15 November 2012
EMA/55126/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Prometax

rivastigmine

Procedure No.: EMEA/H/C/000255/X/0078/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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List of abbreviations

ACh	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer's Disease
ADAS	Alzheimer's Disease Assessment Scale
ADAS-Cog	Alzheimer's Disease Assessment Scale - Cognitive Subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study - Activities of Daily Living
ADCS-CGIC	Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change
AE	Adverse Event
AUC	Area Under The Curve
BID	Twice a day
BL	Baseline
BuChE	Butyrylcholinesterase
Cmax	Peak Plasma Concentrations
ChAT	Choline Acetyl Transferase
ChEI	Cholinesterase inhibitors
CI	Confidence Interval
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
ECG	Electrocardiogram
GI	Gastrointestinal
IOL	Initial open label
ITT	Intent-To-Treat
LOCF	Last Observation Carried forward
MMSE	Mini-Mental State Examination
NINCDS/ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association
NINDS-AIREN	National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences
NPI	Neuropsychiatric Inventory
NPI-D	Neuropsychiatric Inventory – Caregiver Distress Scale
OC	Observed Case
PK/PD	Pharmacokinetic/ Pharmacodynamic
RDO	Retrieved Drop Out
RPR	Rapid Plasma Reagin test
SAE	Serious Adverse Event

1. Background information on the procedure

1.1. Submission of the dossier

The applicant "Novartis Europharm Ltd." submitted on 1 December 2011 an application for an extension of the Marketing Authorisation to the European Medicines Agency (EMA) for Prometax, in accordance with Article 19 of Commission Regulation (EC) No. 1234/2008 and Annex I (2c) thereof.

The applicant applied for a new strength of the transdermal patches formulation: 13.3 mg/24 hours.

Furthermore pursuant to Commission Regulation (EC) No 1234/2008, art.7-2(b), this extension of MA application was grouped with a type II safety variation to update SmPC of transdermal patches with safety and pharmacological properties as result of the new Study CENA713D2340. Safety data of the transdermal patches were outlined in specific paragraph of the SmPC of the oral formulations.

The application proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Novartis Europharm Ltd. is already the Marketing Authorisation Holder for Prometax oral formulation (capsules and oral solution) and transdermal patches (4.6 mg/24 hours, 9.5 mg/24 hours).

The legal basis for this application refers to:

Article 19 of Regulation (EC) No 1234/2008 - Extensions of marketing authorizations

The application submitted a grouping as per Article 7 of Regulation (EC) No 1234/2008 including an extension of MA (13.3 mg/24 h transdermal patches) and a type II variation (update of SmPC based on the results of the new Study CENA713D2340).

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant did not seek scientific advice at the CHMP for the present application. AFSSAPS was consulted in a pre-submission meeting.

Licensing status

Prometax has been given a Marketing Authorisation in the European Union since 12 May 1998.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Pierre Demolis** Co-Rapporteur: **Kristina Dunder**

- The application was received by the EMA on 1 December 2011.
- The procedure started on 21 December 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 09 March 2012.
- During the meeting on 19 April 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 April 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 May 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 July 2012.
- During the CHMP meeting on 19 July 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 October 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 29 October 2012.
- During the meeting on 15 November 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Prometax patch 13.5mg/24 hours.
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2. Scientific discussion

2.1. Introduction

Alzheimer Disease (AD) is a progressive disease and the most common cause of dementia. From epidemiological studies, it is estimated that there are over three million individuals with dementia in the European Union, and of these about 70% have Alzheimer Disease.

Prometax is currently approved for Alzheimer Disease in the European Union (EU) as oral formulations and transdermal patches.

The Prometax oral formulations (capsules and oral solution) are indicated in the symptomatic treatment of the mild to moderately severe Alzheimer's dementia and symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease (EMEA/H/C/169/II/33).

The once daily Prometax transdermal patches were approved in EU for the symptomatic treatment of mild to moderately severe Alzheimer's dementia on 19 July2007 (EMEA/H/C/169/X/39).

The transdermal formulation is available in two sizes (5 cm^2 and 10 cm^2 patch). The 5 cm^2 patch contains 9 mg drug load of rivastigmine base with a nominal delivery rate of 4.6 mg/24 hours. The 10 cm^2 patch contains 18 mg drug load with a nominal delivery rate of 9.5 mg/24 hours.

Therapy is initiated with the 4.6 mg/24 hours dosage strength and after a minimum of four weeks of treatment and if well tolerated, this dose should be increased to 9.5 mg/24 hours, which is the recommended maintenance dose.

Novartis submitted on 1 December 2011 an application for an extension of the Marketing Authorisation to the European Medicines Agency (EMA) for Prometax (13.3 mg/24 h) grouped with a safety type II variation.

Prometax transdermal patch 13.3 mg/24h (15 cm^2) is intended to be used in the same indication if the treating physician considers that increasing the dose could give an additional therapeutic benefit.

2.2. Quality aspects

2.2.1. Introduction

The product is presented as a new strength of 15 cm^2 transdermal patches containing 27.0 mg, of rivastigmine base as active substance, and designed to release approximately 13.3 mg per 24 hours.

Each transdermal patch is a thin, matrix-type transdermal patch consisting of three layers:

- Backing layer: polyethylene terephthalate film, lacquered.

- Medicinal product matrix: alpha-tocopherol, poly(butylmethacrylate, methyl-methacrylate), acrylic copolymer.

- Adhesive matrix: alpha-tocopherol, silicone oil, dimethicone.

- Release liner: polyester film, fluoropolymer-coated.

The finished patches are individually packaged a in child-resistant sachet made of a paper/polyester/aluminium/polyacrylonitrile multi-laminated material. One sachet contains one transdermal patch.

2.2.2. Active Substance

The drug substance used in the 13.3mg/24h (15cm^2) transdermal patch, rivastigmine base, is the same chemical entity as that approved for the currently authorised transdermal patches.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim is to develop an additional strength of 13.3mg/24h (size 15cm^2) to the currently approved lower doses namely 4.6mg/24h (size 5cm^2) and 9.5mg/24h (size 10cm^2).

The composition is proportional to the already approved strengths. All components are already registered for the approved strengths. The manufacturing process is the same as the one in the authorised strengths.

All excipients used for the new transdermal patch strength are already used in the authorised strengths. Except minors changes in the specifications, update of silicone oil according to Ph Eur monograph, or in the method, update of the method for silicone pressure sensitive adhesive to include a change in the specification for appearance, all the data have been already assessed and approved for the current patch strengths.

The new strength is packaged in heat-sealed, child-resistant pouches made of multi-layer composite laminate consisting of paper bonded to polyethylene terephthalate and aluminum, with an inner-sealing layer of polyacrylnitrile-copolymer. The packaging components are identical to the currently approved laminate used for the currently approved strengths. Quality specifications and test procedures are described. The foil laminate pouch is tested for appearance, identity by IR, dimensions as well as sealed seam force. Reference IR spectra are provided. The packaging complies with European Directive 2002/72/ECincl amendment 2004/19 relating to plastic materials and articles intended to come into contact with foodstuffs.

Adventitious agents

No excipients of human or animal origin are used in the manufacture of this new strength.

Manufacture of the product

The manufacturing process is the same as for the currently marketed 4.6mg/24h (size 5cm^2) and 9.5mg/24h (size 10cm^2) transdermal patches.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process**.** The in process controls are adequate.

Three full-scale production batches data show that the patches can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this transdermal preparation.

Product specification

The product specifications include tests by validated methods for appearance, identification (HPLC, TLC), peel force, adhesion force, release rate (HPLC), impurities (HPLC), residual solvents (GC), microbial enumeration test, uniformity of content (HPLC), assay of rivastigmine (90.0-110.0%, HPLC), and assay of D,L-α-tocopherol (80.0 – 110.0%, HPLC).

Degradation products are controlled and their limits are justified by reference to stability studies and toxicology studies.

The tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for their intended purpose.

Batch analysis data confirm satisfactory uniformity of the product at release.

Stability of the product

A bracketed and matrix design was used for the registration stability studies. In this design, the 4.6 mg/24h, 9.5 mg/24 h and a no authorised strength are studied and the 13.3 mg/24h system is bracketed. The 4.6 mg/24h and 9.5 mg/24 h are the currently approved patch strengths; the data from the no approved strength is considered as supportive data.

Most of the stability data have already been provided for the approved strengths. Those data are remain with an update of stability results up to 48 months for the registration batches.

Stability data of 2 batches stored for 18 months at ICH long term storage condition of 30°C/65%RH and alternate long term storage condition of 30°C/75%RH (climatic zones III and IV) was provided for the 13.3 mg/24h proposed strength. The batches were tested for appearance, assay of rivastignine and tocopherol, related substances, release rate, adhesive forces, peel forces, and microbial tests.

Peel force is the stability limiting characteristic, limiting the currently approved finished product shelf-life at 25°C/60%RH to 24 months.

Based on the available data the same shelf life and storage condition as already granted for the approved strengths is acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance manufacture and control is the same as that reviewed for the already authorised patch strengths.

The development of the formulation and manufacturing process for the active substance and finished product are essentially the same and has been performed with a focus on to the critical variables that could affect the efficacy and safety of the product.

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The CHMP considered the quality of this product to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3. Non-clinical aspects

2.3.1. Introduction

Rivastigmine is considered a well-known inhibitor of acetyl cholinesterase (AChE) and butyryl cholinesterase (BChE) thought to facilitate cholinergic neurotransmission in remaining cholinergic neurons.

The pharmacokinetic properties of rivastigmine and its inactive major metabolite NAP226-90 after administration of Prometax patch have been well characterised in adequate studies at time of approval of the transdermal patches currently marketed.

Regarding the absorption upon dermal doses, the Tmax of rivastigmine of 18-24 hours indicated a slow release of rivastigmine from patch to the skin and/or slow dermal absorption. The AUC-ratio of the primary metabolite NAP226-90 to rivastigmine was 0.24 for the intravenous dose, as compared to about 200 for the oral dose. For the dermal doses, the ratio was 0.3-0.5. Data demonstrated the strong first-pass effect after oral administration and the virtual absence of first-pass metabolism after dermal administration.

The results of the in vitro studies indicated that rivastigmine is not metabolised to a significant extent in the dermal compartment. It seems therefore unlikely that novel metabolites would be formed in human skin during treatment with the patch formulation. Rivastigmine and its main metabolite NAP226-90 did not inhibit CYP 1A2, 2C8, 2C9/10, 2C19, 2D6, 2E1 and 3A4/5 up to concentrations of 200 µM.

No new primary or secondary pharmacodynamic studies have been conducted for the current application. For the current application inhibition studies with CYP2B6 were conducted.

2.3.2. Pharmacokinetics

The in vitro study submitted show no or a weak CYP2B6 inhibition up to 200 µM of rivastigmine and NAP226-90. Given that the average systemic concentrations of rivastigmine ranges from 2.71 ng/mL (5 cm2) to 19.5 ng/mL (20 cm2), a clinically relevant interaction with a CYP2B6 substrate (e.g.bupropion, methadone, efavirenz) is not expected.

2.3.3. Toxicology

The toxicological profile of Prometax Transdermal patches has been well characterised at the time of approval of the already marketed transdermal patches.

Repeated dose toxicity studies, mainly using dermal administration were performed in the mouse (up to 13 weeks), rat (up to 4 weeks), rabbit (up to 4 weeks) and minipig (up to 26 weeks duration). The studies in the most relevant animal species based on skin texture, the minipig, were performed with the formulation proposed for marketing, the SDZ ENA 713 patch, and are considered pivotal. The studies in mice, rats and rabbits are considered less important.

Following dermal application of the patch proposed for marketing, the SDZ ENA 713 patch, no signs of systemic toxicity were detected. A dose-related decrease in acetylcholinesteras levels was noted, explained by the pharmacodynamic action of rivastigmine. Local signs evident as erythema, but no oedema, was observed in all animals (3/sex/group), also in those treated with control patches. Macroscopically, a slight to moderate thickened and/or reddened skin was noted and dermatitis was found at the microscopic evaluation of all treated animals including those with control patches. In light of the similar distribution of adverse local reactions between treated and control animals, the erythema/dermatitis were assessed as probably caused by the composition of the patch and not by the active substance itself. This conclusion is supported by the observation that increased rotation of patch application sites reduced inflammation and that there was no dose-relationship for dermatitis in minipigs. Further, as the minipig is a species with a skin texture considered fairly similar to humans, local reaction in human skin would be anticipated.

Toxicokinetic data obtained following dermal administration (solution or patches) in the 26 week minipig study demonstrated a Cmax of 2.9±0.6 ng/ml in males and 2.9±1.0 ng/ml in females and an AUC of 48±16 ng*h/ml in males and 43±14 ng*h/ml in females. In humans for a 15 cm^2 patch with a maximum anticipated daily dose of rivastigmine of 13.3 mg Cmax was determined to 14.1±6.30 ng*h/ml and AUC to 233±83.2 ng*h/ml. Thus, there is no margin to human exposure. Higher dosage in the minipig toxicology studies were not considered feasible due to local reactions. This is considered acceptable.

No genotoxicity studies were performed. Considering that rivastigmine is a well-known substance with a previously investigated negative genotoxicity profile, the absence of new studies was considered acceptable.

A dermal carcinogenicity study in mice with daily administration of rivastigmine 0.25, 0.50 and 0.75 mg/kg dissolved in ethyl alcohol solution demonstrated no carcinogenic potential. The palpable masses sporadically observed in female mice both in treated and control animals were not considered treatment related. Oral carcinogenicity studies in mice and rats did not demonstrate a carcinogenic potential of rivastigmine. No systemic or local adverse events in relation to treatment were observed in the oral carcinogenicity studies. The toxicokinetic evaluation of the dermal carcinogenicity study demonstrated exposure in a fairly dose-related manner to rivastigmine and its main metabolite ZNS 114-666.

Reproductive and developmental toxicity studies by the dermal route were not carried out because a complete package was conducted in rats and rabbits with rivastigmine tartrate using the oral route of administration. These studies conducted with rivastigmine tartrate gave no evidence of a teratogenic potential for rivastigmine. A slightly prolonged duration of gestation in post- and perinatal studies in rats, although considered too small to be of biological relevance, nethertheless was consistently recorded and may be a sequel to cholinergic stimulation.

Juvenile toxicity studies were not conducted with trans-dermal system using rivastigmine.

A large number of local tolerance studies using relevant animal models of acute dermal irritation, contact hypersensitivity, delayed contact hypersensitivity and primary skin irritation demonstrated rivastigmine to be non-irritant to animal skin. Furthermore, no allergenic and sensitization potential of rivastigmine was observed. Primary eye irritation studies demonstrated rivastigmine to be irritating to the rabbit eye. Therefore, patient or the caretaking person should avoid contact with eyes after handling of the patch. Section 4.4 of the transdermal patches formulations has been updated to specifically mention what to do in case of contact with eyes in the current “other warnings and precautions” sub-section.

The performed phototoxicity study did not demonstrate any phototoxic potential of the rivastigmine dermal patch.

Regarding the excipients, non-novel excipients have been used for the patches in this application.

2.3.4. Environmental risk assessment

No new environmental risk assessment was provided for this application.

The MAH considers that an environmental risk assessment is not necessary for the current line extension, based on the fact that the introduction of the 15 cm2 patch on the European market will not lead to a significantly increased use of rivastigmine.

The MAH submitted the justification of use of the STP modelling with the SimpleTreat model and includes a refinement of the $PEC_{surface\ water}$ and $PEC_{sediment}$ in the Phase II Tier B assessment. Rivastigmine is not expected to bio-accumulate in aquatic species according to the screening criteria for bioaccumulation. Adsorption of rivastigmine to sewage sludge is low and therefore partitioning into the soil compartment via spreading of sludge on agricultural soils is not expected. The highest respective risk ratio has been found for the sediment compartment (PEC/PNECsediment) with 0.0026.

Based on these informations available, rivastigmine does not present environmental risk and the CHMP considered the justification for the absence to be acceptable.

2.3.5. Discussion on non-clinical aspects

No new preclinical data has been included for this line extension except for one in vitro inhibition study with CYP2B6. This study did not indicate a relevant inhibition of CYP2B6 at concentrations up to 200 µM (the highest concentration tested).

2.3.6. Conclusion on the non-clinical aspects

The CHMP considers that the application for Prometax transdermal patch 13.3 mg/24 h is approvable from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

Prometax patches, 4,6mg/24 h and 9.5 mg24 h were approved with the procedure EMEA/H/C/169/X/39 in July 2007.

The pharmacokinetic profile of rivastigmine and its metabolite NAP226-90 following Prometax Patch 15 cm2 (13.3mg/24hr) was fully characterized in both healthy volunteers and AD patients, together with the other three Prometax Patch strengths (5 cm2, 10 cm2 and 20 cm2) at time of approval of the already marketed transdermal formulation [Study D2331]. (Summary of results in Section 2.4.2)

The clinical package presented included a 24-week, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled, parallel-group study of the once-daily Prometax 10 cm2 and 20 cm2 patch and the Prometax capsule 6 mg bid in patients with probable AD [Study D2320].

This study included four treatment arms (placebo, once daily 10 cm2 patch, once daily 20 cm2 patch and 6mg/bid oral capsules) and consisted of a 16-week titration period and an 8-week maintenance period.

The 15 cm2 dose was used as a titration dose for the 20 cm2 treatment arm and not evaluated as a randomized dose. Exposure to the 15cm2 dose was for 4-weeks during which time no efficacy assessments were performed.

A risk benefit ratio for the 15 cm2 dosage strength could not be determined and according to the available data the 20 cm2 patch was not approvable due to an unfavourable risk benefit ratio.

For the current application a new clinical study was submitted [Study CENA713D2340].

GCP

The clinical trials included in the application were performed, according to the Applicant, in accordance with the “Declaration of Helsinki” as adopted by the 48th World Medical Assembly held in Somerset West in 1996 and with the laws and regulations of the country in which the studies were conducted.

All studies have been conducted in compliance with ICH E6 guidelines on GCP implemented in the EU by 2005/28/EC as claimed by the applicant.

2.4.2. Pharmacokinetics

Study D2331 was an open-label, parallel group, ascending (titration) dose proportionality study evaluating the Prometax 5 cm2, 10 cm2, 15 cm2, and 20 cm2 once daily dose transdermal patches

and 1.5 mg, 3 mg, 4.5 mg, and 6 mg twice daily dose capsules at steady state in patients with mild-to moderate Alzheimer's disease.

Patients were randomized to receive either patch or capsule. A total of 25 patients were randomized to receive Prometax patch treatment, 13 patch patients completed all 4 study periods. A total of 26 patients were randomized to receive Prometax capsule treatment, 17 completed all 4 study periods.

The results for 25 patch-treated patients showed that after application of the patches, rivastigmine plasma concentrations rose slowly to reach peak concentrations at a median tmax of 8.0 h. Average Cmax observed ranged from 2.71 ng/mL (5 cm2) to 19.5 ng/mL (20 cm2); for the 15 cm2 patch average Cmax was 14.1 ng/mL. Average AUC after 24h was in the range of 46.3 ng•h/mL (5 cm2) to 345 ng•h/mL (20 cm2); for the 15 cm2 patch average AUC after 24h 233 ng•h/mL. Elimination half-life of rivastigmine from plasma, on average, was 3.37 h (t½ was available only for the 20 cm2 patch).

Exposure to rivastigmine (AUC) increased over-proportionally with rising doses after dermal applications. As assessed by compartmental analysis [Modeling and Simulation Report for Study D2331], on escalating through the patch sizes of 5, 10, 15 and 20 cm2, the increase in rivastigmine exposure relative to the lowest dose (5 cm2) was 2.6, 4.9 and 7.8 fold for the 10, 15 and 20 cm2 patch, respectively. However, the deviation from dose-proportionality was less apparent than with oral rivastigmine, and the increase in exposure (AUC) with rising patch size from 10 cm2 to 15 cm2 (i.e. 1.5-fold) was 1.8-fold, indicating an increase close to linearity.

The fluctuation index (i.e. measure of peak/trough fluctuation) was in the range of 0.57 to 0.77 for the patch, demonstrating a low fluctuation between peak and trough concentrations with the patch.

The inter-patient variability in the exposure parameters of rivastigmine (Cmax and AUC 24h) as assessed by the coefficients of variation (CVs) was of 33-45%.

Relationship between rivastigmine exposure at steady state and bodyweight was observed also observed. With this regard Section 4.2 of the SmPC of transdermal patches has been updated to recommend careful titration in patients with a low body weight (< 50 kg). In addition, no specific studies in special populations (renal and hepatic impairment) or interaction studies have been performed with the transdermal patches consequently recommendations on the use of the patch in the mentioned special population have been introduced in relevant sections of the SmPC.

2.4.3. Discussion on clinical pharmacology

Plasma concentrations rose slowly after the application of the patch until plateau concentrations is reached at Tmax of approximately 8 hours with all strengths. From the obtained study it appears clearly that systemic exposure to rivastigmine evolves not linearly with the dose. AUC increased over than proportionally with increasing doses.

2.4.4. Conclusions on clinical pharmacology

Rivastigmine was well released from the transdermal system over 24 hours dermal application period with approximately 50% of the drug load released from the system, which is in full agreement with release rates of the other patch sizes. The Mean Content Uniformity of Batch (loaded dose) for the 15 cm2 patch is 27 mg. The nominal delivery rate was calculated to be 13.3 mg per 24 h.

2.5. Clinical efficacy

2.5.1. Dose response studies and main clinical studies

CENA713D2340: 48-week, multicenter, randomized, DB, parallel-group study of the comparative efficacy, safety, and tolerability of Prometax 10 and 15 cm2 patches.

Here below the general study design:

<table>
<tr><td>Phase</td><td colspan="2">Screening</td><td colspan="6">Initial open-label</td><td colspan="5">Double-blind treatment</td></tr>
<tr><td>Visit</td><td>1</td><td>2</td><td colspan="2">3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>1.1</td><td>1.2</td><td>1.3</td><td>1.4</td><td>1.5</td></tr>
<tr><td>Week</td><td>< -5</td><td>Day 1</td><td colspan="2">4</td><td>8</td><td>12</td><td>24</td><td>36</td><td>48</td><td>4</td><td>12</td><td>24</td><td>36</td><td>48*</td></tr>
<tr><td colspan="15"></td></tr>
<tr><td colspan="3"></td><td colspan="2">Titration</td><td colspan="3">Maintenance</td><td colspan="2">Additional</td><td colspan="5">Maintenance for decliners</td></tr>
<tr><td colspan="3"></td><td colspan="2" rowspan="5">Prometax 5 cm^2</td><td colspan="5"></td><td colspan="5">Prometax 10 cm^2 patch</td></tr>
<tr><td colspan="3"></td><td colspan="5" rowspan="3">Prometax 10 cm^2 patch with demonstrated decline at week 24, 36, or 48</td><td colspan="5" rowspan="2"></td></tr>
<tr><td colspan="3"></td><td colspan="5">Prometax 15 cm^2 patch</td></tr>
<tr><td colspan="3">Treatment</td><td colspan="5">None</td><td colspan="5">Extended open-label for (non decliners)</td></tr>
<tr><td colspan="3" rowspan="2"></td><td colspan="5" rowspan="2"></td><td>Visit</td><td>3.1</td><td>3.2</td><td>3.3</td><td>3.4</td></tr>
<tr><td>Week</td><td>12</td><td>24</td><td>36</td><td>48</td></tr>
<tr><td colspan="3"></td><td colspan="5">Prometax 10 cm^2 patch without demonstrated decline at Week 48</td><td colspan="5">Prometax 10 cm^2 patch</td></tr>
</table>

Baseline for the Initial open-label (IOL) treatment phase was Day 1 prior to first dose. Baseline for the Double-blind (DB) treatment phase was the DB randomization day.

Additional visits were allowed for patients without demonstrated functional and cognitive decline during IOL maintenance visits. Patients randomized to the DB treatment phase began treatment with DB medication on the day following randomization. Down-titration was allowed as required to address tolerability problems.

* or premature discontinuation visit

Prometax 15 cm2 and Prometax 10 cm2 patch doses were selected for evaluation during the 48-week, randomized, double-blind phase. The daily Prometax 10 cm2 dose and regimen was in accordance with product labelling. The selection of the Prometax 15 cm2 once daily dose was based on the results of data previously submitted.

Methods

- Study participants

Main inclusion criteria: The study population consisted of patients between 50 and 85 years of age with a diagnosis of dementia of the Alzheimer's type according to the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) criteria in addition to a clinical diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's disease and Related Disorders Association (NINCDS/ADRDA) criteria, and an initial open-label (IOL) baseline Mini-Mental State Examination (MMSE) score of 10-24, corresponding to mild to moderate dementia.

- Treatments

During the IOL phase, patients who demonstrated decline during the 24-48 week treatment at the approved maintenance dose of Prometax 10 cm2 were eligible for enrolment into the double-blind (DB) treatment period, and were randomized equally into 1 of the 2 treatment arms. Decline during the IOL phase was defined as: functional decline (investigator judgment) and cognitive decline (a decrease of at least 2 points in the MMSE score from the previous visit or at least 3 points from the IOL-baseline). Patients were required to meet both criteria prior to randomization into the DB phase. Patients who did not fulfil the criteria for decline during the IOL phase were offered continued treatment with Prometax 10 cm2 in the extended open-label (EOL) phase.

- Objectives and outcomes/endpoints

The primary efficacy objective was to compare the efficacy of target Prometax 10 cm2 patch vs. target Prometax 15 cm2 patch in patients who have demonstrated cognitive decline in the initial open-label (IOL) phase (Prometax 10 cm2 patch) with respect to:

• The change from DB randomization baseline to Week 48 of the DB phase in cognition as assessed by the ADAS-cog subscale,

• The change from DB randomization baseline to Week 48 of the DB phase in instrumental activities of daily living as assessed by the ADCS-Instrumental ADL subscale.

The secondary efficacy objective was to compare the efficacy of target Prometax 10 cm2 patch vs. target Prometax 15 cm2 patch in patients who have demonstrated cognitive decline in the IOL phase (Prometax 10 cm2 patch) with respect to:

- The time to functional decline (i.e. interval between DB randomization baseline to first decline from DB randomization baseline) in instrumental activities of daily living as assessed by the ADCS-Instrumental ADL subscale over the 48-Week DB phase;
- The change from DB randomization baseline to Week 48 of the DB phase in attention and executive function as assessed by the Trail Making Test (TMT) Parts A and B;
- The change from DB randomization baseline over the 48-Week DB phase in neuropsychiatric symptoms as assessed by the 10-item Neuropsychiatric Inventory (NPI-10).

The safety objective of Study D2340 was to compare the safety and tolerability of target Prometax 15 cm2 patch vs. target Prometax 10 cm2 patch in the DB treatment phase with respect to the incidence of adverse events (AEs), serious AEs (SAEs), and discontinuations due to AEs.

The assumptions on standard deviation of 8 points for the change in ADAS-cog and ADCS-Instrumental ADL were taken from previous long-term Prometax studies on the oral formulation. A sample size of 410 patients per treatment group was required at the end of the DB phase to detect a treatment difference in means of 1.9 points on ADCS-cog and ADCS-Instrumental ADL score in the ITT population using a two group t-test with a 0.050 two-sided significance level. To adjust for 5% of patients who were not be included in the ITT population, a total of 864 patients (432 per group) were needed at the time of randomization (end of IOL phase).

- Participants flow

There were 1979 patients screened for this study. A total of 1571 patients were planned for enrolment into the IOL phase, 1582 patients were enrolled and exposed to study drug. A total of 499 discontinued. The most commonly reported primary reasons for discontinuation were adverse events, withdrawal of consent, and unsatisfactory therapeutic effect.

At the end of the IOL phase, 567 patients were classified as decliners and randomised into the DB phase. The time to meet decline criteria for entry into the DB phase was variable, extending from 24 to 48 weeks. Overall, the patient disposition during the DB phase was well balanced between the treatment groups. The Prometax 15 cm2 patch group had a lower incidence of overall discontinuations compared to the lower dose treatment group, driven primarily by the slightly lower incidences of discontinuations due to AEs. The results of Kaplan-Meier analysis of time to first AE leading to discontinuation and time to discontinuation for any reason show no major differences in the discontinuation pattern over time between the treatment groups during the DB phase. Discontinuation due to unsatisfactory therapeutic effect was reported for 4.6% of patients treated with Prometax 15 cm2 and 4.5% of patients treated with Prometax 10 cm2.

A total of 457 patients were entered the EOL phase and were treated with Prometax 10 cm2. Of the 457 treated patients, 62 patients (13.6%) discontinued.

- Conduct of the study

The study protocol was amended 4 times:

Amendment 1 related to some minor change in laboratory test schedule, SAE reporting routines, biomarker general sampling procedure.

Amendment 2 was implemented at the request of Canadian Health Authority, and was specific to Canadian sites only.

Amendment 3, issued after approximately 1370 patients were enrolled into the IOL treatment phase and 275 patients were randomized to the DB treatment phase, and was implemented based on the response received from the US FDA at the EOP2 meeting. It also modified study objectives to elevate the prior secondary objective of ADCS-Instrumental and ADL subscale as a co-primary outcome variable, clarified the inclusion criteria and added rater qualifications/certification performing the ADAS-cog. It also changed the primary analysis population from PP population to the ITT population and increased the sample size from 1200 to 1571 patients for the IOL treatment phase so that at least 864 patients would be randomized to the DB treatment phase to provide sufficient power for both primary outcome variables. The percentage of patients who were expected to decline during the IOL phase and enter the DB phase was recalculated and reduced.

Amendment 4 issued after the study recruitment was complete,

Added an Intermediate Home/Assisted Living Questionnaire and revised the Patient Instructions to reinforce the importance of the proper use and application of Prometax transdermal patch =.in response to post-marketing reports of medication errors and inappropriate use of Prometax transdermal patch.

All amendments were implemented prior to the un-blinding of study treatments for the DB phase.

During the IOL phase, 17.7% of patients had at least 1 protocol deviation; however, only 1% of patients had major protocol deviations, and these consisted of 1 patient who had a treatable dementia, which was identified prior to the IOL phase; and 15 patients who did not meet the decline criteria during the IOL phase.

During the DB phase, 9.3% of the patients had at least 1 protocol deviation, and only 1 patient had a major protocol deviation. PID 0204/00004 did not meet the protocol defined decline criteria) when the decline criteria was mistakenly compared to Visit 1 instead of baseline. This patient continued in the DB phase until discontinuation due to an AE.

Of the 457 patients included in the EOL phase, 24 patients (5.3%) had protocol deviations; however, none of the deviations resulted in patient exclusion from an analysis population. Drug dispensing errors during the EOL were reported in 3 patients, incorrect study medication or dose was reported in 4 patients, and titration errors were reported in 1 patient. Most of these errors were due to human error.

The protocol deviations are not considered to confound the interpretation of efficacy or safety in a systematic way.

- Baseline data

The majority of patients who entered the IOL phase were female (62.6%) and most were more than 65 years of age (90.2%) (Table 11-2), as is consistent with this condition. The patient population was predominantly Caucasian (95.5%), reflecting the populations in the participating countries.

For the IOL phase, the baseline demographics were generally similar when comparing patients groups of decliners, non-decliners, and those who discontinued. The non-decliners group had a relatively higher proportion of male patients compared to the other groups (42.3% compared to around 35%).

For those patients participating in the IOL, AD characteristics for patients with decline were consistent with a population of patients with more advanced AD, as shown by the longer mean and median durations since first symptoms noticed by the patient caregiver and since first symptoms was diagnosed by a physician, slightly lower IOL baseline mean and median MMSE scores, and higher proportion of patient with prior AD treatments as compared to the non-decliners.

The majority of patients who entered the DB phase were female (64.7%) and most patients were more than 65 years of age (90.8%).

Overall, the treatment groups for the DB phase were similar with respect to the DB-baseline demographics. The Prometax 15 cm2 group had a higher proportion of patients younger than 65 years of age (12.1% vs. 6.3% in the lower dose treatment group).

For patients who entered the DB phase, the mean and median duration of time since the first AD symptom and since the first diagnosis by a physician were slightly shorter in the Prometax 15 cm2 group (mean 3.86 and 1.80 years, respectively) than in the lower dose treatment group (mean 4.31 and 2.04 years, respectively). There were no important differences in other background characteristics assessed.

Mean MMSE at baseline was similar in both treatment groups (14.1 and 14.2 in the Prometax 15 cm2 and Prometax 10 cm2 groups, respectively). At DB-baseline approximately 80% of the patients showed an MMSE score of 10 or above, while at the IOL baseline all but 1 patient had an MMSE score of 10 or above.

For patients who were randomized into the DB period, the medical histories were generally similar to that of the enrolled population. In the following SOCs, the overall incidence was slightly higher (by 3-6%) in patients treated with Prometax 15 cm2 compared to the lower dose treatment group: metabolism and nutrition (51.4% vs. 46.3%), vascular (61.4% vs. 55.7%), gastrointestinal (32.5% vs. 28.9%), nervous system (30.4% vs. 27.5%), and cardiac (22.1% vs. 19.5%). The most common medical histories, depression (36.4% vs. 22.1%) and hypertension (56.8% vs. 51.2%) were between 4% and 5% more prevalent in the higher dose treatment group.

Consistent with the reported past medical histories, nearly all patients were receiving medications and or significant non-drug therapies prior to study enrollment. In the IOL-Safety population, the most common treatments were anticholinesterases, which were taken by more than half the patients. Donepezil was taken by 30% of patients. Nearly a third of patients were taking HMG-CoA reductase (statins). Memantine was also taken by 27% patients. Aspirin (salicylic acid) was also commonly used.

Prior to study enrolment, 628 patients (39.7% of the Safety-IOL population) received treatment with CNS-related medications. Nearly a third of the patients were receiving antidepressant therapy, most commonly sertraline. Hypnotic/anxiolytics, most commonly lorazepam, were taken by approximately 12% of patients. The use of antipsychotics was low (4.6%).

Summary of main efficacy results

Patients treated with the Prometax 15 cm2 patch showed a lesser decline (i.e. improved therapeutic benefit) in activities of daily living as measured by ADCS-Instrumental ADL subscale change from DB-baseline at DB-week 48 (primary endpoint) when compared to Prometax 10 cm2 patch. The differences were statistically significant. The results were similar in the ITT-OC population (2.5 (95%CI 0.8; 4.1) p=0.004). Statistical significance was also achieved at all-time points for the PP-LOCF (2.0, p=0.010) and PP-OC analyses (2.1, p<0.017).

Cognitive decline for the ITT-LOCF analysis, as measured by the mean change from DB baseline in ADAS-cog score, was less at each time point in the Prometax 15 cm2 patch group than in the Prometax 10 cm2 patch group, and the between-treatment group differences were statistically significant in favour of the Prometax 15 cm2 patch at Week 24 (-1.3 points; 95% CI: -2.5,-0.2; p=0.027), but not at Week 48 (-0.8 points; 95% CI: -2.1 , 0.5; p=0.227), which was the primary endpoint. In the ITT-OC, PP-LOCF and PP-OC populations the results show a numerical superiority for the Prometax patch 15 cm2 group over the Prometax 10 cm2 patch group at all time-points.

The difference between treatment group groups was not statistically significant for any of the secondary endpoints even if the results show a numerical superiority for the Prometax patch 15 cm2 group over the Prometax 10 cm2 patch group.

Sub-group analyses

Prospectively defined subgroup analyses of ADCS-Instrumental ADL data and ADAS-Cod data were performed to show homogeneity of treatment effects.

The following are presented here:

1. Change from baseline in ADCS-Instrumental ADL and ADAS-Cog score in the 48-week double-blind phase, **by time to meet decline criteria** in the initial open label phase and treatment group (ITT-DB population)

2. Change from baseline in ADCS-Instrumental ADL and ADAS-Cog score in the 48-week double-blind phase **by disease status** (a) moderate AD or (b) moderate to severe AD only at double-blind baseline (ITT-DB population).

The analysis of change from DB-baseline in ADCS-Instrumental ADL score showed a similar decline within treatment groups for patients who met the decline criteria in >36 weeks or did so in ≤ 36 weeks during the Initial open-label phase. The decline was less in the Prometax 15 cm2 patch group than in the Prometax 10 cm2 patch group at each timepoint except Week 12 for those who met decline criteria in ≤ 36 weeks.
For patients who met the decline criteria in ≤ 36 weeks, the analysis of change from DB-baseline in ADAS-cog score showed less decline within the Prometax 15 cm2 patch group at all time-points compared to those who met the decline criteria in >36 weeks. In the Prometax 10 cm2 patch group, a similar decline was observed for patients who met the decline criteria in ≤ 36 or in >36 weeks. At each time-point, regardless of whether the patients met the decline criteria in ≤ 36 weeks or in >36 weeks, the observed decline was less in the Prometax 15 cm2 patch group than in the Prometax 10 cm2 patch group at all time-points.

The analyses of change from DB-baseline in ADCS-Instrumental ADL score showed a similar decline within treatment groups for patients with moderate or moderate to severe AD; however, at each timepoint the decline was less in the Prometax 15 cm2 patch group than in the Prometax 10 cm2 patch group.

The analysis of change from DB-baseline in ADAS-cog score showed a similar decline within treatment groups for patients with moderate or moderate to severe AD; however, at each timepoint the decline was less in the Prometax 15 cm2 patch group than in the Prometax 10 cm2 patch group.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study CENA713D2340 was designed to investigate the optimal use of Prometax Patch in longer term treatment to provide evidence on the benefit of a higher Prometax patch size (15 cm2) for those patients who seem to derive limited or no benefit on standard doses.

The design of the study D2340 was appropriate. The co-primary efficacy variables ADAS-cog total score and ADCS-Instrumental ADL total score are accepted, they are commonly used as primary variables in clinical trials of Alzheimer's disease. The defined objectives and outcomes were appropriate. The statistical methods for analysing efficacy were appropriate.

Patients demographic and background characteristics, medical history and prior medication are typical for the targeted population. With respect to other baseline demographics and baseline data the treatment groups for the DB phase were comparable.

There were no major differences in the discontinuation pattern with respect to amount, cause and time between the treatment groups during the DB phase, therefore discontinuation is not likely to have any major influence on the conclusion drawn from the efficacy data.

Efficacy data and additional analyses

For the ITT-LOCF analysis, decline in function measured by the mean change from DB-baseline in ADCS-Instrumental ADL score, was less at each time-point in the Prometax 15 cm2 patch group than in the Prometax 10 cm2 patch group. The between-treatment group differences were statistically significant in favour of the Prometax 15 cm2 patch group at Week 48 (primary endpoint) (2.2 points; 95% CI: 0.8, 3.6; p=0.002).

Cognitive decline for the ITT-LOCF analysis, as measured by the mean change from DB baseline in ADAS-cog score, was less at each time-point in the Prometax 15 cm2 patch group than in the Prometax 10 cm2 patch group, and the between-treatment group differences at Week 48 (-0.8 points; 95% CI: -2.1, 0.5; p=0.227), were not statistically significant (primary endpoint). The between-treatment group differences were statistically significant in favour of the Prometax 15 cm2 patch at Week 24 (-1.3 points; 95% CI: -2.5,-0.2; p=0.027).

The results of the secondary efficacy endpoints (time to functional decline, Trail Making Test, NPI-10) showed that the difference between treatment group groups was not statistically significant for any of the criteria even if a numerical superiority for the Prometax patch 15 cm2 group over the Prometax 10 cm2 patch group was observed.

The prospective subgroups analysis of change from DB-baseline in ADCS-Instrumental ADL and ADAS-cog scores showed a similar functional and cognitive decline within treatment groups for patients who met the decline criteria in >36 weeks or in ≤ 36 weeks and independently of the disease status.

2.5.3. Conclusions on the clinical efficacy

Prometax 15 cm2 patch showed a statistically significant difference in instrumental activities of daily living when compared to Prometax 10 cm2 patch at weeks 24 and 48 but failed to show an efficacy at 48 weeks (the endpoint) for cognitive decline. The difference for this co-primary endpoint was numerically in favour of Prometax 15 cm2 patch at week 48 and statistically significant in favour or Prometax 15 cm2 at 24 weeks compared to Prometax 10 cm2 patch.

For the secondary efficacy criteria the difference between treatment group groups was not statistically significant for any of the criteria. Nevertheless, the results show a numerical superiority for the Prometax patch 15 cm2 group over the Prometax 10 cm2 patch group for the Time to functional decline and Trail Making Test.

Study 2340 failed to formally show the superiority of Prometax 15 cm2 patch over Prometax 10 cm2 patch. Nevertheless, patients treated with Prometax 15 cm2 patch showed a lesser decline than patients treated by Prometax 10 cm2 patch in both domains. Thus, some patients treated initially with Prometax 10 cm2 patch with beneficial effect follows by a decline could benefit from the new dosage.

2.6. Clinical safety

The overall safety objective of Study D2340 was to compare the safety and tolerability of target Prometax 15 cm2 patch vs. target Prometax 10 cm2 patch in the DB treatment phase with respect to the incidence of adverse events (AEs), serious AEs (SAEs), and discontinuations due to AEs.

The safety results from the double-blind phase of Study D2340 are presented here in the context of those reported from the pivotal double-blind, placebo-controlled (Study D2320). As the AD indication for Prometax 10 cm2 was approved based on the evaluation of data from (Study D2320), the safety data from this 24-week study are not presented for evaluation, but for comparison to data from the first 24 weeks of treatment in Study D2340.

Patient exposure

The mean and median duration of exposure to study drug was similar in the 15 cm2 and 10 cm2 treatment groups during the 48-week DB phase of Study D2340 (41.39 and 41.28 weeks, respectively) and in the 20 cm2, 10 cm2 and placebo groups during the 24 weeks of Study D2320 (22.0, 21.4 and 23.0 weeks, respectively).

Adverse events

In the DB phase of Study D2340 no new safety signals emerged from the analysis of AEs with either the Prometax 15 cm2 or 10 cm2 patches.

During the full 48-week double-blind phase of Study D2340, the most frequently affected SOCs were Gastrointestinal disorders, Psychiatric disorders, General disorders and administration site conditions, and Nervous system disorders. The incidence of AEs in each of these SOCs was higher in the Prometax 15 cm2 patch group compared to the Prometax 10 cm2 patch group. Of the commonly observed AEs (≥ 3% in any treatment group) the most frequent event in the Prometax 15 cm2 patch group was nausea, followed by vomiting, fall, weight decreased, application site erythema, decreased appetite, diarrhea and urinary tract infection. The percentages of patients with these events were higher in the Prometax 15 cm2 patch group than in the 10 cm2 patch group. With the exception of weight decreased, the percentages of patients with these events decreased over time in both treatment groups.

Other AEs of interest which occurred less frequently, but were observed in a markedly higher percentage of patients in the Prometax 15 cm2 group than in the 10 cm2 group, included dizziness and upper abdominal pain. The percentages of patients with these events also decreased over time in both treatment groups.

The majority of patients reported AEs of mild to moderate severity. The AE severity profile was generally similar for both the Prometax 15 cm2 and 10 cm2 patch groups.

When the first 24 weeks of treatment in the DB phase of Study D2340 was compared to the 24 weeks of treatment in Study D2320, the AE profiles of the Prometax 10 cm2 groups in both studies were generally similar, but many individual AEs were more frequent in the Study D2320. The most common gastrointestinal AEs were all reported in substantially lower percentages of patients in the Prometax 15 cm2 patch group from Study D2340 than in the Prometax 20 cm2 patch group from Study D2320. However, these events were generally reported in a higher percentage of patients in the Prometax 15 cm2 patch group from Study D2340 than in the Prometax 10 cm2 patch group from either study.

This pattern was also observed for the majority of commonly reported psychiatric and nervous system related AEs. However, as noted above, a substantially higher percentage of patients in the Prometax 10 cm2 patch group of Study D2320 than in the Prometax 10 cm2 patch group from Study D2340 reported these AEs making the comparison between the Prometax 20 cm2 patch group and the Prometax 15 cm2 patch group difficult to evaluate.

After 24 weeks of treatment in Study D2340, the overall incidence rate of AEs was similar in both treatment groups and lower than during the first 24 weeks of treatment. Other than AEs of nausea, fall, weight decreased, and urinary tract infection in the Prometax 15 cm2 patch group, all AEs observed after Week 24 were reported in less than 3% of patients.

Serious adverse event and deaths

Serious adverse events

During the full 48-week DB phase, no new safety signals emerged from the analysis of the events. The overall incidence of SAEs was approximately 15% in both treatment groups. The most frequently affected SOCs were Nervous system disorders, Infections and infestations, Injury, poisoning and procedural complications, Psychiatric disorders, and Gastrointestinal disorders. Only 8 SAEs were reported in greater than 2 patients (0.7%) in either treatment group. The most frequent events in the 15 cm2 group, were pneumonia and urinary tract infection, each reported in 4 (1.4%) patients; in the 10 cm2 group, the most frequent SAE was urinary tract infection also reported in 4 (1.4%) patients.

During the first 24 weeks of the DB phase, the overall incidence of SAEs was similar for the Prometax 15 cm2 and 10 cm2 patch groups (10% and 9.5%, respectively); the most frequent SAEs were agitation, pneumonia, and urinary tract infection, each reported in 3 patients (1.1%) in the Prometax 15 cm2 patch group. When the first 24 weeks of treatment in the DB phase of Study D2340 was compared to the 24 weeks of treatment in Study D2320, the overall incidence of SAEs was highest in the Prometax 20 cm2 patch group from Study D2320 (11.9%), and the lowest in the Prometax 10 cm2 patch and placebo groups from Study D2320 (7.9% and 8.6% respectively).

During the period of Prometax patch treatment after Week 24 in Study D2340 (DB phase), the overall incidence rate of SAEs was lower in the Prometax 15 cm2 patch group than in the Prometax 10 cm2 group (7.5% vs. 9.8%, respectively) and lower than during the first 24 weeks of treatment (7.5% vs. 10.0%, respectively). Nine SAEs were reported in ≥ 0.5% of patients.

Deaths

The safety profile for deaths was similar between the treatment groups. The Prometax 15 cm2 patch group had a lower incidence of AEs and SAEs leading to discontinuations compared to the Prometax 10 cm2 patch group (Table 5-11).

Table 5-11. Number of patients who died, had SAEs or discontinued due to adverse events in the 48 week double-blind phase, by treatment group (Safety-DB population)

Patients with serious or other significant events	Prometax 15 cm^2 N = 280 n (%)	Prometax 10 cm^2 N = 283 n (%)	Total N = 563 n (%)
Death	3 (1.1)	5 (1.8)	8 (1.4)
SAE(s) [(a)]	44 (15.7)	44 (15.5)	88 (15.6)
Discontinued due to AE(s) [(a)]	27 (9.6)	36 (12.7)	63 (11.2)
Discontinued due to SAE(s)	12 (4.3)	18 (6.4)	30 (5.3)

[(a)] Deaths are included.

Source: [Study D2340- PT-Table 14.3.1-1.4b], [Study D2340-PT-Table 14.3.1-1.5b], [Study D2340-PT-Table 14.3.1-1.6b], [Study D2340-PT-Table 14.3.1-1.7b]

Study D2340

There were 8 (1.4%) deaths during the 48-week DB phase of this study. Three (1.1%) deaths occurred in Prometax 15 cm2 patch group and 5 (1.8%) deaths occurred in the Prometax 10 cm2 group. One additional death occurred 27 days after the last dose of study medication and was not captured in the clinical database. No pattern was seen in the frequency of death by SOC or preferred term. None of the deaths were attributed by the investigator to study treatment.

Study D2320

During the 24 weeks of Study D2320, 5 (1.7%) patients died in the Prometax 20 cm2 patch group, 4 (1.4%) died in the Prometax 10 cm2 group and 3 (1.0%) died in the placebo groups. None of the deaths was attributed by the investigator to study treatment.

Laboratory findings

Laboratory evaluations were only performed at screening and baseline in Study D2340. The results of these evaluations were recorded as source data and not captured in the clinical database; therefore, no laboratory data are presented.

The incidence of patients with newly-occurring ECG abnormalities was similar (17.5% vs. 15.2%) in the Prometax 15 cm2 and Prometax 10 cm2 patch treatment groups, respectively.

A clinically notable decrease in weight (≥ 7%) was observed in a higher percentage of patients in the Prometax 15 cm2 group, than in the Prometax 10 cm2 group (18.6 %. vs. 15.2%, respectively).

Safety in special populations

Safety related to drug-drug interactions and other interactions

Prometax has a low potential for pharmacokinetic interactions (minimal metabolism via the core cytochrome P450 isoenzymes). Prometax may show pharmacodynamic interactions with other cholinomimetic drugs, which should not be used at the same time as Prometax.

Discontinuation due to adverse events

During the full 48-week DB phase of Study D2340 no new safety signals emerged from the analysis of the events. Overall, the percentage of patients with AEs leading to discontinuation was lower in the Prometax 15 cm2 patch group compared to the Prometax 10 cm2 patch group (9.6% vs. 12.7%, respectively). The most frequent AE leading to discontinuation was vomiting, which was reported in 4 (1.4%) patients in the Prometax patch 15 cm2 group and 1 (0.4%) patients in the Prometax patch 10 cm2 group. Nausea was reported as an AE leading to discontinuation in one patient (0.4%) in both groups and diarrhoea in 1 patient (0.4%) in the Prometax patch 10 cm2 group. Other than an AE of application site pruritus, which led to discontinuation in 3 (1.1%) of patients in both treatment groups and aggression which led to discontinuation in 3 (1.1%) of the Prometax patch 10 cm2 group, all the remaining discontinuations were reported in less than 1% of patients.

During the first 24 weeks of the DB phase in Study D2340, the overall percentage of patients with AEs leading to discontinuation was lower in the 15 cm2 patch group than in the 20 cm2 group from Study D2320 (7.9% vs. 10.2%, respectively) and lower than the 10 cm2 group from either study. Gastrointestinal-related AEs led to discontinuation most frequently in the Prometax 20 cm2 patch group from Study D2320, with discontinuations due to nausea and vomiting each occurring in 1.7% of patients compared to 0.4% and 1.1%, respectively in the Prometax 15 cm2 patch group from Study D2340.

During the period of Prometax patch treatment after Week 24 of the DB Phase in Study D2340, the overall incidence rate of AEs leading to discontinuation was lower in the Prometax 15 cm2 patch group than in the Prometax 10 cm2 group (2.5% vs. 4.9%, respectively) and lower than during the first 24 weeks of treatment (7.9% vs. 8.5%, respectively). Only 2 AEs leading to discontinuation were reported in ≥ 0.5% of patients (cerebrovascular accident [0.8%] and atrial fibrillation [0.8%]).

Post marketing experience

A cumulative review of medication errors in the 20th PSUR (01 February 2011 – 31 January 2012), showed a total of 778 events grouping for medication error for the patch formulation (283 cases in the last review period). Medication errors is the most important cause of overdose with Prometax patches (61/65 overdoses reported in the PSUR were in the context of a medication error).

The analysis of notified cases of medication errors, before and after the Direct Healthcare Professional Letter (DHPC), disseminated on 10 April 2010, showed that cases are still being reported and no clear trends of improvement were observed after the issuance of the DHPC. The MAH acknowledges that the concern on medication misuse and medication error remains. As a consequence further measures have been proposed by the MAH to manage the risk, these include:

- Educational material which will be provided to all physician who are expected to prescribe Prometax,

- Drug utilization study (CENA713D2409) to assess the appropriate use and estimation of inappropriate drug use of rivastigmine patches (5 cm2, 10 cm2, 15 cm2) and titration patterns of rivastigmine patches, particularly regarding increases from a lower to a higher dose and switches from rivastigmine capsule/oral solution to patches,

- Targeted follow-up checklists will be employed to ascertain both past and ongoing issues leading to multipatch use at both the healthcare provider as well as the patient/caregiver level,

- Training of Novartis Prometax personnel sales and marketing personnel who will distribute the above listed materials.

In addition, the SmPC of all transdermal formulation have been updated in order to include information on recommendation on administration of patches and warning message related to the risk of overdose resulting from misuse of the medicinal product and dosing errors.

2.6.1. Discussion on clinical safety

Safety data from the 48-week DB phase of study D2340, demonstrated that:

- Adverse events most frequently reported involved the Gastrointestinal disorders SOC, followed by Psychiatric disorders, General disorders and administration site conditions, and Nervous system disorders SOCs.

- The most frequently reported AEs with Prometax 15 cm2 patch, and in a higher frequency compared to Prometax 10 cm2 patch, were nausea, followed by vomiting, fall, application site erythema, decreased appetite and diarrhoea.

- No conclusion can be definitely drawn when comparing for both Prometax patch groups the proportion of cases of decrease in weight in patients with nausea [15 cm2 : 2/27(7.4%) vs 10 cm2 : 2/10 (20%)] or vomiting [15 cm2 : 5/25(20%) vs 10 cm2 :0] or diarrhoea [15 cm2 : 4/14 (26.6%) vs 10 cm2 : 2/12 (16.6%)], even if this one is relatively more important with the higher Prometax patch dosage, when considering vomiting and diarrhoea. In addition, the slightly higher percentage of patients who had relevant medical histories for gastrointestinal disorders in the Prometax 15 cm2 group compared to the 10 cm2 group (32.5% vs. 28.9 %, respectively) should be taken into consideration in the interpretation of these data. More females than males were included in the Prometax 15 cm2 group compared to the 10 cm2 group; however no conclusion can be drawn on specific risk factors for clinically notable decrease in weight (≥ 7%) with Prometax 15 cm2 patch based on the small number of patients presenting this event.

- Prometax 15 cm2 patch showed a higher incidence of gastrointestinal disorders (nausea, vomiting, weight decrease, appetite decreased, and upper abdominal pain) compared to Prometax 10 cm2 patch. With the exception of weight decreased, the percentages of patients with these events decreased over time in both treatment groups.

- AE severity profile was generally similar for both the Prometax 15 cm2 and 10 cm2 patch groups, with the majority of patients reporting mild to moderate severity. Severe gastrointestinal disorders were at similar frequency between the treatment groups, vomiting being the most reported.

- Dizziness was also reported in higher proportions of patients in the Prometax 15 cm2 patch group compared to the lower dose treatment group, without correlation with falls.

- Deaths were reported at similar frequencies in the treatment groups and did not raise no new safety issue.

- Serious AEs were reported at similar frequencies in the treatment groups. The most common preferred terms were urinary tract infection, pneumonia, dehydration, vomiting and falls.

- Discontinuations due to AEs were lower in the Prometax 15 cm2 dose treatment group compared to Prometax 10 cm2 patch group. The most frequent AEs leading to discontinuation were application site pruritus and application site rash, which was reported in the same percentage of patients in each of the treatment groups. Vomiting, was more frequent in the Prometax patch 15 cm2 group compared to the lower dose treatment group. Time to first AE leading to discontinuation showed no major differences in the discontinuation pattern over time between the two treatment groups.

- Medication errors is the most important cause of overdose with Prometax patches (61/65 overdoses reported in the PSUR were in the context of a medication error).

2.6.2. Conclusions on the clinical safety

As a conclusion, the safety results from the DB phase of Study D2340 showed that the type and severity of adverse events reported with the Prometax 15 cm2 patch were consistent with the known safety profile of the Prometax 10 cm2 patch. A dose-dependent effect is clearly observed primary for gastrointestinal events that represented the most frequently adverse events reported with Prometax 15 cm2 in study D2340. The potential consequences (i.e weight decrease) of GI side effects observed more frequently in patients treated by Prometax 15 cm2 patch compared to Prometax 10 cm2 patch in the first 24 weeks did not raise major concerns in study D2340, considering the unlikely relationship between clinically notable decrease in weight and GI events occurring concomitantly in patients, based on the short duration of the GI events and/or the long time period between the events in majority of cases.

The dose dependent pattern is also observed for the majority of commonly reported psychiatric and nervous system related AEs. No new safety signals emerged from the analysis of AEs, AEs leading to discontinuation, or SAEs. Post-hoc analysis showed that during the EOL phase, the type and severity of adverse events were consistent with the known safety profile of the Prometax 10 cm2 patch.

The CHMP considered appropriate the risk minimisation measure proposed by the MAH to reduce the risk of medication error and misuse. However the CHMP requested that a review of new medication error cases should be provided by the MAH. The full Study protocol, including feasibility assessment accompanied by a report on the status of new risk minimisation tools implementation in each country will be presented for CHMP consideration (Section 4).

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system approved in July 2011 fulfils the legislative requirements.

Risk Management Plan

The following table presents the summary of risk management activities, as proposed by the MAH in RMP version 6.3. (for easier lecture, summary tables for patches and oral forms were merged in one only table; risks specific to patch form are pointed out):

Safety concern	Proposed Pharmacovigilance activities (routine and additional)	Proposed Risk Minimization activities (routine and additional)
Important identified risks		
Gastrointestinal symptoms (Nausea, vomiting and diarrhea; dehydration resulting from prolonged	Routine pharmacovigilance including cumulative analysis in PSUR.	Routine risk minimization Identified in the following sections of the SPC (see Annex 2) • Section 4.2 Posology and method of administration: Dose titration: If adverse reactions (e.g. nausea, vomiting, abdominal pain or

vomiting or diarrhea)		loss of appetite), weight decrease or worsening of extrapyramidal symptoms (e.g. tremor) in patients with dementia associated with Parkinson's disease are observed during treatment, these may respond to omitting one or more doses. If adverse reactions persist, the daily dose should be temporarily reduced to the previous well-tolerated dose or the treatment may be discontinued. • Section 4.4 Special warnings and precautions for use: Dose titration: Gastrointestinal disorders such as nausea, vomiting and diarrhoea are dose-related, and may occur particularly when initiating treatment and/or increasing the dose (see section 4.8). These adverse reactions occur more commonly in women. Patients who show signs or symptoms of dehydration resulting from prolonged vomiting or diarrhoea can be managed with intravenous fluids and dose reduction or discontinuation if recognised and treated promptly. Dehydration can be associated with serious outcomes. In case of severe vomiting associated with rivastigmine treatment, appropriate dose adjustments are recommended in section 4.2 must be made. Some cases of severe vomiting were associated with oesophageal rupture (see section 4.8). Such events appeared to occur particularly after dose increments or high doses of rivastigmine. • Section 4.8 Undesirable effects: The most commonly reported adverse drug reactions are gastrointestinal including nausea (38%) and vomiting (23%), especially during titration. Female patients in clinical studies were found to be more susceptible

		to gastrointestinal adverse drug reactions and weight loss. Table 1, Gastrointestinal disorders: nausea, vomiting and diarrhoea are listed with frequency (very common), abdominal pain and dyspepsia (common), some cases of severe vomiting associated with oesophageal rupture is listed with frequency (not known). Table 2, Gastrointestinal disorders: Nausea, vomiting (very common) Diarrhoea (common) Abdominal pain, dyspepsia and salivary hypersecretion (common) • Section 4.9 Overdose: Symptoms Most cases of accidental overdose have not been associated with any clinical signs or symptoms and almost all of the patients concerned continued rivastigmine treatment. Where symptoms have occurred, they have included nausea, vomiting and diarrhoea, hypertension or hallucinations. Due to the known vagotonic effect of cholinesterase inhibitors on heart rate, bradycardia and/or syncope may also occur. Ingestion of 46 mg occurred in one case; following conservative management the patient fully recovered within 24 hours. Treatment As rivastigmine has a plasma half-life of about 1 hour and a duration of acetylcholinesterase inhibition of about 9 hours, it is recommended that in cases of asymptomatic overdose no further dose of rivastigmine should be administered for the next 24 hours. In overdose accompanied by severe nausea and vomiting, the use of antiemetics should be

		considered. Symptomatic treatment for other adverse reactions should be given as necessary. In massive overdose, atropine can be used. An initial dose of 0.03 mg/kg intravenous atropine sulphate is recommended, with subsequent doses based on clinical response. Use of scopolamine as an antidote is not recommended.
Worsening of motor symptoms associated with Parkinson's disease	Routine pharmacovigilance including cumulative analysis in PSUR.	Routine risk minimization Identified in the following sections of the SPC (see Annex 2) • Section 4.2 Posology and method of administration Dose titration: If adverse reactions (e.g. nausea, vomiting, abdominal pain or loss of appetite), weight decrease or worsening of extrapyramidal symptoms (e.g. tremor) in patients with dementia associated with Parkinson's disease are observed during treatment, these may respond to omitting one or more doses. If adverse reactions persist, the daily dose should be temporarily reduced to the previous well-tolerated dose or the treatment may be discontinued. • Section 4.4 Special warnings and precautions for use: Dose titration: Adverse reactions (e.g. hypertension and hallucinations in patients with Alzheimer's dementia and worsening of extrapyramidal symptoms, in particular tremor, in patients with dementia associated with Parkinson's disease) have been observed shortly after dose increase. They may respond to a dose reduction. In other cases, Prometax has been discontinued (see section 4.8). Like other cholinomimetics, rivastigmine may exacerbate or induce extrapyramidal symptoms. Worsening

		(including bradykinesia, dyskinesia, gait abnormality) and an increased incidence or severity of tremor have been observed in patients with dementia associated with Parkinson's disease (see section 4.8). These events led to the discontinuation of rivastigmine in some cases (e.g. discontinuations due to tremor 1.7% on rivastigmine vs 0% on placebo). Clinical monitoring is recommended for these adverse reactions. • Section 4.8 Undesirable effects Table 1, Nervous system disorders Tremor (common) Extrapyramidal symptoms (including worsening of Parkinson's disease) (very rare) Table 2, Nervous system disorders Tremor (very common) Worsening of Parkinson's disease (common) Bradykinesia (common) Dyskinesia (common) Dystonia (uncommon) Hypokinesia (common) Cogwheel rigidity (common) Gait disturbance/Parkinson gait (common) Table 3 lists the number and percentage of patients from the specific 24-week clinical study conducted with Prometax in patients with dementia associated with Parkinson's disease with pre-defined adverse events that may reflect worsening of parkinsonian symptoms.
Pancreatitis	Routine pharmacovigilance including cumulative analysis in PSUR.	Routine risk minimization Identified in the following sections of the SPC (see Annex 2) • Section 4.8 Undesirable effects: Table 1, Gastrointestinal disorders Pancreatitis (very rare).
Cardiac	Routine pharmacovigilance including cumulative analysis in	Routine risk minimization

arrhythmias	PSUR.	Identified in the following sections of the SPC (see Annex 2) • Section 4.4 Special warnings and precautions for use: Care must be taken when using rivastigmine in patients with sick sinus syndrome or conduction defects (sino-atrial block, atrio-ventricular block) (see section 4.8). • Section 4.8 Undesirable effects: Table 1, Cardiac disorders Angina pectoris (rare) Cardiac arrhythmia (e.g. bradycardia, atrio-ventricular block, atrial fibrillation and tachycardia) (very rare) Sick sinus syndrome (not known) Table 2, Cardiac disorders Bradycardia (common) Atrial fibrillation (uncommon), Atrioventricular block (uncommon) Sick sinus syndrome (not known) • Section 4.9 Overdose: Most cases of accidental overdose have not been associated with any clinical signs or symptoms and almost all of the patients concerned continued rivastigmine treatment. Where symptoms have occurred, they have included nausea, vomiting and diarrhoea, hypertension or hallucinations. Due to the known vagotonic effect of cholinesterase inhibitors on heart rate, bradycardia and/or syncope may also occur. Ingestion of 46 mg occurred in one case; following conservative management the patient fully recovered within 24 hours
Exacerbation of Asthma and COPD	Routine pharmacovigilance including cumulative analysis in PSUR.	Routine risk minimization Identified in the following section of the SPC (see Annex 2) • Section 4.4 Special warnings and precautions for use: Cholinesterase inhibitors

		should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.
Application site skin reactions and irritations (with patches)	Routine pharmacovigilance including cumulative analysis in PSUR	Routine risk minimization, Identified in the following sections of the SPC (see Annex 2) • Section 4.2 Posology and method of administration: Method of administration The transdermal patch should not be applied to skin that is red, irritated or cut. Reapplication to the exact same skin location within 14 days should be avoided to minimise the potential risk of skin irritation • Section 4.3 Contraindications The use of this medicinal product is contraindicated in patients with known hypersensitivity to the active substance, rivastigmine, to other carbamate derivatives or to any of the excipients listed in Section 6.1 used in the formulation. Previous history of application site reactions suggestive of allergic contact dermatitis with rivastigmine patch (see Section 4.4). • Section 4.4 Special warnings and precautions for use Skin application site reactions may occur with rivastigmine patch and are usually mild or moderate in intensity. These reactions are not in themselves an indication of sensitisation. However, use of rivastigmine patch may lead to allergic contact dermatitis. Allergic contact dermatitis should be suspected if application site reactions spread beyond the patch size, if there is evidence of a more intense local reaction (e.g. increasing erythema, oedema, papules, vesicles) and if symptoms do not significantly improve within 48 hours after patch removal. In these cases,

		treatment should be discontinued (see Section 4.3). Patients who develop application site reactions suggestive of allergic contact dermatitis to rivastigmine patch and who still require rivastigmine treatment should only be switched to oral rivastigmine after negative allergy testing and under close medical supervision. It is possible that some patients sensitised to rivastigmine by exposure to rivastigmine patch may not be able to take rivastigmine in any form. There have been rare post-marketing reports of patients experiencing disseminated skin hypersensitivity reactions when administered rivastigmine irrespective of the route of administration (oral, transdermal). In these cases, treatment should be discontinued (see Section 4.3). Patients and caregivers should be instructed accordingly. • Section 4.8 Undesirable effects Table 1, Skin and subcutaneous tissue disorders Rash (common) Pruritus, erythema, urticaria, vesicles, allergic dermatitis are listed with frequency (not known)
Hypertension	Routine pharmacovigilance including cumulative analysis in PSUR.	Routine risk minimization Identified in the following section of the SPC (see Annex 2) • Section 4.4 Special warnings and precautions for use: Under dose titration, adverse reactions (e.g. hypertension and hallucinations in patients with Alzheimer's dementia and worsening of extrapyramidal symptoms, in particular tremor, in patients with dementia associated with Parkinson's disease) have been observed shortly after dose increase. They may respond to a dose reduction. In other cases, Prometax has been

		discontinued. Section 4.8 Undesirable effects: Table 1: Vascular disorders Hypertension (very rare) Table 2: Vascular disorders Hypertension (common) • Section 4.9 Overdose: Most cases of accidental overdose have not been associated with any clinical signs or symptoms and almost all of the patients concerned continued rivastigmine treatment. Where symptoms have occurred, they have included nausea, vomiting and diarrhoea, hypertension or hallucinations.
Gastrointestinal ulceration, haemorrhage, and perforation	Routine pharmacovigilance including cumulative analysis in PSUR.	Routine risk minimization Identified in the following sections of the SPC (see Annex 2) • Section 4.4 Special warnings and precautions for use: Rivastigmine may cause increased gastric acid secretions. Care should be exercised in treating patients with active gastric or duodenal ulcers or patients predisposed to these conditions. • Section 4.8 Undesirable effects: Table 1: Gastrointestinal disorders Gastric and duodenal ulcers (rare), Gastrointestinal hemorrhage (very rare)
Seizures	Routine pharmacovigilance including cumulative analysis in PSUR	Routine risk minimization Identified in the following sections of the SPC (see Annex 2) • Section 4.4 Special warnings and precautions: Cholinomimetics may induce or exacerbate urinary obstruction and seizures. Caution is recommended in treating patients predisposed to such diseases. • Section 4.8 Undesirable effects: Table 1, Nervous system disorders Seizures (rare)
Hallucinations	Routine pharmacovigilance	Routine risk minimization

	including cumulative analysis in PSUR	Identified in the following sections of the SPC (see Annex 2) • Section 4.2 Posology and method of administration: Individual response to rivastigmine cannot be predicted. However, a greater treatment effect was seen in Parkinson's disease patients with moderate dementia. Similarly a larger effect was observed in Parkinson's disease patients with visual hallucinations. • Section 4.4 Special warnings and precautions: Dose titration: Adverse reactions (e.g. hypertension and hallucinations in patients with Alzheimer's dementia and worsening of extrapyramidal symptoms, in particular tremor, in patients with dementia associated with Parkinson's disease) have been observed shortly after dose increase. They may respond to a dose reduction. In other cases, Prometax has been discontinued (see section 4.8). • Section 4.8 Undesirable effects: Table 1, Psychiatric disorders Hallucinations (very rare) Table 2, Psychiatric disorders Visual hallucination (common) • Section 4.9 Overdose: Symptoms Most cases of accidental overdose have not been associated with any clinical signs or symptoms and almost all of the patients concerned continued rivastigmine treatment. Where symptoms have occurred, they have included nausea, vomiting and diarrhoea, hypertension or hallucinations. Due to the known vagotonic effect of cholinesterase inhibitors on heart rate, bradycardia and/or syncope may also occur. Ingestion of 46 mg occurred in one case; following

		conservative management the patient fully recovered within 24 hours. Treatment As rivastigmine has a plasma half-life of about 1 hour and a duration of acetylcholinesterase inhibition of about 9 hours, it is recommended that in cases of asymptomatic overdose no further dose of rivastigmine should be administered for the next 24 hours. In overdose accompanied by severe nausea and vomiting, the use of antiemetics should be considered. Symptomatic treatment for other adverse reactions should be given as necessary. In massive overdose, atropine can be used. An initial dose of 0.03 mg/kg intravenous atropine sulphate is recommended, with subsequent doses based on clinical response. Use of scopolamine as an antidote is not recommended.
Syncope and loss of consciousness	Routine pharmacovigilance including cumulative analysis in PSUR.	Routine risk minimization Identified in the following sections of the SPC (see Annex 2) • Section 4.7 Effects on ability to drive and use machines: Rivastigmine can induce dizziness and somnolence, mainly when initiating treatment or increasing the dose. • Section 4.8 Undesirable effects: Table 1, Nervous system disorders Syncope (uncommon) • Section 4.9 Overdose: Symptoms Most cases of accidental overdose have not been associated with any clinical signs or symptoms and almost all of the patients concerned continued rivastigmine treatment. Where symptoms

		have occurred, they have included nausea, vomiting and diarrhoea, hypertension or hallucinations. Due to the known vagotonic effect of cholinesterase inhibitors on heart rate, bradycardia and/or syncope may also occur. Ingestion of 46 mg occurred in one case; following conservative management the patient fully recovered within 24 hours. Treatment As rivastigmine has a plasma half-life of about 1 hour and a duration of acetylcholinesterase inhibition of about 9 hours, it is recommended that in cases of asymptomatic overdose no further dose of rivastigmine should be administered for the next 24 hours. In overdose accompanied by severe nausea and vomiting, the use of antiemetics should be considered. Symptomatic treatment for other adverse reactions should be given as necessary. In massive overdose, atropine can be used. An initial dose of 0.03 mg/kg intravenous atropine sulphate is recommended, with subsequent doses based on clinical response. Use of scopolamine as an antidote is not recommended.
Medication misuse (*with patches)*	Routine Pharmacovigilance including cumulative analysis in PSUR Targeted follow-up of all spontaneous reports using a targeted follow-up checklist CENA713D2409 Prometax Transdermal Patch: A Drug Utilization Study	Routine risk minimization Patient/Caregiver memory aids Instructions on how to minimize medication misuse are provided in multiple sections of SPC (see Annex 2). • Section 4.2 Posology and method of administration: The transdermal patch should be replaced by a new one after 24 hours. Only one transdermal patch should be worn at a time (see Section 4.9). The transdermal patch should not be cut into pieces. Patients and

		caregivers should be instructed accordingly. • Section 4.9 Overdose: Symptoms Overdose with Prometax transdermal patch resulting from misuse/dosing errors (application of multiple patches at a time) has been reported in the post-marketing setting. The typical symptoms reported among these cases are similar to those seen with cases of overdose associated with Prometax oral formulations.
Medication errors *(whit patches)*	Routine Pharmacovigilance including cumulative analysis in PSUR Targeted follow-up of all spontaneous reports using a targeted follow-up checklist CENA713D2409 Prometax Transdermal Patch: A Drug Utilization Study	Routine risk minimization Patient/Caregiver memory aids Instruction on how to minimize medication errors are provided in multiple sections of the SPC (see Annex 2). • Section 4.2 Posology and method of administration: The transdermal patch should be replaced by a new one after 24 hours. Only one transdermal patch should be worn at a time (see Section 4.9). The transdermal patch should not be cut into pieces. Patients and caregivers should be instructed accordingly. • Section 4.9 Overdose: Symptoms Overdose with Prometax transdermal patch resulting from misuse/dosing errors (application of multiple patches at a time) has been reported in the post-marketing setting. The typical symptoms reported among these cases are similar to those seen with cases of overdose associated with Prometax oral formulations.
Dehydration	Routine pharmacovigilance including cumulative analysis in PSUR.	Routine risk minimization Identified in the following sections of the SPC (see Annex 2) • Section 4.4 Special Warnings and precautions for use: Patients who show signs or symptoms of dehydration resulting from prolonged vomiting or diarrhoea can be

		managed with intravenous fluids and dose reduction or discontinuation if recognized and treated promptly. Dehydration can be associated with serious outcomes. • Section 4.8 Undesirable effects: Table 1, Metabolism and nutrition disorders Dehydration (not known) Table 2, Metabolism and nutrition disorders Dehydration (common)
Liver disorders	Routine pharmacovigilance including cumulative analysis in PSUR.	Routine risk minimization Identified in the following sections of the SPC (see Annex 2) • Section 4.2 Posology and method of administration: Renal and hepatic impairment: No dose adjustment is necessary for patients with mild to moderate renal or hepatic impairment. However, due to increased exposure in these populations dosing recommendations to titrate according to individual tolerability should be closely followed as patients with clinically significant renal or hepatic impairment might experience more adverse reactions (see Sections 4.4). Patients with severe hepatic impairment have not been studied (see Section 4.4). • Section 4.4 Special warnings and precautions for use/ Special populations: Patients with clinically significant renal or hepatic impairment might experience more adverse reactions (see Sections 4.2). Patients with severe hepatic impairment have not been studied. However, Prometax may be used in this patient population and close monitoring is necessary. • Section 4.8 Undesirable effects: Table 1, Hepatobiliary disorders

		Elevated liver function tests (uncommon) Hepatitis (not known) Table 2, Hepatobiliary disorders Hepatitis (not known)
Severe skin reactions (bullous reactions)	Routine pharmacovigilance including cumulative analysis in PSUR.	Routine risk minimization Identified in the following sections of the SPC (see Annex 2) • Section 4.3 Contraindications The use of this medicinal product is contraindicated in patients with known hypersensitivity to the active substance, rivastigmine, to other carbamate derivatives or to any of the excipients listed in Section 6.1 used in the formulation. Previous history of application site reactions suggestive of allergic contact dermatitis with rivastigmine patch (see Section 4.4). • Section 4.4 Special warnings and precautions for use Skin application site reactions may occur with rivastigmine patch and are usually mild or moderate in intensity. These reactions are not in themselves an indication of sensitisation. However, use of rivastigmine patch may lead to allergic contact dermatitis. Allergic contact dermatitis should be suspected if application site reactions spread beyond the patch size, if there is evidence of a more intense local reaction (e.g. increasing erythema, oedema, papules, vesicles) and if symptoms do not significantly improve within 48 hours after patch removal. In these cases, treatment should be discontinued (see Section 4.3). Patients who develop application site reactions suggestive of allergic contact dermatitis to rivastigmine patch and who still require rivastigmine treatment should

		only be switched to oral rivastigmine after negative allergy testing and under close medical supervision. It is possible that some patients sensitised to rivastigmine by exposure to rivastigmine patch may not be able to take rivastigmine in any form. There have been rare post-marketing reports of patients experiencing disseminated skin hypersensitivity reactions when administered rivastigmine irrespective of the route of administration (oral, transdermal). In these cases, treatment should be discontinued (see Section 4.3). Patients and caregivers should be instructed accordingly. • Section 4.8 Undesirable effects Table 1, Skin and subcutaneous tissue disorders Hyperhydrosis (common) Rash (rare) Pruritus, disseminated cutaneous hypersensitivity reactions (not known) Table 2, Skin and subcutaneous tissue disorders Hyperhydrosis (common) Disseminated cutaneous hypersensitivity reactions (not known)
Important potential risks		
Myocardial infarction	Routine pharmacovigilance including cumulative analysis in PSUR.	Not listed in the SPC. Angina pectoris is identified in the following section of the SPC (see Annex 2) • Section 4.8 Undesirable effects: Table 1, Cardiac disorders Angina pectoris (rare)
Cerebrovascular accidents	Routine pharmacovigilance including cumulative analysis in PSUR.	Not listed in the SPC.
Pulmonary infections	Routine pharmacovigilance including cumulative analysis in PSUR.	Not listed in the SPC.
Death	Routine pharmacovigilance including cumulative analysis in PSUR.	Not listed in the SPC.

Acute renal failure	Routine pharmacovigilance including cumulative analysis in PSUR.	Routine risk minimization Identified in the following section of the SPC (see Annex 2) • Section 4.2 Posology and method of administration No dose adjustment is necessary for patients with mild to moderate renal or hepatic impairment. However, due to increased exposure in these populations dosing recommendations to titrate according to individual tolerability should be closely followed as patients with clinically significant renal or hepatic impairment might experience more adverse reactions (see Sections 4.4). Patients with severe hepatic impairment have not been studied (see Section 4.4). • Section 4.4 Special warnings and precautions for use Patients with clinically significant renal or hepatic impairment might experience more adverse reactions (see Sections 4.2).

As no new safety concerns were highlighted by the study D2340, the list of ongoing safety concerns is still considered adequate.

The below pharmacovigilance activities are needed to further investigate the medication error and medication misuse safety concern associated to transdermal patches:

Description	Due date
Drug Utilisation study: Full Study protocol, including feasibility assessment for CHMP consideration	31 July 2013
Report on the status of implementation of additional risk minimisation measures in each country (e.g timing of educational material distribution)	31 July 2013
Medication Errors: A review of reported cases of medication errors should be provided in a 6-months basis, in order to capture any new findings related to this risk between PSURs.	31 July 2013 (first submission)

2.8. User consultation

A user consultation with target patient groups on the package leaflet has not been submitted by the applicant and CHMP considered this to be acceptable as the patient leaflet proposed for the new strengths (13.3 mg/24 h) is similar with the patient leaflet of the approved strengths (4.5 mg/24 hours and 9.5 mg/24 hours).

3. Benefit-Risk Balance

Benefits

Beneficial effects

The study (D2340) was designed to investigate the optimal use of Prometax Patch in longer term treatment to provide evidence on the benefit of a higher Prometax patch size (15 cm2) for those patients who seem to derive limited or no benefit on standard doses.

The primary efficacy analysis variables are the change from baseline DB randomization to DB Week 48 in the ADAS-cog total score and ADCS-Instrumental ADL score.

Activities of daily living as measured by ADCS-Instrumental ADL subscale showed the superiority of Prometax 15 cm2 patch when compared to Prometax 10 cm2 patch. A statistically significant lesser decline (i.e. improved therapeutic benefit) was observed in the Prometax 15 cm2 patch compare to Prometax 10 cm2 patch at week 24.

Uncertainty in the knowledge about the beneficial effects

The between treatment group differences for cognitive decline were statistically significant in favour of the Prometax 15 cm2 patch at Week 24 (-1.3 points; 95% CI: -2.5,-0.2; p=0.027), but not statistically significant at Week 48 (-0.8 points; 95% CI: -2.1 , 0.5; p=0.227), which was one of the co-primary endpoint. The MAH stated that the controlled clinical trials aimed at demonstrating short term improvement in AD (at least 6 months). Nevertheless, Prometax patch treatment could be used for at least 12 months. However, cognitive decline in ADAS-cog score was less at each time-point in the Prometax 15 cm2 patch group than in the Prometax 10 cm2 patch group.

The results of the secondary efficacy endpoints (Time to decline, Trial Making Test, Neuropsychiatric Inventory) showed that the difference between treatment groups was not statistically significant for any of the criteria. However, a numerical superiority in favour of Prometax 15 cm2 patch was observed for time to decline and TMT.

Risks

Unfavourable effects

The safety profile of Prometax 15 cm2 patch in study D2340 appears to be consistent with what has been observed in previous studies and in post-marketing with Prometax patch, and demonstrates a dose-dependence effect, in particular for gastro-intestinal events. GI side effects are expected to be more frequent in the patients treated with the already approved capsule than in the patients treated with the 15 cm2 patch. However, GI events (nausea, vomiting, diarrhoea) are identified risks for Prometax oral and transdermal formulations, as well described in the RMP and observed in PSUR.

This dose dependent pattern is also observed for the majority of commonly reported psychiatric and nervous system related AEs. However, no new safety signals emerged from the analysis of AEs, AEs leading to discontinuation, or SAEs.

Uncertainty in the knowledge about the unfavourable effects

The potential consequences (i.e weight decrease) of GI side effects, observed more frequently in patients treated by Prometax 15 cm2 patch compared to Prometax 10 cm2 patch in the first 24 weeks,

did not raise major concerns in study D2340, considering the unlikely temporal relationship between clinically notable decrease in weight and GI events occurring concomitantly in patients (i.e.short duration of the GI events and/or long time period between the events in majority of cases).

No conclusion can be definitely drawn when comparing for both Prometax patch groups the proportion of cases of decrease in weight in patients with nausea, vomiting or diarrhoea, even if this one is relatively more important with the higher Prometax patch dosage, when considering vomiting and diarrhoea. In addition, the slightly higher percentage of patients who had relevant medical histories for gastrointestinal disorders in the Prometax 15 cm2 group compared to the 10 cm2 group (32.5% vs. 28.9 %, respectively) should be taken into consideration in the interpretation of these data.

The identified risk of overdose associated with medication errors (multiple patches or incorrect doses during switch from oral to transdermal formulations), is currently not entirely managed with existing patches (5 and 10 cm^2) as demonstrated in the last PSURs. This risk is expected to be greater if a new higher dosage patch is approved and risk minimisation activities have been identified accordingly.

Benefit-risk balance

Importance of favourable and unfavourable effects

Although the superior efficacy of Prometax 15 cm2 patch as compared to Prometax 10 cm2 patch was not statistically demonstrated for the co-primary endpoint, patients treated with the Prometax 15 cm2 patch showed a consistent lesser decline (i.e. improved therapeutic benefit) in activities of daily living as measured by ADCS-Instrumental ADL subscale and cognition measured by ADAS-cog score when compared to Prometax 10 cm2 patch.

The safety profile of Prometax 15 cm2 patch appears to be consistent with what has been observed with currently approved Prometax patch formulations. A dose-dependent effect is clearly observed for gastrointestinal events that represented the most frequently adverse events reported with Prometax 15 cm2 in study D2340, but these events do not appear to be associated with a significant higher risk of potential consequences (i.e weight decrease). This dose dependent pattern is also observed for the majority of commonly reported psychiatric and nervous system related AEs, and no new safety signals emerged from the analysis of AEs, AEs leading to discontinuation, or SAEs. New minimisation activities (for all patch dosages) are established to better manage the risk of overdose, and their efficiency will be prospectively evaluated. In addition, the CHMP requested that a review of reported cases of medication errors is provided on a 6-monthly basis by the MAH, in order to capture any new findings related to this risk between PSURs.

Benefit-risk balance

Discussion on the benefit-risk balance

The CHMP considered appropriate the risk minimisation measure proposed by the MAH to handle the risk of medication error associated with the use of transdermal patches. Additionally as a result of the efficacy study it is clear that patient could benefit from the new dosage. As a consequence the CHMP considered that the overall Benefit Risk of Prometax 15 cm2 patch is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the benefit-risk balance of Prometax 13.3 mg/24 hours in the symptomatic treatment of mild to moderately severe Alzheimer's dementia is favourable and therefore recommends granting the extension of the marketing authorisation subject to the conditions below.

In addition, the CHMP considered by consensus the following variation acceptable and recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) requested		**Type**
C.I.4	Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

Update of sections 4.8 and 5.2 of transdermal patches formulation to reflect safety and pharmacological findings of the study CENA713D2340, respectively. Sections 4.2 and 4.4 were updated with information on recommendation on administration of patches, special population, precautions to avoid contact with eyes and misuse of medicinal product and dosing errors associated to the use of transdermal patches.

Additionally, section 4.8 of the SmPC of oral formulation was updated to include safety finding of the study CENA713D2340.

The package leaflet of all formulation was updated in accordance. The list of local representative was also updated. Changes to the PI were introduced in line with the QRD template version 8.1.

The application proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription

Conditions and requirements of the Marketing Authorisation

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree the final educational material with the National Competent Authority.

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where PROMETAX is marketed, at launch and after launch of the 13.3mg/24 h (15cm^2) transdermal patch all physicians who are expected to prescribe PROMETAX are provided with an information pack containing the following elements:

- The Summary of Product Characteristics
- Patient reminder card
- Instructions to provide patients and caregivers with the patient reminder card

The patient reminder card should contain the following key messages:

- Take off the previous patch before putting ONE new patch on.
- Only one patch per day.
- Do not cut the patch into pieces.
- Press the patch firmly in place for at least 30 seconds using the palm of the hand.
- How to use the reminder card to record patch application and removal.

- **Risk Management Plan (RMP)**

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency