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 PROTIUM AND ASSOCIATED NAMES (SEE ANNEX I)

Protium (pantoprazole) is a proton-pump inhibitor and is used to treat gastroesophageal reflux disease (GERD), a condition in which backward flow of acid from the stomach causes heartburn and injury of the food pipe (oesophagus). It is also used to treat conditions where the stomach produces too much acid, such as Zollinger-Ellison syndrome. It works by decreasing the amount of acid made in the stomach. Pantoprazole is not registered in Iceland and Malta. In all other EU countries and Norway pantoprazole 20 mg and 40 mg, gastro-resistant tablets, are registered. No marketing authorisations exist for Pantoprazole i.v., powder for solution for injection, in Bulgaria, Estonia, Latvia and Lithuania. Protium was included in the list of products for Summary of Product Characteristics (SPC) harmonisation, drawn up by the CMD(h), in accordance with Article 30(2) of Directive 2001/83/EC, as amended. In agreement with the EMEA, Module 3 was also harmonised during this procedure.

Section 4.1: Therapeutic indications

Indications proposed for pantoprazole 20 mg gastro-resistant tablets:
The CHMP noted the MAH proposal. For the treatment of mild reflux disease and associated symptoms, several studies in adult patients with mild GERD have shown pantoprazole to be superior to placebo and ranitidine for the relief from the key GERD symptoms (heartburn, acid regurgitation, pain on swallowing) and healing of lesions and comparable to omeprazole and lansoprazole regarding the rate of symptom relief and healing in patients with mild GERD. This was supported by several guidelines recommending the use of PPIs in GERD regardless of severity. For the long-term management and prevention of relapse in reflux oesophagitis the MAH summarised 7 studies in long term treatment (between 6-12 months) showing that pantoprazole is superior in maintaining the healing and relapse rates compared to placebo and ranitidine. The relapse of erosive oesophagitis in subjects with GERD was shown to be dramatically decreased by PPI treatment and reflux symptoms were also better controlled with maintenance-dose PPI therapy than with placebo. In the case of non-erosive disease, PPI treatment also proved a reasonable strategy in symptoms control but the role of daily maintenance therapy is less clear than the "on demand" use.

For the prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs, a summary of three clinical trials was provided, showing superiority of pantoprazole versus placebo and misoprostol and similar effectiveness to omeprazole. The association between NSAIDs and the presence of upper gastrointestinal (GI) complications is considered well established and evidence that acid aggravates NSAID-induced injury provides a rationale for minimizing such damage by acid suppression.

In conclusion, based on the data provided by the MAH and the existing clinical evidence the CHMP adopted three harmonised therapeutic indications for the 20 mg gastro-resistant tablets.

Indications proposed for pantoprazole 40 mg gastro-resistant tablets:
The CHMP noted the submitted randomized clinical trials results demonstrating that pantoprazole is therapeutically superior to placebo and to ranitidine in patients with moderate and severe reflux oesophagitis and equivalent in healing rates after 4/8 weeks and/or symptom relief after 2/4 weeks of treatment with omeprazole, esomeprazole and lansoprazole. Abundant data supports treating patients with oesophageal GERD syndromes with antisecretory drugs and there is ample evidence that, as a drug class, PPIs are more effective in these patients than H2 receptor antagonist.

For the combination with two appropriate antibiotics for the eradication of *H. pylori* in patients with peptic ulcers with the objective of reducing the recurrence of duodenal and gastric ulcers caused by this microorganism, there is a vast knowledge about the eradication of *H. Pylori* and the role of PPIs.

Currently, ulcers related to *H. Pylori* infection can be healed and prevented from recurring and in NSAIDs naïve patients with *H. Pylori* infection, pantoprazole is better than placebo in preventing peptic ulcer and upper gastrointestinal bleeding at six months. Antibiotic resistance is a major cause of treatment failure and as the prevalence of resistance in *H. pylori* shows regional variation, alternative antibiotics based on local resistance rates may improve eradication rates. Regarding duodenal ulcer, data from several randomized trials was provided, comparing pantoprazole with ranitidine. Superiority of pantoprazole over ranitidine and comparable healing rates after two and four weeks of treatment with omeprazole were demonstrated. A randomized, dose-finding study showed statistically significant differences between 20 mg and 40 mg, thus indicating that pantoprazole at a daily dose of 40 mg is the recommended efficacious and safe dosage. For gastric ulcer, data from two clinical trials and one meta-analysis was provided. The trials showed that pantoprazole is superior to ranitidine and comparable to omeprazole in ulcer healing while the meta-analysis suggests that first-line drug therapy for patients diagnosed with gastric ulcer should preferably be PPI, rather than a H2 antagonist.

Finally, for the Zollinger-Ellison syndrome (ZES) and other pathological hypersecretory conditions, data from two studies comparing the efficacy of pantoprazole in reducing gastric acid secretion in 11 ZES patients who previously had received omeprazole and lansoprazole was provided. Pantoprazole was shown to be equally effective to the other PPIs in terms of antisecretory potency. Numerous studies have demonstrated that PPIs are both efficacious and well tolerated in patients with hypersecretory conditions; consequently, they are currently the anti-secretory agents of choice to control gastric acid hypersecretion. In conclusion, based on the data provided by the MAH and the existing clinical evidence, the proposed indications are considered appropriate; however, the CHMP proposed a new wording for the moderate and severe reflux oesophagitis, taking into account the current classification of gastroesophageal reflux disease. In addition the indication for *H. Pylori* eradication was simplified.

The CHMP adopted four harmonised therapeutic indications for the 40 mg gastro-resistant tablets.

Indications proposed for pantoprazole 40 mg i.v.:
For duodenal ulcer, gastric ulcer, moderate and severe reflux oesophagitis, open-label studies have shown that pantoprazole 40 mg/d, p.o. is comparably effective and safe to pantoprazole 40 mg/d, i.v. in the healing of reflux oesophagitis, and that 40 mg pantoprazole p.o. and i.v. formulations are equivalent in their ability to suppress gastric acid output. Pantoprazole treatment in these studies was well tolerated and had a favourable benefit-risk ratio. For the Zollinger Ellison syndrome and other pathological hypersecretory conditions, two studies showed that pantoprazole 80 mg i.v. bid for up to 6 days was efficacious and safe for controlling gastric acid. A further study in patients with ZES under stable oral PPI therapy showed that a switch to pantoprazole i.v. at doses of 80 mg up to 120 mg every 8 to 12 hours was able to control acid output. The CHMP considered that the proven clinical efficacy of pantoprazole 40 mg p.o. and the documented equivalence of pantoprazole 40 mg p.o. and pantoprazole 40 mg i.v. justify use in the treatment of moderate and severe reflux oesophagitis, duodenal ulcer, gastric ulcer and ZES and other pathological hypersecretory conditions.

The CHMP noted that all the indications have been previously fully justified and adopted three harmonised therapeutic indications for the 40 mg intravenous formulation.

Section 4.2 - Posology and method of administration

Pantoprazole 20 mg gastro-resistant tablets
The CHMP noted the MAH proposal and adopted a harmonised text for this section. It was noted that concomitant intake of food had no influence on AUC and maximum serum concentration but that the variability of the lag-time will be increased. Instructions that the tablets should not be chewed or crushed, and should be swallowed whole 1 hour before a meal with some water was harmonised.

The safety in long-term treatment was discussed and the data collected since the original licensing of the product is re-assuring for long-term safety.

Treatment for 2 to 4 weeks usually results in relief of symptoms and if this is not sufficient, symptom relief will normally be achieved within a further 4 weeks in patients 12 years and above. When symptom relief has been achieved, reoccurring symptoms can be controlled using an on-demand regimen of 20 mg once daily, when required.

It was considered that patients under long-term treatment should be kept under regular surveillance, especially when exceeding a treatment period of 1 year. Regarding use in adolescents and the safety and efficacy in children, Protium is not recommended for use in children below 12 years of age due to limited data on safety and efficacy in this age group.

Regarding on-demand treatment, data shows that pantoprazole at a daily dose of 20 mg for 4 weeks is effective and safe in the treatment of mild GERD and its associated symptoms and that an extension of treatment duration to 8 weeks resulted in an increase in cumulative healing rates. The CHMP agreed that on demand treatment is an appropriate option for symptomatic gastro-oesophageal reflux disease.

Regarding special populations, the CHMP noted that for patients with hepatic impairment, specific information related to monitoring liver enzymes and discontinuation of treatment in severe liver impairment is available and concluded that a daily dose of 20 mg pantoprazole should not be exceeded. No dose adjustment is considered necessary for patients with renal impairment and elderly patients as the primary route of elimination for pantoprazole is hepatic, thus elimination of pantoprazole is minimally affected by renal dysfunction and the slight increase in AUC and C_{max} in elderly compared with younger volunteers is not considered clinically relevant.

Pantoprazole 40 mg gastro-resistant tablets

The CHMP noted the MAH proposal and adopted a harmonised text for this section. The recommendation on how to take the tablets was aligned with the 20 mg formulation. The dose, schedule and duration of treatment are in line with the clinical practices. Expert opinions are unanimous in recommending twice-daily dosing of PPIs to improve symptom relief in patients with an oesophageal GERD syndrome with an unsatisfactory response to once daily treatment. The provided meta-analyses and controlled clinical studies support the efficacy of the proposed *H. Pylori* eradication combinations but with wide divergences between member states. Clarithromycin, metronidazole, tinidazole and amoxicillin are widely used in Europe for eradication of *H. Pylori*, however the prevalence of antimicrobial resistance in *H. pylori* shows regional variability and alternative antibiotics based on local resistance rates may improve eradication rates. Similarly, the most effective length of treatment is debated as European guidelines contradict recent studies, which may reflect varying resistance rates within the populations studied. Currently, triple therapy for seven days is still a valid and cost effective duration of treatment. The CHMP considered that the optimal duration is one week, and that another course of seven days might be recommended in individual cases. The text referring to "official local guidance" is agreed as it allows the inclusion of alternative antibiotics without stating all the alternatives used nationally.

Based on the available data from clinical trials, the harmonised dosage guidelines for monotherapy where combination therapy is not an option and the posology for Zollinger-Ellison syndrome and other pathological hypersecretory conditions were considered justified. In line with the assessment of the 20 mg gastro-resistant tablets, Protium is not recommended in children below 12 years. The CHMP also stated that a daily dose of 20 mg pantoprazole should not be exceeded in patients with severe liver impairment. For patients with impaired renal function, no dose adjustment is necessary as the primary route of elimination of pantoprazole is hepatic; therefore, elimination is minimally affected by renal dysfunction.

Protium should not be used in combination treatment for eradication of *H. pylori* in patients with impaired renal function or moderate to severe hepatic dysfunction since currently no data is available on the

efficacy and safety in combination treatment for these patients. Regarding elderly patients, and patients with mild hepatic impairment, no dose adjustment is necessary.

Pantoprazole 40 mg i.v.
The CHMP noted the MAH proposal and adopted a harmonised text for this section. The dose and schedule for the indications is appropriate, based on the available data with pantoprazole 40 mg p.o. and the pharmacodynamic and therapeutic equivalence of pantoprazole 40 mg i.v. The experience in children is limited and therefore Protium i.v. 40 mg powder for solution for injection is not recommended in patients below 18 years of age until further data become available. Dose recommendations in special populations were inserted in section 4.2. For patients with hepatic impairment, only a maximum of 20 mg daily is recommended although the proposed posology of 40 mg on alternate days can not be supported as the lack of efficacy data has not been addressed.

Section 4.3 – Contraindications

For the pantoprazole 20 mg tablets, the CHMP noted the MAH proposal and adopted a harmonised text. In particular, the interaction between atazanavir and others PPIs has been moved to Sections 4.4 and 4.5. The literature shows that this interaction exists and is related to changes in gastric pH that can lead to a reduction in the bioavailability of atazanavir and other HIV medications whose absorption is pH-dependent. However, as it can be overcome, a contraindication is inappropriate. Co-administration of atazanavir with proton pump inhibitors is not recommended and if the combination of atazanavir with a proton pump inhibitor is judged unavoidable, close clinical monitoring is recommended while high doses of proton pump inhibitors should be avoided. Section 4.5 states that 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 efficacy. The CHMP did not consider it justified to contraindicate pantoprazole 20 mg in hepatically impaired patients.

For the pantoprazole 40 mg tablet formulation, the CHMP noted the MAH proposal and adopted a harmonised text. The dosage of pantoprazole may need to be reduced in patients with severe hepatic impairment, and liver enzymes should be monitored regularly during treatment with pantoprazole. Since efficacy of low dose (20 mg) pantoprazole in triple therapy for the eradication of *H. pylori* has not been investigated, the use of Protium is considered contraindicated and the dose needed to eradicate this infection (40 mg twice daily) cannot be administrated to these patients. In order to reduce the risk in this population, the statement was moved to Section 4.2. Regarding hypersensitivity and concomitant use with atazanavir, the comments provided for the 20 mg tablet dose apply.

For the pantoprazole 40 mg i.v. formulation, the CHMP noted the MAH proposal and adopted a harmonised text, in particular regarding hypersensitivity to the active substance or to any of the excipients. Regarding hypersensitivity and concomitant use with atazanavir, the comments provided for the 20 mg tablet dose apply.

Section 4.4 - Special warnings and precautions for use

The CHMP noted the MAH proposal for this section. The statement on a possible increase in gastrointestinal infections is supported by a case-control study comparing 6,414 patients with an episode of gastroenteritis (GE) with a healthy control group of 50,000 and showing that the use of PPIs is associated with an increased risk of bacterial GE, regardless of the treatment duration. Doubling the PPI dose further increased the risk of GE, with *Campylobacter* and *Salmonella* the most frequently responsible. The CHMP also noted that the published literature on the concomitant use of PPIs and clopidogrel suggests that clopidogrel may be less effective in patients receiving PPIs and requested the MAH to discuss this potential interaction. The MAH discussed the concomitant use of PPIs and clopidogrel, noting a trend towards a potential clinical interaction between PPIs and clopidogrel. However, the epidemiological studies were considered to be conflicting and heterogeneous and the clinical PD/PK

studies failed to demonstrate any impact on the antiplatelet effect of clopidogrel on pantoprazole specifically, which was reassuring. The CHMP requested the input of the cardiovascular subgroup of the Efficacy Working Party (EWP-CVS) on this issue. The EWP-CVS concluded that there was no evidence supporting an interaction between pantoprazole and clopidogrel. The CHMP therefore decided that a statement regarding this interaction was unwarranted. In conclusion, the CHMP adopted a harmonised text for section 4.4.

Specifically for 20 mg tablets, a statement was inserted recommending that patients under long treatments should be kept under regular surveillance, especially when exceeding a treatment period of 1 year. Warnings related to prevention of gastroduodenal ulcers induced by NSAIDs were added. Specifically for the 40 mg tablets, information regarding patients with Zollinger-Ellison syndrome and other pathological hypersecretory conditions was included and the statement "Diagnosis of reflux oesophagitis should be confirmed by endoscopy" was removed as this is no longer the clinical practice. Warnings related to long term treatment and for prevention of gastroduodenal ulcers induced by NSAIDs were added, and the statement on hepatically impaired patients was maintained.

Section 4.5 - Interaction with other medicinal products and other forms of interaction

The CHMP noted the MAH proposal and adopted a harmonised text for this section. In particular, a description of the metabolic pathway which adequately reflects what is known about pantoprazole metabolism and a text on antibiotics interactions were adopted. The specific mention of levonorgestrel and ethinyl oestradiol is justified as a general extrapolation to the whole group of oral contraceptives cannot be made. The inclusion of substances for which an involvement of CYP 3A4 or CYP 2C19 is known (such as carbamazepine, diazepam, glibenclamide, and nifedipine) is justified. The inclusion of the substances diclofenac, naproxen, and piroxicam is justified by their recommended co-prescription according to the NSAID related ulcer prevention indication and are mentioned separately. The separate inclusion of caffeine and ethanol is justified by their widespread use.

Section 4.6 - Pregnancy and Lactation

The CHMP noted the MAH proposal and adopted a harmonised text for this section, applicable to all Protium formulations. Although one multi-centre study indicates that the use of PPIs during the first trimester of pregnancy is not associated with an increased teratogenic risk, clinical experience is limited during pregnancy. Therefore, pantoprazole should only be used when the benefit exceeds the potential risk. The same applies for the lactation period. Apart from a single case report which indicated a slight burden for the infant, further clinical experience is missing. Section 4.6 now states that "*a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Protium should be made taking into account the benefit of breast-feeding to the child and the benefit of Protium therapy to the woman.*"

Section 4.7 - Effects on ability to drive and use machines

The CHMP noted the MAH proposal and adopted a harmonised text for this section, applicable to all Protium formulations. Because the MAH presented a study performed to provide information regarding the effects of pantoprazole on the ability to drive and use machines, Section 4.7 now states that "a*dverse drug reactions such as dizziness and visual disturbances may occur (see section 4.8). If affected, patients should not drive or operate machines.*"

Section 4.8 - Undesirable effects

The CHMP noted the MAH proposal and adopted a harmonised text for this section, applicable to all Protium formulations. The general text of frequencies classification, and the adverse reaction obtained from postmarketing experience were clarified, and the frequency of a number of events was revised. In

particular, gynaecomastia was added to the list of undesirable effects. The method and the statistical approach together with the data provided were reviewed and the CHMP considered the estimated frequency to be appropriate.

Section 4.9 – Overdose

The CHMP noted the MAH proposal and adopted a harmonised text for this section. In particular, no particular risks regarding overdosing are anticipated and the MAH quoted a number of studies showing that doses of 120 mg/d, po. and even up to 320 mg/d, p.o. for years in single patients and 240 mg i.v. were well tolerated.

Section 5 – Pharmacological properties

The CHMP adopted a harmonised text for all sections under Section 5. In particular, the text on the general pharmacokinetics, the bioavailability, the characteristics in patients/special groups of subjects and the characteristics in patients/special groups of subjects and in children was harmonized. Under Section 6.6, for the i.v. formulation, a text with detailed information on the reconstitution of the solution and on the special precautions was adopted.

CMC Harmonisation

The MAH submitted the module 2.3 for pantoprazole gastro-resistant tablets 20 and 40mg dated March 2009 and for pantoprazole powder for solution for injection dated December 2008 as well as the module 3 for pantoprazole gastro-resistant tablets 20 and 40mg and for pantoprazole powder for solution for injection dated April 2009. The dossier for the Drug Substance was harmonised and the CHMP noted the Ph. Eur. monograph. The CHMP considered the general information of drug substance to be acceptable. In general, the elucidation of structure, the batch testing, the specifications and the stability tests were considered acceptable. Similarly, the dossier for the Drug Product (gastro-resistant tablets) was harmonised. Tablet characterisation, excipient compliance with the requirements of the Ph. Eur, specifications for dissolution, tests on colorants, stress and impurities, certificates of analysis of the reference substances and packaging and containers are considered generally acceptable. Finally, the dossier for the Drug Product (powder for solution for injection) was harmonised. The pharmaceutical development, the description of the manufacturers and their activities, the packaging and containers, the excipients used, the release specifications, the lower assay limit in drug product shelf-life specifications, the inclusion of related substances, the peak purity test, the reference standards of the drug substance and related substances and the stability of the drug product are considered generally acceptable.

For Module 1, the submitted current manufacturing authorisations for all manufacturers of the drug products in EU countries and GMP certificates of EU inspectorates for manufacturers of the drug products in non-EU countries, together with the declaration of the QP of the manufacturer for drug product release in the EU were considered acceptable. In conclusion, the provided information was in general adequate; however, a number of unresolved minor concerns were identified. The CHMP is of the opinion that a commitment to address these concerns is sufficient, and to reduce administrative work, a common time of 1 year after the issue of the EC decision is proposed for all response documents to be handed in as a single data package (see Annex IV).

In conclusion, the harmonisation procedure led to the adoption by the CHMP of a harmonised set of Product Informations for the three Protium formulations included in the scope and the CHMP was of the opinion that the benefit/risk ratio of Protium and associated names is considered to be favourable.

In summary, the CHMP adopted the following sets of indications for Protium and associated names:

20 mg gastro-resistant tablets

- Symptomatic gastro-oesophageal reflux disease
- For long-term management and prevention of relapse in reflux oesophagitis
- Prevention of gastroduodenal ulcers induced by non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in patients at risk with a need for continuous NSAID treatment (see section 4.4)

40 mg gastro-resistant tablets
- Reflux oesophagitis
- 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

Intravenous (i.v.) 40 mg powder for solution for injection
- Reflux oesophagitis
- Gastric and duodenal ulcer
- Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions

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

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 Protium and associated names (see Annex I). The recommend conditions of the Marketing Authorisations are listed in Annex IV.