulations of Losec on the market: gastro-resistant tablets, capsules, powder for solution for infusion and powder for solution for injection. Losec MUPS (multiple unit pellet system) tablets are also available as OTC. The MAH proposed 5 separate SPCs: one for the 10mg, 20 mg, and 40 mg capsules; one for the 10 mg, 20 mg, and 40 mg tablets, one for the 40 mg powder for infusion, one for the 40 mg powder for injection and one for the 10mg and 20 mg tablets for OTC use. With this proposal, prescription only tablets and capsules will have the same indications for all strengths (bioequivalence between the tablets and the capsules of same strength has been demonstrated), as will the solutions for infusion and injection. The OTC SPC will diverge most notably in the indications, posology and warnings sections.

Omeprazole is a substituted benzimidazole belonging to the therapeutic group of proton pump inhibitors (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.

PRESCRIPTION-ONLY PRESENTATIONS

Section 4.1 - Therapeutics indications in adults - capsules and tablets

The CHMP assessed the MAH proposal taking into account the current national SPCs and scientific knowledge and discussed indications for each individual medical condition. The prophylactic use of Losec, as distinct from the treatment indications was also discussed and justified.

a) "Treatment of symptomatic gastro-oesophageal reflux disease (GERD)"
The MAH proposed that both duodenal and gastric ulcers be presented in individual indications separate from the GERD indication. Whilst definition of what constitutes typical reflux disease may differ, in general terms, GERD is applied to patients with symptoms suggestive of reflux or complications thereof, but not necessarily with oesophageal inflammation. The cardinal symptoms associated with GERD are heartburn and regurgitation. The latest guidelines include symptoms as the most important part for the diagnosis of GERD. The most common and effective treatment of peptic oesophagitis or symptomatic GERD is to reduce gastric acid secretion with either H_2 blockers or a PPI and the CHMP therefore considered this indication approvable.

b) *"Treatment of reflux oesophagitis"* and *"Long-term management of patients with healed reflux oesophagitis"*
Reflux oesophagitis results from the combination of excessive gastro-oesophageal reflux of gastric juice and impaired oesophageal clearance of the refluxate. The likelihood of developing reflux symptoms or oesophageal epithelial injury is a function of a quantitative abnormality of the number of reflux events and/or oesophageal acid exposure. Treatment of reflux oesophagitis includes acid reduction and PPIs are currently considered the most effective treatment for reflux oesophagitis and the CHMP therefore considered this indication to be approvable.

c) *"Treatment of duodenal ulcers"* and *"Prevention of relapse of duodenal ulcers"*
The indication in *H. pylori* negative ulcers was split from the indication with concomitant *H. pylori* infection. Regarding the prevention of relapse of *H. pylori* negative duodenal ulcers, the available

literature was reviewed. It is in the so-called "idiopathic ulcers" that the prevention of relapse of *H. pylori* negative duodenal and gastric ulcer indications are indicated. Since such ulcers are difficult to treat and are associated with more frequent and more serious complications, preventing relapse is a reasonable course of action. The CHMP considered that prevention of relapse of *H. pylori* negative duodenal ulcers is sufficiently demonstrated and considered these indications to be approvable.

d) "Treatment of gastric ulcers" and "*Prevention of relapse of gastric ulcers"*
The gastric ulcer indications were separated from the duodenal ulcer indications as well as from the NSAID-related and *H.* pylori positive ulcers. Gastric ulcers in elderly patients may be located more proximally in the stomach than in younger patients. Proximal gastric ulcers are often large, tend to heal slowly, and may be more prone to recur. Such ulcers are also associated with a high frequency of potentially fatal complications. Therefore, prevention of relapse of gastric ulcers is a reasonable course of action. The CHMP considered that the prevention of relapse of *H. pylori* negative gastric ulcers is sufficiently demonstrated and considered these indications to be approvable.

e) "Treatment of NSAID-associated gastric and duodenal ulcers" and *"Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk"*
Regarding the prevention of non-steroidal anti-inflammatory drug (NSAID) -associated gastric ulcers, duodenal ulcers or gastroduodenal erosions in patients at risk, prevention of ulcer formation in at risk NSAID users is a reasonable course of action, given the high and increasing incidence. Prevention of ulcers is currently started on a regular basis in a considerable number of patients using NSAIDs and the superior efficacy PPIs over H_2 antagonists in the healing of gastroduodenal ulcers associated with NSAIDs when NSAIDs cannot be discontinued has been demonstrated. PPIs are also effective for primary prevention of NSAID-associated ulcers. The CHMP considered that the prevention of NSAID ulcers is sufficiently demonstrated and considered these indications to be approvable. However, peptic ulcers and erosions are different clinical entities. Peptic ulcers are associated with increased risk of upper gastrointestinal complications, such as bleedings, but the same may not be true for the superficial erosions commonly seen during treatment with NSAIDs. The CHMP considered that the available data does not allow concluding on whether patients with erosions alone benefit from the treatment with PPI. The mention of erosions was therefore deleted from the indication.

f) "In combination with appropriate antibiotics, Helicobacter pylori (H. pylori) eradication in peptic ulcer disease"
The CHMP considered that according to almost all existing guidance, all patients with erosions or ulcers associated with *H. pylori* infection should undergo therapy to eradicate the organism. This recommendation is based upon overwhelming data showing that the cure of *H. pylori* infections reduces ulcer recurrence and complications such as bleeding. Further information on recommended antibiotic combinations is stated in Section 4.2. The CHMP considered this indication to be approvable.

g) Acid-related dyspepsia
The CHMP noted that heartburn was not included in the definition of dyspepsia agreed upon by an international committee of clinical investigators (Rome III Committee). In addition, H_2 receptor antagonists have a more immediate effect. Based on the European guidelines and literature, and due to the lack of conclusive studies relevant to this indication, this indication and the associated posology was removed from the proposed harmonised SPC.

h) "Treatment of Zollinger-Ellison syndrome"
The indication for the treatment of *Zollinger Ellison* syndrome is already harmonised throughout the EU and the CHMP considered this indication to be approvable.

i) Patients considered to be at risk of aspiration of gastric contents during general anaesthesia/Acid aspiration prophylaxis
The CHMP considered that this indication is similar to chemical pneumonia (among others caused by gastric acid aspiration). This indication is not generally accepted and the use of PPIs in the treatment of

chemical pneumonia is not advocated in the various guidance on treatment/prevention of this pneumonia. The data submitted by the MAH did not sufficiently support the claimed indication and although no unexpected or new safety concerns emerged from these studies, the CHMP considered this indication to be unacceptable given the undemonstrated efficacy. The indication and the associated posology were removed from the harmonised SPC.

Section 4.1 - Therapeutics indications in paediatric patients - capsules and tablets

The CHMP agreed on the following indications in paediatric patients, in line with the outcome of the EU work-sharing assessment of paediatric data:

In children over 1 year of age and ≥ 10 kg
- *Treatment of reflux esophagitis*
- *Symptomatic treatment of heartburn and acid regurgitation in gastro-esophageal reflux disease*

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

Section 4.1 - Therapeutics indications in adults - powder for injection and powder for infusion

The intravenous indications were largely harmonised already. After discussing the various existing texts in the national SPCs and noting that experience on use of intravenous formulations of Losec in paediatric patients is limited, the CHMP adopted the following harmonised indications in adults for Losec for intravenous use, as an alternative to oral therapy:

- *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 esophagitis*
- *Long-term management of patients with healed reflux esophagitis*
- *Treatment of symptomatic gastro-esophageal reflux disease*
- *Treatment of Zollinger-Ellison syndrome"*

Section 4.2 - Posology and method of administration

Regarding the method of administration of the capsules and tablets, with regards to patients with swallowing difficulties, the CHMP agreed that the capsule can be opened and the contents swallowed based on the in-vivo (bioequivalence) as well as in-vitro studies on the intake as dispersed/suspended tablets/granules of the oral pharmaceutical forms. Alternatively, patients can suck the capsule and swallow the pellets with water. The CHMP agreed that the available data on administration of the MUPS tablet immediately after a high-fat breakfast shows delayed and decreased absorption of omeprazole. Although this food interaction is not likely to be of any clinical relevance, it warrants the recommendation that Losec should preferably be taken without food.

Adult posology: capsule and tablet

For the treatment of symptomatic gastro-oesophageal reflux disease, the recommended dose is 20 mg daily. Patients may respond adequately to 10 mg daily, and therefore individual dose adjustment should

be considered. If symptom control has not been achieved after four weeks treatment with 20 mg daily, further investigation is recommended.

For the treatment of reflux oesophagitis, the recommended dose is 20 mg once daily. In most patients healing occurs within four weeks. In patients with severe oesophagitis 40 mg once daily is recommended and healing is usually achieved within eight weeks. For long-term management of patients with healed reflux oesophagitis, the recommended dose is 10 mg once daily.

For the treatment of duodenal ulcers, the recommended dose is 20 mg once daily. In most patients healing occurs within two weeks. In patients with poorly responsive duodenal ulcer 40 mg once daily is recommended and healing is usually achieved within four weeks. For the prevention of relapse of duodenal ulcer in *H. pylori* negative patients or when *H. pylori* eradication is not possible the recommended dose is 20 mg once daily.

For the treatment of gastric ulcers, the recommended dose is 20 mg once daily. In most patients healing occurs within four weeks. In patients with poorly responsive gastric ulcer 40 mg once daily is recommended and healing is usually achieved within eight weeks. For prevention of relapse in patients with poorly responsive gastric ulcer the recommended dose is 20 mg once daily.

For the treatment of NSAID-associated gastric and duodenal ulcers, the recommended dose is 20 mg once daily. In most patients healing occurs within four weeks. For the prevention of NSAID-associated gastric ulcers or duodenal ulcers in patients at risk (age> 60, previous history of gastric and duodenal ulcers, or of upper GI bleeding) the recommended dose is 20 mg once daily.

Regarding the eradication of *H. pylori* in peptic ulcer disease, a number of triple-regimen therapies (Losec plus two antibiotics) are proposed. These are based on established data and are currently confirmed as the most efficacious combinations, and are intended to allow treatment alternatives according to local needs and clinical practice. The 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. The CHMP considered that dual therapies are less effective than triple therapies, but that they could be considered in cases where known hypersensitivity precludes use of any triple combination.

For the treatment of Zollinger-Ellison syndrome, the dose should be individually adjusted and treatment continued as long as clinically indicated. The recommended initial dose is 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 20-120 mg daily. When the dose exceeds 80 mg daily, it should be divided and given twice daily.

Paediatric posology: capsule and tablet
The CHMP agreed on specific dosage and treatment duration recommendations for each individual indication for paediatric patients, taking into account the patients age (≥ 1 year of age, ≥ 2 years of age and children and adolescents over 4 years of age) and weight. For children and adolescents over 4 years of age treated for duodenal ulcers caused by *H. pylori*, the selection of the appropriate combination therapy should take into consideration the official national, regional and local guidance regarding bacterial resistance, duration of treatment and appropriate use of antibacterial agents.

Powder for infusion and powder for injection
The CHMP considered the IV formulations to be 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. The SPC also provides guidance on dose adjustments and practical advice on the administration of the formulations. Experience on use of intravenous formulations of Losec in paediatric patients is limited, however no specific safety issues are predicted.

Special populations: all formulations
Regarding special populations, dose adjustment is not needed in patients with impaired renal function, as omeprazole is almost completely metabolized by CYP450, renal impairment does therefore not influence the pharmacokinetics. In patients with impaired hepatic function, however, a daily dose of 10–20 mg may be sufficient. For the elderly (>65 years old), no dose adjustment is needed.

Section 4.3 - Contraindications

Omeprazole has been reported to interact with some antiretroviral drugs. Increased gastric pH during omeprazole treatment may affect absorption, while other possible interaction mechanisms are via CYP2C19. The SPC therefore states that co-administration of atazanavir and nelfinavir with proton pump inhibitors is not recommended and that if co-administration is judged unavoidable, close clinical monitoring is recommended together with an increase of the anti-retroviral drug dose, as plasma levels of nelfinavir and atazanavir are decreased in case of co-administration with omeprazole. Nelfinavir co-administration is contraindicated, atazanavir co-administration is not recommended.

While literature data strongly indicates that there is no cross-reactivity between the various substituted benzimidazoles, there is data indicating suspected cross-reactivity. Due to the high potential risk to patients, a statement contraindicating use in patients hypersensitive to omeprazole, substituted benzimidazoles or to any of the excipients was adopted by the CHMP.

Section 4.4 - Special warnings and precautions for use

A warning that the *H. pylori* status should be determined before treatment was included in the SPC. The use of endoscopy and/or x-ray in case of acid related ulcers is no longer necessary according to current practice and these techniques are therefore omitted. A statement on the potential increased or decreased absorption of active substances with a gastric pH dependent absorption due to decreased intragastric acidity was inserted. The SPC also mentions that the benefit-risk of omeprazole treatment in the maintenance setting should be continuously re-evaluated and that patients should be kept under regular surveillance, especially when exceeding a treatment period of 1 year.

The CHMP considered that the increased occurrence of gastrointestinal bacterial infections due to decreased gastric acidity should be mentioned in the SPC. Salmonella and Campylobacter are mentioned; however the mention of *C. difficile* infections was removed, as the available data did not establish a possible causal relationship between *C. difficile* infection and the use of PPIs.

The CHMP was of the opinion that prolonged acid inhibition by PPIs may promote vitamin B12 malabsorption and inserted a warning stating that omeprazole may reduce the absorption of vitamin B12 and that this should be considered in patients on long-term therapy.

The CHMP assessed the potential omeprazole-clopidogrel interaction and considered that a warning is warranted, given the potential seriousness of the observed adverse events. After consultation of the Cardiovascular subgroup of the Efficacy Working Party, the CHMP confirmed that a PK and PD interaction between CYP2C19 inhibitors and clopidogrel is observed, although the clinical implication of this finding is not clear. The SPC therefore states that omeprazole is a CYP2C19 inhibitor and that inconsistent data has been reported from observational and clinical studies on the clinical implications of the PK/PD interaction in terms of major cardiovascular events. Concomitant use of omeprazole and clopidogrel is therefore discouraged

Section 4.5 – Interactions with other medicinal products and other forms of interactions – all formulations

This section was rewritten in a more reader friendly style by grouping the possible interactions, increasing

the visibility of the most severe clinical consequences and indicating the magnitude of the interaction effects. The interaction with tacrolimus and phenytoin were retained and monitoring was recommended but an interaction with methotrexate was considered unwarranted. Concomitant use with posaconazol and erlotinib should be avoided.

Section 4.6: Pregnancy and lactation – all formulations

The CHMP considered that there is sufficient information on human experience to state that excretion of omeprazole in milk is low and unlikely to influence the child. Data from epidemiological studies on use of Losec during pregnancy indicates no adverse effects and the CHMP considered that omeprazole can be used during pregnancy.

Section 4.7: Effects on ability to drive and use machines – all formulations

The CHMP noted that although Losec is not likely to affect the ability drive or use machines, dizziness and visual disturbances have been observed with the use of Losec, and stated that patients experiencing these adverse drug reactions should not drive or operate machinery.

Section 4.8 - Undesirable effects

Identified or suspected adverse drug reactions are listed in this sections. None have been found to be dose-related and the reactions are classified according to frequency. The SPC states that for the tablet and capsule formulations the clinical trial safety experience shows that the adverse event profile in children up to 16 years of age is generally the same as for adults in short- as well as in long-term treatment and that there is no long-term data on the effects on puberty and growth.

Section 4.9 - Overdose

There have been no reports of serious outcomes following overdoses with omeprazole, and thus, no specific treatment has been needed or can be recommended. The statement "symptomatic treatment", provides some guidance to the physician on how to handle an overdose. An additional statement was inserted for the infusion and injection formulations, stating that based on clinical trials, excessive doses have not led to any dose-related adverse reactions.

Section 5.1: Pharmacodynamic properties

The CHMP discussed the association of omeprazole with the occurrence of bone fracture/hip fracture in the elderly, especially osteoporosis affected population. The CHMP considered that the currently available information is not sufficient for a warning in the SPC, however, due to the concerns raised, the outcome of the proposed MAH epidemiological study on the risk of falls and fractures will be assessed in order to determine the implications for the Losec SPC.

Section 5.2 - Pharmacokinetic properties

The CHMP noted data showing that omeprazole does not increase the incidence or seriousness of the side effects in the poor metaboliser population and considered that although poor metabolisers show 5 to 10 times higher mean AUC than subjects having a functional CYP2C19 enzyme, there is no evidence that patients who are poor CYP2C19 metabolisers are at increased risk when treated with omeprazole at recommended doses..

OVER THE COUNTER PRESENTATIONS: LOSEC 10 AND 20 MG TABLETS (OTC)

Initial GERD treatment is managed by a symptom-based approach; an empiric trial of acid suppression can be used. Symptoms responding adequately to an acid suppressant and returning upon discontinuation

allow a diagnosis of GERD. The CHMP considered that the available scientific information sufficiently demonstrates the efficacy of omeprazole in the treatment of heartburn and acid reflux and its superiority to placebo, in particular for the short-term OTC use of 20 mg daily. Similarly, the CHMP considered that there is sufficient evidence from the literature and long-term post marketing experience that omeprazole 20 mg daily is a safe dosage over 14 days. The legal status of Losec as a ”medicinal products not subject to medical prescription” was considered to be in accordance with the EC Guideline on Changing the Classification for the Supply of a Medicinal Product for Human Use. The known safety profile of omeprazole confirms the absence of direct or indirect danger to human health and the cautionary measures restricting the use to 2 weeks treatment are considered acceptable. The CHMP concluded that omeprazole is a suitable medication to relief heartburn and acid regurgitation in the OTC setting, provided that the patient complies with the recommended dosing and correct use, as instructed by the SPC and the Patient Leaflet.

Harmonisation of the SPC and PL for the OTC product

In general, the SPC and the PL of the OTC Losec presentation was aligned to that of the Prescription-only products. Regarding Section 4.1, the CHMP adopted the following harmonised indication:

“Losec gastro-resistant tablets are indicated for the treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults”

The CHMP noted that study data showed that 20 mg once daily produces a more pronounced and consistent inhibition than the lower doses and therefore agreed on a maximum daily dose of 20 mg. 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. Patients with impaired hepatic function should be advised by a doctor before taking Losec. Relief of symptoms after the start of treatment with PPIs may take time, therefore a statement informing patients that 2-3 days might be needed before symptom improvement is perceived was also added. In line with the indication, this product should not be used in children.

Information on the need for regular surveillance when exceeding a treatment period of one year was inserted and patients with long-term recurrent symptoms of indigestion or heartburn should see their doctor at regular intervals, especially patients over 55 years as the increasing age is a risk factor for the development of gastric disorders. Patients are also instructed to consult a doctor if they have had previous gastric ulcer or gastrointestinal surgery, in case of jaundice, hepatic impairment, or liver disease and if they are on continuous symptomatic treatment of indigestion or heartburn for 4 or more weeks. Patients are also told not to take omeprazole as a preventive medication. Regarding the interaction with clopidogrel, in line with the prescription-only recommendation, patients should specifically tell their doctor or pharmacist if they are taking clopidogrel.

QUALITY – MODULE 3

The MAH submitted a proposal for harmonisation of the Quality module. The proposed harmonisations mainly concern the drug product and the MAH provided satisfactory information on the appearance, polymorphisms, specifications and stability of the drug substances (omeprazole magnesium for the MUPS tablets, omeprazole for the capsules and omeprazole sodium for the injection and infusion formulations). Appropriate information on the drug product was also provided, and the physical appearance, manufacture, specification, stability, shelf-life, storage were covered. However a number of clarifications were requested, mainly with regards to the Manufacture, Control of Drug Product, Container Closure System and Stability sections, for all formulations. Based on the review of data and taking into account the commitments provided by the MAH to submit an update of Module 3 in May 2010, the CHMP adopted a harmonised Module 3.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

In conclusion, based on the assessment of the MAH proposal and responses and following the discussions of the committee, the CHMP adopted harmonised sets of Product Information documents for the various presentations of Losec and associated names, taking into account the pharmaceutical forms and differentiating between the prescription-only and the OTC presentations. In particular, the indications and their associated posology recommendations were harmonised. A harmonised Module 3 was also adopted. Commitments by the MAH were agreed, as listed in the Letter of Undertaking dated 14 December 2009. Based on the above, the CHMP considers the benefit/risk ratio of Losec to be favourable and the harmonised Product Information documents to be approvable.

Whereas

- the scope of the referral was the harmonisation of the Summary of Products Characteristics, labelling and package leaflet.

- the Summary of Products Characteristic, labelling and package leaflet proposed by the Marketing Authorisation Holders have been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CHMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Losec and associated names (see Annex I). The conditions of the Marketing Authorisations are described in Annex IV.