

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Pantoprazol Sandoz injectie 40 mg,
powder for solution for injection
Sandoz B.V., the Netherlands

pantoprazole

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/0806/001/DC
Registration number in the Netherlands: RVG 33902

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Pharmacotherapeutic group:	drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), proton pump inhibitors
ATC code:	A02BC02
Route of administration:	intravenous
Therapeutic indication:	treatment of duodenal ulcer, gastric ulcer, moderate and severe reflux esophagitis, Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions.
Prescription status:	prescription only
Date of authorisation in NL:	11 June 2008
Concerned Member states:	Decentralised procedure with AT, BE, DK, ES, FI, IT, NO, PL, PT, SI, SK, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1), Article 10(3) for SK only

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the concerned member states have granted a marketing authorisation for Pantoprazol Sandoz injectie 40 mg, powder for solution for injection, from Sandoz B.V., the Netherlands. The date of authorisation was on 11 June 2008 in the Netherlands.

The product is indicated for treatment of:

- gastric ulcer
- duodenal ulcer
- moderate and severe reflux oesophagitis
- Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions.

A comprehensive description of the indications and posology is given in the SPC.

Pantoprazole is a substituted benzimidazole which inhibits the secretion of hydrochloric acid in the stomach by specific action on the proton pumps of the parietal cells (a gastric proton pump inhibitor, (PPI). 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. As other proton pump inhibitors and H_2 receptor inhibitors, treatment with pantoprazole causes a reduced acidity in the stomach and thereby an increase in 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, the substance can affect 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.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product. Pantozol i.v., powder for solution for injection 40 mg (RVG 22084), containing 40 mg pantoprazole, is registered in the Netherlands by Altana Pharma B.V. since 1998. In addition, reference is made to Pantozol authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC in AT, BE, DK, ES, FI, IT, NL, NO, PL, PT, SI and the UK, whereas the legal basis in SK is Article 10(3) a so-called hybrid application. This deviation is made because of the absence of the powder for solution for injection 40 mg in Slovakia. The observed differences in legal basis are allowed.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Pantoprazol Sandoz injectie 40 mg is a product for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance and excipients

The active substance is pantoprazole sodium sesquihydrate. There is no Ph.Eur. monograph on pantoprazole sodium sesquihydrate, but a draft Ph.Eur. monograph exists (XXXX: 2296, Pharmeuropa 18.2, April 2006). This draft has been used as guidance. (Note: The official monograph was published in the Ph.Eur. in April 2008.). Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU. The active substance specification is considered adequate to control the quality and meets the requirements of the draft monograph with in-house specifications for residual solvents. Batch analytical data demonstrating compliance with this specification have been provided for 5 batches. The MAH committed to evaluate the draft monograph as soon as it will be published in the Ph.Eur. and to revise the specifications accordingly. The MAH committed to submit a research study on the identification of impurities, and to provide validation data for specific impurities.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Stability data on the active substance have been provided for 6 production batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 36 months. Based on the data submitted a re-test period of 36 months was granted at 2-8°C.

Medicinal Product

Composition

Pantoprazol Sandoz injectie 40 mg, powder for solution for injection, contains 45.11 mg pantoprazole sodium sesquihydrate, corresponding to 40 mg pantoprazole, and is a white to yellowish powder. The reconstituted solution is a colourless to faintly yellow solution.

The powder is packed in a colourless type I glass vial, closed with a red rubber stopper and sealed by aluminium cap.

There are no excipients used; water for injections is used as production adjuvant but removed during lyophilization, and nitrogen is used as protective gas.

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The objective was to develop a product that would be equal to the innovator product Pantozol.

Manufacturing process and quality control of the medicinal product

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 batches in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification of the finished product includes tests for appearance, identification, water content, clarity and colour of solution, dissolving time, leakage testing of containers, pH value, particulate contamination, related substances and assay. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site has been provided, demonstrating compliance with the specification.

Stability tests on the finished product

Stability data on the powder have been provided for 3 batches in accordance with applicable European guidelines demonstrating the stability of the product for 12 months. The labelled storage conditions are: *Do not store above 25°C. Keep container in the outer carton.* Stability data on the powder for solution after reconstitution (and dilution) have been provided for 1 batch in accordance with applicable European guidelines demonstrating the stability of the product for 12 hours, with the labelled storage conditions: *Do not store above 25°C and use within 12 hours.* The MAH committed to perform initiated stability studies for the reconstituted powder for solutions diluted with two solutions, with powder samples stored up to the end of shelf life (3 years). The MAH committed to evaluate the shelf life specifications at the end of shelf life of the on-going stability studies. After marketing authorisation the shelf life was changed by a type IB variation from 12 to 18 months (see table Steps taken after finalisation of the initial procedure at Page 8).

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Pantazol, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of pantoprazole released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Pantoprazole is a well-known active substance with established efficacy and tolerability.

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Pantozol.

Pantoprazol Sandoz injectie 40 mg, powder for solution for injection, is a parenteral formulation and therefore fulfills the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an

aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Pantoprazol 40 mg is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

Risk Management Plan

Pantoprazole was first approved in 1994, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of pantoprazole can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation, which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test is of an acceptable quality.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Pantoprazol Sandoz injectie 40 mg, powder for solution for injection, has a proven chemical-pharmaceutical quality and is a generic form of Pantazol i.v., powder for solution for injection 40 mg. Pantazol® is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary. The SPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in agreed templates. Braille conditions are met by the MAH.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Pantoprazol Sandoz injectie 40 mg with the reference product, and have therefore granted a marketing authorisation. Pantoprazol Sandoz injectie 40 mg was authorised in the Netherlands on 11 June 2008.

A European harmonised birth date has been allocated (23 August 1994) and subsequently the first data lock point for pantoprazole is August 2006. The first PSUR is therefore expected in October 2009, after which a PSUR should be submitted every 3 years.

The date for the first renewal will be: 1 May 2010.

The following post-approval commitments have been made during the procedure:

Quality - active substance

- The MAH committed to evaluate the draft monograph as soon as it will be published in the Ph.Eur. and to revise the specifications accordingly.
- The MAH committed to submit a research study on the identification of impurities.
- The MAH committed to provide validation data for specific impurities.

Quality - medicinal product

- The MAH committed to perform initiated stability studies for the reconstituted powder for solutions diluted with two solutions, with powder samples stored up to the end of shelf life (3 years).
- The MAH committed to evaluate the shelf life specifications at the end of shelf life of the on-going stability studies.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of procedure	Approval /non approval	Assessment report attached, Y/N
Change in shelf life of the finished product from 12 to 18 months	NL/H/0806/001/IB/002	IB	31-1-2008	1-3-2008	Approval	N
Addition of an active substance supplier.	NL/H/0806/001/II/003	II	7-4-2008	25-12-2008	Approval	N
Update of SPC section 4.3 and 4.5	NL/H/0806/001/II/004	II	8-5-2008	7-7-2008	Approval	N
Change in primary packaging not in contact with the finished formulation.	NL/H/0806/001/IA/005	IA	21-5-2008	--	Non-Approval	N
Addition of a supplier of the primary packaging material.	NL/H/0806/001/IB/006	IB	22-5-2008	9-9-2008	Approval	N
Change in the address of the MAH.	NL/H/0806/001/IA/007	IA	25-8-2008	8-9-2008	Approval	N
Renewal	NL/H/0806/001/R/001	R	20-6-2010	3-9-2010	Approval	Y, Annex I
Implementation of the outcome of a referral for which no additional data are submitted by the MAH.	NL/H/0806/001/IB/008	IB	5-2-2011	21-4-2011	Approval	N
Grouped IA variations. MAH change for UK only.	NL/H/0806/001/IA/009/G	IA/G	13-11-2010	13-12-2010	Approval	N
Change in the batch size (including batch size ranges) of the finished product.	NL/H/0806/001/IB/010	IB	17-3-2011	18-4-2011	Approval	N

ANNEX I – Renewal marketing authorization

I.1 Introduction

Pantoprazole is a proton pump inhibitor and is indicated for the treatment of duodenal and gastric ulcers, moderate and severe reflux esophagitis and Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions.

Pantoprazol Sandoz was first authorised in Brazil as Pantopaz on 4 June 2001. Other applications of Pantoprazol Sandoz are marketed and launched in 29 countries.

The MAH submitted within the renewal dossier:

- Periodic Safety Update Report (JP1), covering the period 01-Feb-2004 to 31-Aug-2006 (dated 15 September 2009, signed)
- Periodic Safety Update Report (HP1), covering the period 01-Sep-2006 to 31-Aug-2009 (dated 16 September 2009, signed)
- Summary Bridging Report (JP1 + HP1), covering the period period 01-Feb-2004 to 31-Aug-2009, (dated 16 September 2009, signed)
- Clinical Expert statement, dated 29 September 2009.

These data have been assessed and are discussed below.

I.2 Data review

Quality aspects

In accordance with the CMD(h) Best Practice Guide on the processing of renewals in the mutual recognition and decentralised procedure (version November 2008), a quality expert statement has been submitted for Pantoprazol Sandoz, confirming:

- that the product complies with the requirements of Directive 2001/83/EC which obliges the MAH “.... to take account of technical and scientific progress and introduce any changes...”.
- that all changes relating to the quality of the products have been made following applications for variations and that the product conforms to the current CHMP quality guidelines.

The currently authorised specifications for the active substance and the finished products with the qualitative and quantitative composition have been provided.

Clinical efficacy and safety

Clinical efficacy

No new clinical data have become available during the previous period.

Clinical safety

During the period covered by the PSUR, there were no marketing authorisation withdrawals, revocations or suspensions, failures to obtain a marketing authorization renewal, restrictions on distribution, clinical trial suspensions, dosage modifications, changes to target population or indications or formulation changes made for safety reasons.

Recently an article 30 procedure (June 2010; EMEA/H/A-30/1002) to harmonise the SPC of pantoprazole was finalised. Furthermore pantoprazole takes part in the PSUR worksharing project of the HMA (DE/H/PSUR/0039). The assessment and the establishment of the core safety profile are currently ongoing.

The MAH provided the estimate on patient exposure, being 417.335.207 patient days in regular use. The calculation is based on the sales volume of 16.693.408.281 mg and the assumption of a DDD (defined daily dose) of 40 mg. No patients were exposed during clinical studies.

Adverse events

In the period under review the MAH received a total of 114 case reports concerning pantoprazole. The source of these reports was as follows:

Source	Serious		Non-Serious		Total
	Listed	Unlisted	Listed	Unlisted	
Spontaneous (HCP)	7	6	14	3	30
Clinical study	-	-	-	-	-
Literature	2	10	-	4	16
Consumer reports	-	-	37	31	68
Total	9	16	51	38	114

The 46 medically confirmed cases contained a total of 157 adverse reactions; 55 non-serious events and 102 serious events.

Adverse reactions occurred most frequently in the MedDRA system organ classes 'Gastrointestinal disorders' (n=34), 'General disorders and administration site conditions' (n=21) and 'Skin and subcutaneous tissue disorders' (n=21). The most frequently reported adverse reactions were 'Abdominal pain upper' (n=7) and 'Tubulointerstitial nephritis' (n=6).

Serious unlisted cases

In the period under the review the MAH received a total of 16 serious unlisted reports. Of 15 of the 16 reports the MAH concluded that no new safety issues arose from these cases as other co-suspected drugs or the underlying condition of the patient provided a possible explanation.

The MAH discussed the following case on dyspnoea:

A 49 year old male patient with a medical history of reflux oesophagitis, intervertebral disc prolapse and pollinosis developed dyspnoea during treatment with pantoprazole from 16 July 2009 to 18 July 2009. The outcome was reported as recovered/resolved. The causality was assessed as possible.

This serious spontaneous report was assessed as unlisted. The information in this individual case does not warrant a change to the Core Data Sheet (CDS). The topic dyspnoea will be re-evaluated.

RMS comment:

In the PSURs and the clinical overview the MAH states that the topic dyspnoea will be re-evaluated in the next PSUR. The MAH should discuss this topic in the next PSUR. This is accepted.

Fatal cases

Three cases with a fatal outcome were received by the MAH.

Pseudomembranous enterocolitis (N=1) [spontaneous report]

A 78 year old male developed pseudomembranous enterocolitis during treatment with pantoprazole and ceftriaxone, suspected as interacting drug. Other suspected drugs were moxifloxacin and ciprofloxacin. The patient took several other concomitant drugs. The outcome of the adverse events was fatal. For ceftriaxone and pantoprazole causality was assessed as possible.

The MAH noted that pseudomembranous enterocolitis is unlisted for pantoprazole. The information provided in this individual case does not warrant a change to the CDS.

RMS comment:

Pseudomembranous enterocolitis is listed for ceftriaxone. This is a single case in which there is a possible causal relationship with pantoprazole. At this moment no actions are deemed necessary since it is a single case that is confounded by several concomitant drugs.

Toxic epidermal necrolysis (N=1) [literature report]

A 45-year old female patient on a multiple drug therapy experienced toxic epidermal necrolysis and died due to septic shock. Her past medical history revealed APS I (Autoimmune polyendocrine syndrome), with chronic hypoparathyroidism, Addison's disease, chronic mucocutaneous candidiasis, vitiligo, pernicious

anaemia, non-infectious chronic hepatitis and hypergonadotropic hypogonadism.

She presented tetanic hypocalcaemia, onset of Addison's disease and primary hypogonadism. The patient was admitted to the hospital and her condition worsened, with the onset of vomiting, hypotension and marked hypokalaemia. She had crises of agitation and hallucinations. A febrile (38.2 C) cutaneous eruption of red maculae on the trunk was observed, exanthema involved the face, extremities and oral mucosa, and blistering began, so that toxic epidermal necrolysis was diagnosed. Physical examination showed confluent erythematous lesions and blisters, with widespread loss of epidermis over the body. Diffuse bleeding ulcerations and erosions involved lips and oral cavity. She died of septic shock. An autopsy was performed.

The MAH noted that toxic epidermal necrolysis and septic shock are unlisted for pantoprazole. However, other alternative causes provide a possible explanation for the reported adverse events. Severe skin reactions such as Lyell syndrome and Stevens-Johnson Syndrome are listed. No further measures are deemed necessary.

RMS comment:

Toxic epidermal necrolysis (TEN) is currently not listed in the SPC of pantoprazole while Lyell syndrome and Stevens-Johnson Syndrome are.

TEN is listed in the SPC of other proton pump inhibitors as omeprazole and esomeprazole which may indicate a possible class effect.

The MAH is requested to closely monitor TEN and report this back in the next PSUR. In this PSUR the MAH should give a cumulative overview of all TEN cases and indicate whether TEN should be included in the safety information of pantoprazole.

Subacute cutaneous lupus erythematosus (N=1) [literature report]

A 51-year old female patient experienced subacute cutaneous lupus erythematosus (SCLE) while receiving pantoprazole. The latency period between drug introduction and the onset of the event was 4-8 weeks. A lesion skin biopsy confirmed the diagnosis of SCLE. The patient had positive ANA screening with a speckled pattern as well as positive RF. Testing for ds-DNA-, Anti-Ro/SSA- and Anti-La/SSB-antibodies was negative. Pantoprazole was not discontinued. The patient died of another cause, but with active SCLE, after treatment with pantoprazole for up to 2 years.

This report was assessed as unlisted. The information provided in this individual case does not warrant a change to the CDS.

RMS comment:

It is unclear if there is a relationship between the (unknown) cause of death and the use of pantoprazole. No actions are deemed necessary.

Consumer reports

A total of 68 consumer reports were received by the MAH. These reports contained a total of 160 adverse events; all reports were non-serious. Of the 160 adverse events 113 events were listed and 47 events were unlisted.

Adverse reactions occurred most frequently in the MedDRA system organ classes 'Gastrointestinal disorders' (n=61), 'General disorders and administration site conditions' (n=33) and 'Nervous system disorders' (n=30). The most frequently reported adverse reactions were 'Drug ineffective' (n=20), 'Nausea' (n=14) and 'Diarrhoea' (n=10).

RMS comment:

No new safety issues were identified based on these consumer reports.

Studies

No studies were analysed or targeted during the reported period. The MAH discussed six publications retrieved from literature. These included two publications on efficacy, one on long-term safety in children, one on safety in pregnancy, and two publications on possible interactions.

In the period covered by this renewal period a possible interaction between clopidogrel and proton pump inhibitors has been identified (public statement EMA 29 My 2009). Since the discussion on this topic is still ongoing, and in view of the current worksharing and article 30 procedures no additional actions are

deemed necessary at this moment.

Overall, no new safety issues or indications of lack of efficacy were identified based on the studies. Any required changes to the SPC are covered by article 30 referral text, which will be adopted by the MAH.

Conclusion on Safety

Based on the reports received, the MAH will monitor the topic 'dyspnoea' and discuss this in the next PSUR. In future PSURs the MAH will discuss and summarize all serious unlisted cases.

The MAH received a fatal case with Toxic epidermal necrolysis (TEN). TEN is currently not listed in the SPC of pantoprazole while Lyell syndrome and Stevens-Johnson Syndrome are. Since TEN is listed in the SPC of other proton pump inhibitors as omeprazole and esomeprazole, this may concern a class effect. The MAH will monitor TEN closely and report on this AE in the next PSUR.

I.3 Assessment SPC / package leaflet / labelling

SPC

In the period under review the Company Core Data Sheet was amended. The changes of the CCDS are already adequately presented in the currently approved SPC. No actions are required.

The MAH committed to harmonise the SPC with the article 30 referral text, which was recently finalised (June 2010; EMA/H/A-30/1002) within 3 months after the finalisation of the renewal procedure.

Package Leaflet and labelling

The MAH will harmonise the package leaflet and labelling with the article 30 referral text.

I.4 Conclusions

No new safety issue that warrants regulatory action was identified. The benefit-risk balance remains positive. The member states consider that the renewal can be granted with unlimited validity.

The PSUR submission cycle is 3 years. Pantoprazole takes part in the PSUR synchronisation project of the Heads of Medicine Agencies, with a next data lock point of August 2012. The next PSUR will cover the period to August 2012.

The following commitment has been made:

Product information

- The MAH committed to adapt the product information in accordance with the accepted article 30 referral (EMA/A-30/1002) after finalisation of the renewal. This commitment has been fulfilled through variation NL/H/0806/001/IB/008.