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Product Name: **Prometax**
Procedure No: **EMEA/H/C/255/X/39**

SCIENTIFIC DISCUSSION

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1. INTRODUCTION

The availability of the patch formulation will offer patients a reduced side-effect profile in comparison to the currently approved capsule formulation and the convenience of a once daily application, together with proven efficacy. Compliance and ease of use of medications in patients with dementia, is considered a significant achievement in this population.

2. QUALITY ASPECTS

Introduction

The product is presented as 5 cm^2 and 10 cm^2 transdermal patches containing respectively 9.0 mg and 18 mg of rivastigmine base as active substance, and designed to release approximately 4.6 mg (5cm^2) and 9.5mg (10 cm^2) respectively per 24 hours.

The transdermal patch is a four-layer matrix transdermal patch consisting of:

- Backing film which contains: lacquered polyethylene terephthalate film
- Drug product (acrylic) matrix which contains: alpha-tocopherol, poly(butylmethacrylate, methyl-methacrylate), acrylic copolymer.
- Adhesive (silicone) matrix containing alpha-tocopherol silicone oil, dimethicone.
- Release liner containing polyester film, fluoropolymer-coated.

The finished patches are individually packaged in child-resistant, heat-sealed sachets made of a paper/adhesive/polyethylene terephthalate/adhesive/aluminum/adhesive/polyacrylonitrile multi-laminated material.

Active Substance

Rivastigmine free base is used as active substance and is developed from rivastigmine hydrogentartrate which is used in the currently approved formulations Exelon/Prometax capsule and oral solution.

It is a viscous, clear, colourless to yellow or to very slightly brown liquid and is slightly soluble in water and has pronounced hygroscopic behaviour. It has one asymmetric carbon atom and confirmed that all batches of drug substance used for technical, toxicological and clinical investigations contain the same absolute configuration S as the starting material rivastigmine hydrogentartrate.

The drug substance rivastigmine is prepared in one step by base liberation with sodium hydroxide of rivastigmine hydrogentartrate. Adequate in-process controls are applied during the synthesis. The specifications and control methods for starting materials and reagents have been presented

The active substance specification includes tests for description, physicochemical properties (clarity and colour of the solution), identification (IR), impurities (HPLC and GC), water (Karl Fischer), heavy metals, sulphated ash, specific optical rotation, residual solvents (GC), and assay (HPLC). The specifications reflect all relevant quality attributes of the active substance. The analytical methods used in the routine controls are suitability described. Batch analysis data for the development batches used in non-clinical and clinical studies are provided.

Long term stability and accelerated stability studies of 3 pilot batches covering storage periods up to 5 years and stress testing under different conditions were obtained. Photo-stability study has been performed with one pilot batch. Supportive stability data have been obtained with 2 pilot batches. The stability studies have shown that rivastigmine free base is very sensitive to oxidation, moisture and light exposure. Degradation is accelerated by the influence of heat. The stability results showed that storage at 5°C $\pm$ 3°C with protection from light and with protective gas is recommended. The proposed retest period of 5 years is accepted.

Medicinal Product

Pharmaceutical Development

The aim of transdermal administration was to improve the tolerability of the active substance and to avoid the first-pass and to deliver a sufficiently high concentration of the active substance to achieve and maintain a sufficiently high plasma concentration.

The development of the patches was based on the intrinsic physico-chemical properties of the active substance, active substance concentration, physical properties of the matrix, etc.

A bi-layer patch formulation with optimal skin adhesion not affecting the transdermal drug delivery was identified and selected as final marketing formulation. This formulation was used in a clinical study evaluating the skin adhesive properties, pharmacokinetics, local skin irritation, safety and tolerability.

The excipients used are DL-α-tocopherol (vitamin E), ethyl acetate and silicone oil which are described in the Ph.Eur and/or the USP., and silicone pressure sensitive adhesive (Bio PSA Q7-4302 high-tack, amine resistant silicone adhesive), Durotak 387-2353 (acrylic pressure sensitive adhesive) and poly(butylmethacrylate methylmethacrylate) which are no-compendial but are commercially available products.
The chosen backing film is made of polyethylene terephthalate (PET) and the protective release liner made of fluoropolymer-coated PET film which are commercially available.

Each patch is individually packaged in heat-sealed child resistant sachets made of a paper, polyester, aluminium, polyacrylonitrile (Barex) multi-laminated sachet stock to assure the hygiene as well as protection of the pharmaceutical product against light, air, and humidity.

Manufacture of the Product

The manufacturing process is typical of transdermal patches. The process comprises 4 steps.
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 for this presentation.
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), Microbial limit, uniformity of content (HPLC), assay of rivastigmine (HPLC), and assay of D,L-α-tocopherol (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

9 production batches covering storage periods up to 36 months were placed on stability under ICH conditions (25°C/60%RH, 30°C/65%RH and 40°C/75%RH) . In view of the use of the products in climate zones III and IV, storage at 30°C/65% RH and alternate 30°C/75% RH was chosen as the long term storage condition for stability studies. Bracketing concept was applied in order to reduce the number of samples to be tested. The bracketing concept is justified since all patch strengths have the identical percentage composition and since all patch strengths of each study are made from the same

master laminate roll. The batches were tested for appearance, content of active substance and tocopherol, degradation products, *in vitro* release, adhesive and peel forces.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory 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.

3. NON-CLINICAL ASPECTS

Introduction

The active substance of Prometax is an enantiomeric pure compound. ENA713 is the name used throughout this report, however, SDZ 212-713; SDZ ENA 713; 212-713 are also names for the active substance rivastigmine used in the non-clinical documentation. ENA713D (rivastigmine transdermal patch), SDZ ENA 713 TDS or Prometax Patch are names of the finished product that are used in the non-clinical documentation. ENA713D contains the free rivastigmine base, whereas oral Prometax contains the hydrogen tartrate salt.

Pharmacology

Rivastigmine is a slowly reversible (pseudo-irreversible) inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) of the carbamate type which exerts its therapeutic effect by enhancing cholinergic function. Inhibitors of AChE are thought to facilitate cholinergic neurotransmission by enhancing the concentrations of the neurotransmitter acetylcholine and its action in the cholinergic synapse.

Safety pharmacology studies or pharmacodynamic drug-interaction studies using the dermal route of administration have not been conducted; and no primary and secondary pharmacodynamic studies have been conducted either by the dermal route of administration. However, the Prometax hard capsules studies have demonstrated that rivastigmine inhibits both, acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), thereby exhibiting the desired pharmacological profile, i.e., dual and selective inhibition of ChE within specific regions of the brain, and a long duration of action. The pharmacodynamics effects of Prometax hard capsules are well established.

Pharmacokinetics

The pharmacokinetic properties of rivastigmine and its inactive major metabolite NAP226-90 after administration of Prometax patch have been well characterised in adequate studies.

Regarding the **absorption**, upon dermal doses, the T_{max} 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 demonstrate the strong first-pass effect after oral administration and the virtual absence of first-pass metabolism after dermal administration, explaining the better bioavailability from dermal patches than after oral administration.

After oral administration radioactive-labelled product to rat and mouse, the **distribution** of radioactivity throughout the body was extensive, without retention in any tissue. Plasma protein binding was low (15, 19 and 43% for rat, dog and human). Radioactivity was associated with red blood cells (fraction 0.67, 0.53 and 0.43 for rat, dog and human). Levels in the placenta were greater than maternal blood levels at 1 h (Day 13 and 17) and 3 h (Day 17). Radioactivity was detected only at Day 17 in foetal liver. The transfer of radioactivity into milk was rapid. The overall milk:plasma concentration ratio of radioactivity was 1.9, based on $AUC_{0-\infty}$.

The major pathway was hydrolytic decarbamoylation, giving the major metabolite NAP226-90. Oxidative N-demethylation at the dimethylaminoethyl side chain was a minor pathway. **Metabolism** of rivastigmine in plasma is mediated by BuChE. However, hydrolytic metabolism in plasma contributes only to a small extent to the overall metabolism of rivastigmine in human.

Concerning the **excretion**, after oral administration to rat and mouse, the excretion of radioactivity was mainly with urine and in the form of metabolites. Based on previously reported data on metabolism in rat, dog and human, the large majority of the drug-related material in urine was in the form of hydrophilic metabolites *e.g.* glucuronic acid and sulfate conjugates.

In the radiolabeled **ADME/pharmacokinetics** study in minipigs, following dermal dosing, the mass balance of radioactivity amounted to 77–86 % of the dose, with 62–70% recovered in the patch, and 1.7-4.1% at the application site. The recovery in urine and faeces amounted to 14.2-17.8% and 0.4-0.5% of the doses after a 24-hour patch application to abraded skin.

The results of **toxicokinetics** studies showed that approximately 50% of the dose was absorbed from the patch, and the actual administered doses were approximately 50% of the nominal doses. Exposure of the test species was dose-related if not dose-proportional, and proportional to the patch area. There was no obvious gender difference.

Toxicology

No topical single dose toxicity studies have been carried out with ENA713D (rivastigmine trans-dermal patch), however **single dose** toxicity studies with rivastigmine tartrate had been carried out in mice (oral and intravenous route), rats (oral and intraperitoneal route), which found no unexpected toxicities.

Regarding the **repeat-dose dermal toxicity studies**, in the preliminary toxicity studies in mice, no treatment-related changes in the skin were observed. In 13-week dermal toxicity, no treatment-related histopathological effect was observed. The no-toxic-effect level (NTEL) was set at 0.4 mg/kg/day. In percutaneous toxicity study, treatment of rats with ENA713D for 4 weeks was associated with exaggerated pharmacological effects. The no-toxic effect level of ENA713D was set at 15 mg/kg for males, and 5 mg/kg for females, respectively.

In a 4-week **dermal tolerability study** in minipigs, a dose-related reduction in butyryl cholinesterase activity was seen in males but not females. The NTEL for systemic toxicity was set at 72 mg/animal/day. In a 26-week dermal study, exposure of minipig to ENA713D trans-dermal patches for 23 hours per day for 26 weeks caused no signs of toxicity. Acute epidermal inflammation of comparable severity occurred primarily in minipigs at multiple sites such as application site, tape-treated and untreated sites. Correlated microscopic findings consisted of spongiosis, perivascular inflammation and parakeratosis with encrustation. In the superficial dermis, there was perivascular accumulation of lymphocytes and, to a lesser extent, eosinophils. There was no tissue necrosis, sclerosis, or vascular damage. However, the patch formulation or application itself induces inflammation. 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. Regarding the weak dermal tolerance of the patch in the minipig, clinical observations should be considered as a priority.

No additional **genotoxicity tests** were carried out for the ENA713D trans-dermal patch since a complete genotoxicity package had been conducted with rivastigmine tartrate showing that rivastigmine is devoid of mutagenic potential.

Concerning the **carcinogenicity aspects**, no ENA713D-related neoplastic or non-neoplastic lesions were detected in the topical study performed in mice with rivastigmine.

Reproductive and developmental toxicity studies by the dermal route were not carried out because a complete package had been 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. Nevertheless a slightly prolonged duration of gestation in post- and perinatal studies in rats was consistently recorded (although considered too small to be of biological relevance) and may be a sequel to cholinergic stimulation.

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

Local tolerance studies have been carried out with ENA713D by dermal application of patches and topical or intradermal administration of solutions to rabbits and guinea pigs. ENA713D is considered a weak but reversible ocular irritant in rabbits. Skin irritation studies in rabbits indicate that ENA713D transdermal patch is considered as non-irritant to the skin of rabbits. Sensitization studies with ENA713D trans-dermal patch conducted in guinea pigs using the modified Buehler method and maximization test showed that ENA713D transdermal patch was considered to be a non-sensitizer. ENA713D transdermal patches or placebo patches indicating that ENA713D trans-dermal patches were not capable of eliciting a phototoxic response in the guinea pig.

Regarding the excipients, no novel excipients are used for the ENA713D transdermal patches. The drug product matrix of the Prometax patch consists of a mixture of acrylate and methacrylate polymers which have also been used in other trans-dermal systems. The local tolerability of these substances is well known. In addition, different formulations have been used which contained varying amounts and/or different excipients. In most cases, the local tolerance studies showed that ENA713D transdermal patch compositions were considered as “not irritating” and not to be a sensitizer.

Ecotoxicity/environmental risk assessment

The MAH performed an Environmental Risk Assessment in accordance with guideline EMEA/CHMP/SWP/4447/00. Rivastigmine was found not to be readily biodegraded and not bioaccumulative. Acute toxicity was studied in the base-set of aquatic organisms. Potential environmental risks were identified for surface water and groundwater using literature ecotoxicity data of low relevance for the aquatic environmental risk assessment for rivastigmine. The risk for microorganism was evaluated, and concluded by the MAH to be unlikely, using MIC-results for soil micro-organisms.

The CHMP concluded that the adequacy of the obtained risk quotients and identified possible environmental risk potential cannot be assessed at this stage due to limited data. Therefore, the MAH was asked to complete the ERA with several tests, including chronic ecotoxicity, toxicity to a sludge microbial community, and sludge and sediment partitioning tests.

In Phase I the F_{pen} can be refined if there are reasonable epidemiologic data showing that less than the default 1 % of the EU population is suffering from the indication. In Phase II, Tier A this epidemiological based $PEC_{surfacewater}$ is used in the PEC/PNEC calculation. If still necessary, human metabolism, environmental fate data, and STP modelling is acceptable for refining the PEC in Tier B. The CHMP considered the use of unsupported sales data forecast questionable and the use of patent expiry and projected patient share based sales data was not accepted.

The MAH committed to provide the studies asked for and a revised ERA is awaited for June 2008. If the revised ERA indicates a need for Tier B assessment the PEC should be re-calculated accordingly.

4. CLINICAL ASPECTS

GCP

The Clinical trials were performed in accordance with GCP, as claimed by the MAH. The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

Due to its high lipophilicity and relatively low molecular weight, rivastigmine exhibits an adequate profile for administration by trans-dermal route.

Biopharmaceutical and pharmacokinetic studies have demonstrated that rivastigmine is well released from the patch and that the released amounts remain steady. The overall systemic exposure is substantially higher with the patch than with oral solution and the plasma concentrations fluctuation is reduced with the patch. Lower inter-individual variability is also observed with the patch compared to the oral formulations.

There is no available data to allow a valid estimation of the intra-individual variability of PK parameters of rivastigmine. Nevertheless, the assimilation of the residuals from the mixed effect models to the intra-subject variability are considered an acceptable approximation. In order to reduce the variability inherent to the site of application, only three application sites showing homogeneous bioavailability profiles are recommended for application in the SPC. Rivastigmine release through the skin is reduced by 20-30 % when the patch is applied to the thigh or the abdomen comparatively to upper back, chest or upper-arm. The SPC recommends therefore, application on the upper or lower back, upper arm or chest, which is considered acceptable.

No specific metabolic pathway was observed with the trans-dermal route and no metabolism shift was identified. The metabolism profile is comparable to that observed with the I.V. route.

No gender effect was evidenced. Thus no dosage adjustment in females as compared male patients is to be considered.

Pharmacokinetic behaviour of rivastigmine patches is almost similar in Caucasians and Japanese individuals. No reliable data are available in blacks and other ethnic groups. However considering the very good absorption level of rivastigmine through the skin, the difference in PK behaviour due to ethnicity is unlikely.

It appears that systemic exposure to rivastigmine is inversely related to bodyweight. The findings of this analysis are reflected in the SPC.

There is no reliable estimation of the PK behaviour of rivastigmine in elderly patients (specially older than 75 years). However, the potential difference in PK behaviour in the elderly is related to the reduced renal and liver function in this patient group, and no dosage adjustment is required in renal and hepatic impaired patients using rivastigmine.

The overall pharmacokinetic data presented by the MAH was considered appropriate to support the SPC recommendations regarding the switch from oral to transdermal dosing.

Pharmacodynamics

Rivastigmine has a slowly reversible mechanism of acetylcholinesterase and butyrylcholinesterase inhibition that induces an increase in the concentration of acetylcholine.

The extent of inhibition of plasma butyrylcholinesterase (BuChE) was evaluated in 3 clinical pharmacology studies: **Study 2335, Study 1101, Study 2331** and in one Phase II study in Japanese patients with AD: **Study 1201** (trough values only).

Plasma BuChE inhibition data appears fairly consistent, demonstrating under-proportional dose-dependency, with maximum observed inhibition approaching 70% with the 20 cm^2 patch at steady state. Inhibition appears slightly higher in Japanese than in Caucasian subjects, and slightly higher with multiple than with single dosing. Peak inhibition at each of the four patch dose levels (5, 10, 15 and 20 cm^2) is about the same as at the four oral doses, but trough and average (over time) inhibition is higher with the trans-dermal route BuChE inhibition at steady state appeared higher in Japanese patients than in Japanese healthy volunteers, but it needs to be borne in mind that also plasma concentrations of rivastigmine were higher in those patients.

The oral b.i.d. rivastigmine administration resulted in two peaks of plasma BuChE inhibition in each 24-hour period, similarly to what was observed in rivastigmine plasma concentrations. Fluctuations of BuChE inhibition between peaks and troughs were much wider than with trans-dermal route of administration.

Exposure (PK)–response (PD) relationships were investigated using data from Study CENA713D2331 and the pivotal clinical trial CENA713D0401, both conducted in the target population (Alzheimer Disease, AD) following multiple doses of rivastigmine patch and oral capsule.

There was a direct exposure-response (PK/PD) relationship between the rivastigmine metabolite NAP226-90 and plasma BuChE inhibition. There was a trend for increased efficacy with increasing drug exposure. This was observed for the change from baseline in ADAS-Cog score and for ADAS-CGIC response rate. No such trends could be seen for ADCS-ADL or NPI scores.

Although no direct PK/PD relationship between rivastigmine or NAP226-90 plasma concentrations and adverse events (AEs) was seen with the available data, there were indications that the frequency of the AEs increased with increasing doses, especially the risk of nausea and vomiting.

Clinical efficacy

The overview of the main efficacy studies is summarised below.

Table 1- Overview of trials or sources of data

Source of data	Details
Dose-selection trials	Dose selection was based on safety and tolerability data from phase II studies CENA713D0401
Controlled trials	1 large placebo- and active-controlled phase III study CENA713D2320
Long-term data	1 large open label extension study CENA713D2320E1 to the controlled phase III trial
Uncontrolled trials	1 uncontrolled study CENA713D1201 in Japanese patients

Dose selection was based on the phase II safety and tolerability data (including **study CENA713D0401**) and preliminary pharmacokinetic modeling data.

The pivotal **study CENA713D232**0 (placebo and active-controlled) was conducted in 1195 patients with Alzheimer's disease to support the efficacy claims of the patch in the target indication "mild to moderately severe Alzheimer's disease".
The design of study CENA713D2320 (24-week prospective, randomized, multicenter, double-blind, placebo-controlled, parallel-group) and the methodology of the study was in line with the CHMP's Scientific Advice of 18 October 2002.
The inclusion and exclusion criteria ensured recruitment of consistent population representative of AD. Other dementia types were excluded. The selection of the primary (ADAS-cog and ADCS-CGIC) and secondary efficacy measures were considered acceptable to explore the severity of cognitive functions (memory, language and praxis), attention, activities of daily living and non-cognitive behavioural dysfunctions characteristic of people with dementia.
A total of 1464 patients were screened, of whom 1195 were randomized in 21 countries. Mean MMSE at baseline was 16.5, which is representative of a moderate disease state and is reflected in the high proportion (86.1%) of patients living with a caregiver or other individual.
Two different Prometax target patch sizes (10 and 20 cm^2) were evaluated. Prometax 20 cm^2 patch is equivalent to a capsule dose of approximately 18 mg/day. The 10 cm2 daily patch is equivalent to a capsule dose of approximately 9.5 mg/day (within the recommended 6-12 mg/day dose range for Prometax capsules).
Prometax 5 cm^2 patch is equivalent to a capsule dose of approximately 5 mg/day and Prometax 15 cm^2 patch to 13 mg/day were use in the titration phase.
The initial patch dose was Prometax patch 5 cm^2 and was up-titrated in 5 cm^2 increments at a minimum interval of 4 weeks up to the target patch dose.
The doses were titrated over a 16 week period, followed by an 8 week maintenance period.
The **primary efficacy criteria** assessments were:

- the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog): The analysis variable was the change from baseline to Week 24 in the total sum score (0-70) of the 11items included in the scale.
- the Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change (ADCS-CGIC): The analysis variable was the overall clinical rating of change from baseline to Week 24 measured by a 7-point scale.

Clinically relevant improvement was defined a priori as at least 4-point improvement on the ADAS-Cog, no worsening on the ADCS-CGIC, and no worsening on the ADCS-ADL.
The primary objectives of the study were assessed by testing four hypotheses, prospectively ordered according to clinical relevance. A hierarchical testing procedure was selected.

The **first hypothesis** was composed of two comparisons (ADAS-Cog and ADCS-CGIC) between the 20 cm^2 rivastigmine patch and placebo treatment groups. In order to demonstrate superiority of the 20 cm^2 rivastigmine patch over placebo, superiority needed to be shown for both primary efficacy variables simultaneously,
The **second hypothesis** (non-inferiority) compared the 20 cm^2 rivastigmine patch and rivastigmine capsule treatment groups for the ADAS-Cog variable, in order to demonstrate non-inferiority of the 20 cm^2 rivastigmine patch to rivastigmine capsules.
The **third hypothesis** was composed of two comparisons (for ADAS-Cog and ADCS-CGIC) between the 10 cm^2 rivastigmine patch and placebo treatment groups. In order to demonstrate the superiority of the 10 cm^2 rivastigmine patch over placebo, superiority needed to be shown for both primary efficacy variables simultaneously.
The **fourth hypothesis** compared ADCS-ADL between the 20 cm^2 rivastigmine patch and placebo treatment groups.

Statistical superiority of the target Prometax 20 cm^2 patch versus placebo at Week 24 was based on simultaneous testing of ADAS-Cog and ADCS-CGIC. Superiority was demonstrated for ADAS-Cog ($p < 0.001$). The p-value (0.054) for ADCS-CGIC exceeded the predefined significance level of 0.05. Nevertheless, supportive analyses for ADCS-CGIC at Week 24 have shown statistically significant results across all other pre-specified efficacy population datasets (ITT+RDO and RND) with respective p-values of 0.034 and 0.029.
Although the first objective was not formally achieved as planned, testing was continued for the remaining three hypotheses. This was considered acceptable.
Non-inferiority of the Prometax 20 cm^2 patch over capsules (12 mg/day) at Week 24 was established as the 95%-CI was below non-inferiority margin of 1.25 based only on ADAS-Cog (-2.06; 0.17).
For Prometax 10 cm^2 patch, statistical superiority versus placebo at Week 24 was demonstrated by simultaneous testing of ADAS-Cog and ADCS-CGIC, with respective p-values of 0.005 and 0.010.
Superiority of Prometax 20 cm^2 patch versus placebo at Week 24 with regard to ADCS-ADL was achieved with a p-value of 0.017.
An overall responder analysis was conducted based on patients with ADAS-Cog improvement of at least 4 points and ADCS-CGIC categories 1-4 (any improvement or no change) and ADCS-ADL change ≥ 0 points (no change or improvement). The analysis showed that at Week 24, a statistically significant greater proportion of patients responded to Prometax patch 10 cm^2 or 20 cm^2 or capsule treatment than to placebo.
Overall it can be concluded that both the Prometax 10 cm^2 and 20 cm^2 patch sizes showed efficacy vs placebo in the domains of cognition (measured by ADAS-Cog), clinical global assessment of change (measured by ADCS-CGIC) and function (measured by ADCS-ADL). The p-value for ADCS-CGIC marginally exceeded the predefined significance level of 0.05, by 0.004. However, supportive analyses for ADCS-CGIC at week 24 yielded consistent and statistically significant results across all other prespecified efficacy population datasets (ITT, ITT+RDO and RND with their respective imputation schemes) as well as for the predefined proportional odds model.

Secondary efficacy criteria showed that Prometax patch groups and the Prometax capsule group were superior to placebo for the MMSE score, the Ten Point Clock Test score and the Trail Making Test Part A. There were no significant differences versus placebo on the NPI-10 or NPI-12 for any of the Prometax treatment groups. For caregiver distress scores, there was a similar improvement from baseline in Prometax patch groups, the Prometax capsule group and the placebo group.
Supportive data were provided from the open-label extension phase of the pivotal study which is completed (**study CENA713D2320E1**) and an uncontrolled study in AD patients. Patients who received open-label treatment and had previously been randomized to double-blind Prometax 20 cm^2 patch treatment maintained their baseline (Week 0) levels at the end of 52 week treatment and achieved better scores in the efficacy assessments at 52 weeks compared to those received Prometax 10 cm^2 patch, capsule or placebo. No conclusion can be drawn taking into account the methodology of these studies.
The uncontrolled **study CENA713D1201** in Japanese patients was a multicenter, open-label, randomized study that assessed in parallel groups a 4-week titration intervals of increasing sizes of Prometax transdermal patch to assess safety and tolerability in Japanese patients with mild to moderate

AD. Prometax patch was well tolerated at patch sizes up to 10 cm^2 in Japanese patients with mild to moderate AD, with improved tolerability when there were additional titration steps.
Overall it can be concluded that Prometax 20 cm^2 patch showed superiority versus placebo.
Prometax 15 cm^2 patch may provide additional efficacy benefits over Prometax 10 cm^2. However, the clinical program for the Prometax transdermal patch was not designed to answer this question. Without additional data, the sponsor is unable to provide sufficient information on the relative efficacy profile of this dose.
Prometax 10 cm^2 patch demonstrated statistical superiority versus placebo at Week 24 by simultaneous testing of ADAS-Cog and ADCS-CGIC. Non-inferiority of Prometax 10 cm^2 versus Prometax capsule was explored by a pre-planned analysis documented in the statistical analysis plan prior to unblinding and not included in the primary hypotheses. The CHMP considered these results acceptable for the claimed indication.
Prometax 5 cm^2 patch was considered acceptable as the initial treatment dose. After a minimum of four weeks of treatment and if well tolerated, this dose should be increased to the 10 cm^2 patch, which is the recommended effective dose.
The efficacy and safety of rivastigmine patches in patients with Parkinson Disease Dementia (PDD) have not been investigated in a clinical study. The CHMP concluded that with the current available data, the safety and efficacy could not be extrapolated to the PDD indication and the MAH agreed that the safety and tolerability should also be demonstrated in this population.

Clinical safety

Studies were pooled to provide an integrated safety profile, and data were organized into 4 datasets (see Table 2).

Table 2 Population groupings for safety assessment

Database	**Studies**	**Number of patients (safety population)**	**Safety topics** **Subgroup analyses**
Group 1 (All Prometax patch-, capsule- and placebo-treated AD patients in double-blind controlled studies)	2320	1190	Topics: deaths, SAEs, other significant AEs, all AEs, skin irritation, patch adhesion, vital signs, ECGs Subgroups: by age group, gender, race, baseline weight and MMSE at baseline
Group 2 (All treated patients in Study 2320 and Study 2320E1)	2320, 2320E1	919	Topics: deaths, SAEs, other significant AEs, all AEs, skin irritation, patch adhesion
Group 3 (All Prometax patch-treated AD patients*)	2320, 2320E1, 401, 1201 and 2331	1071*	Topics: deaths, SAEs, other significant AEs, skin irritation, patch adhesion
Group 4 (All Prometax patch-treated healthy volunteers)	W155, W159, W160, 2332, 2333, 2334, 2335, 2338, and 1101	432	Topics: deaths, SAEs, other significant AEs, all AEs, skin irritation, patch adhesion

* One patient in Study 1201 commenced treatment but was lost to follow-up and did not return for any evaluations. As a result, the patient was excluded from the safety population.

The primary groups mainly used for the evaluation of safety are Group1 (all Prometax patch, capsule and placebo treated AD patients in double-blind controlled studies) and Group2 (all Prometax patch treated patients in Study 2320 and it is open-label long term extension).

In Group1, approximately 60% of patients received treatment for the full 24 week period. In this group, for the available evaluations of patch adhesion, more than 94% of all patches remained either completely on or were only detached at the edges.

In Group2, including long-term safety data, 23,1% of patients received Prometax patch treatment for at least 52 weeks.

In Group3 (all Prometax patch treated AD patients in studies 2320, 2320E1, 0401, 1201 and 2331), the mean duration of exposure was 28.7 weeks. In the healthy volunteer studies (Group4), a total of 432 subjects were exposed to Prometax patch for a maximum of 3 weeks.

Overall, these data do not highlight new or unexpected adverse events, in association with Prometax patch administration, which were not already known for Prometax capsule.

A dose response relationship is suggested, based on the difference between the incidence of AEs in patients in the higher and lower patch size groups, for gastrointestinal AEs (nausea, vomiting, diarrhea, decreased weight, decreased appetite, anorexia), for asthenia, and for nervous system AEs (dizziness, insomnia, agitation).

The 20 cm^2 patch was overall associated with a higher incidence of adverse events compared to Prometax 12 mg capsule. In particular, gastrointestinal disorders (such as diarrhea, vomiting, abdominal pain), and other disorders such as decreased appetite, weight decreased, insomnia and anxiety, were more frequently observed in the 20 cm^2 patch group compared to Prometax 12 mg capsule. These data constitute an area of concern regarding the safety profile of the 20 cm^2 patch formulation.

Prometax 20 cm^2 patch group was associated with more cardiac disorders than other treatment groups. However, ECG evaluations at baseline revealed more arrhythmic abnormalities in patients randomized to the Prometax 20 cm^2 patch group (8.2% vs 4.6-5.6% in other groups). Baseline myocardial abnormalities were more common in the Prometax 20 cm^2 patch and the Prometax capsule groups which might explain the higher rate of cardiac disorders in the Prometax 20 cm^2 patch group.

The incidence of serious adverse events in Group1 was highest in the Prometax 20 cm^2 patch size group compared to the other groups. The most frequently reported serious AEs were in the nervous system, cardiac and gastrointestinal system organ classes for the 10 cm^2 and 20 cm^2 Prometax patch and Prometax capsule groups.

In Group1, the 10 cm^2 patch is better tolerated than the Prometax capsule (except for diarrhea, abdominal pain and anxiety, which were slightly more frequent in the 10 cm^2 patch group) and than the 20 cm^2 patch (particularly regarding nausea, vomiting, decreased weight, decreased appetite,anorexia, dizziness, insomnia).

Regarding Prometax 5 cm^2 patch size, data are insufficient for an accurate evaluation of adverse events for this dose, since patients were not randomized to this patch size in the main study 2320. The data provided are reassuring regarding the low number of patients who experienced severe skin irritation (0.76%) with the 5 cm^2 and 10 cm^2 patch sizes.

Discontinuations due to gastrointestinal disorders were higher in the Prometax 20 cm^2 patch group and Prometax capsule group than in the Prometax 10 cm^2 patch or placebo groups. These data support the improvement of the rivastigmine tolerability with Prometax 10 cm^2 patch regarding gastrointestinal events.

Since Prometax 5 cm^2 patch size is expected to be given mainly at initiation and during the titration period, appropriated data on adverse events with this patch were provided as compared with 1.5 mg b.i.d. The overall incidence of AEs, SAEs and AEs leading to discontinuation in patients treated with Prometax 5 cm^2 patch and Prometax 1.5 mg b.i.d capsule (corresponding to a comparable exposure) were similar for the first 4 weeks of treatment. The most common AEs in the Prometax patch group were nausea, diarrhoea and dizziness. Nausea and vomiting incidences were both lower in patients treated by Prometax patch than in patients treated by Prometax capsule. The incidences of headaches, decreased weight and decreased appetite were lower in the Prometax patch group than in the Prometax capsule group.

In patients treated with a maximum Prometax 1.5 mg b.i.d. capsule, the incidence of AEs was higher than in patients treated with a maximum Prometax patch of 5 cm^2.

Thus, although initiation of treatment with the Prometax 5 cm^2 patch results in exposure (on the basis of AUC) that is substantially greater than for Prometax 1.5 mg b.i.d. capsule, it appears to have comparable safety and improved gastrointestinal tolerability over the Prometax 1.5 mg b.i.d capsule. Therefore, the Prometax 5 cm^2 patch is a suitable initiation dose.

Regarding extrapyramidal symptoms, 1,4% are reported with the 10 cm^2 Prometax patch (including one serious case), compared to 0% with higher doses of patch groups. The four cases reported with 10 cm^2 Prometax patch do not allow concluding to a higher risk of adverse events related to extrapyramidal system, despite the higher incidence with this patch dose in study 2320. However, extrapyramidal symptoms may occur with rivastigmine, as reported in the SPC of Prometax capsules.

A total of 27 patients who received study treatment (Prometax patch, capsule and placebo) died during the clinical development program. According to the data provided, no signal raised from the death cases reported in the Prometax patch groups, compared to other treatment groups. In all cases, patient's history could have explained the fatal event. Moreover, cardiac failure, cerebrovascular accident, respiratory failure are common causes of death in the general elderly population.

Skin reactions are expected side-effects associated with the use of patch. Patients treated with Prometax patches experienced more frequently slight or mild skin irritation, compared to placebo patches (33.3% vs 27.6% for the 20 cm^2 patch, 29.9% vs 17.3% for the 15 cm^2 patch, 38.2% vs 22.3% for the 10 cm^2 patch, 21.4% vs 11.8% for the 5 cm^2 patch).
The majority of skin reactions were very slight or mild erythema or pruritus. The skin irritation appears to be due to mechanical stress caused by adhesion and removal of the patches, and is exacerbated by rivastigmine which acts as an additional chemical irritant. Allergic dermatitis or sensitization do not seem to be the cause of application site reaction, however the number of patients who received Prometax capsules after study discontinuation due to application site dermatitis is very low, and then it is difficult to draw any definitive conclusion.
No patient in any of the Prometax patch studies experienced a skin reaction that was reported as a serious adverse event, and 19 patients discontinued due to skin irritation in study 2320. Non serious skin reactions were collected and even solicited and were common.
Site skin irritation data, assessed by the investigator for patients who completed 52 weeks of Prometax patch treatment, and based on the ratings scale, show that in these patients there was no apparent increase in the overall incidence or severity of skin irritation over the 52-week period.

Safety data observed in Groups 2, 3 and 4 are consistent with the results from the double-blind, controlled study population (Group1).

No specific data related to immunological events are available for Prometax patches.
No specific safety interaction studies have been conducted with Prometax patches.

No data comparing compliance of Prometax patches and capsules have been provided. However, to further assess Prometax patch compliance, adhesion and the risks of application site skin reactions and irritations in the long term daily use of the Prometax patch, Novartis will conduct a drug utilization study after the patch launch. It is expected that the drug utilization study will provide information on the practicalities of the Prometax patches in the real conditions of use.

In **conclusion** the CHMP agreed on the following:

- the safety profile of Prometax patch 5 cm^2 and 10 cm^2 was considered acceptable
- the safety profile and benefit/risk of Prometax 20cm^2 patch was considered negative due to a high incidence of adverse effects, even if efficacy had been demonstrated
- the safety and benefit/risk of the 15 cm^2 should be further justified

The MAH agreed that Prometax 15 cm^2 patch may provide additional efficacy benefits over Prometax 10 cm^2 patch with fewer tolerability concerns than those associated with Prometax 20 cm^2 patch. However, the clinical program for the Prometax transdermal patch was not designed to answer this question. Without additional data, the MAH was unable to provide sufficient information on the

relative efficacy, tolerability and safety profile of the Prometax 15 cm^2 patch size to the CHMP. Therefore the MAH will continue to evaluate the 15 and 20 cm^2 Prometax patch sizes to confirm a favourable benefit/risk profile of these strengths.

5. PHARMACOVIGILANCE

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the MAH fulfills the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan resumed below.

Summary of the risk management plan: Summary of actions proposed for each safety concern

Safety concern	Proposed Pharmacovigilance activities (routine and additional)	Proposed Risk Minimization activities (routine and additional)
AD		
Worsening of symptoms associated with Parkinson's disease	• **Routine pharmacovigilance** • **Detailed review in PSUR**	• **Routine risk minimization (***Extrapyramidal symptoms* **are identified in the transdermal patch SmPC Sections 4.2 in posology, 4.4 as warning and 4.8 as very rare Adverse Drug Reaction. The SmPC/PIL maybe updated if new patterns develop during ongoing review)**
Nausea, vomiting and diarrhea	• **Routine pharmacovigilance** • **Detailed review in PSUR**	• **Routine risk minimization (***Nausea, Vomiting and Diarrhea* **are identified in the transdermal patch SmPC Section 4.4 as warning and in Section 4.8 as common Adverse Drug Reaction. The SmPC/PIL maybe updated if new patterns develop during ongoing review)**
Increased Amylase, Lipase and Pancreatitis	• **Routine pharmacovigilance** • **Detailed review in PSUR**	• **Routine risk minimization (***Pancreatitis* **is identified in the transdermal patch SmPC Section 4.8 as very rare Adverse Drug Reaction observed with oral formulation only. The SmPC/PIL maybe updated if new pattern develops during ongoing review)**
Application site skin reactions and irritations (patch only)	• **Routine pharmacovigilance** • **Detailed review in PSUR** • **Monthly line listings of all application site skin reactions for the first 12 month period after the Prometax patch launch**	• **Drug utilization study to assess Prometax patch compliance, adhesion and the risks of application site skin reactions and irritations in the long term daily use** • *Application site skin reactions are* **identified in the transdermal patch SmPC Section 4.8 as common Adverse Drug Reactions. The**

Safety concern	Proposed Pharmacovigilance activities (routine and additional)	Proposed Risk Minimization activities (routine and additional)
		SmPC/PIL maybe updated if new patterns develop during ongoing review.
Anaemia	• **Routine pharmacovigilance** • **Detailed review in PSUR**	• **Routine risk minimization (SmPC/PIL maybe updated as appropriate based on ongoing review)**
Eye irritation (patch only)	• **Routine pharmacovigilance** • **Detailed review in PSUR**	• **Drug utilization study to assess Prometax patch compliance, adhesion and the risks of application site skin reactions and irritations in the long term daily use** • **Identified in the transdermal patch SmPC Sections 4.2 posology, 4.4 warnings, 5.3 pre-clinical safety. The SmPC/PIL maybe updated if new patterns develop during ongoing review**
Pulmonary infections	• **Routine pharmacovigilance** • **Detailed review in PSUR**	• **Routine risk minimization (SmPC/PIL maybe updated as appropriate based on ongoing review)**
Cardiac arrhythmias	• **Routine pharmacovigilance** • **Detailed review in PSUR**	• **Routine risk minimization (Identified in the transdermal patch SmPC Section 4.4 as warning:** *to patients with sick sinus syndrome or conduction defects (sino-atrial block, atrio-ventricular block),* **in Section 4.8 as uncommon Adverse Drug reactions:** *Bradycardia,* **and** *Cardiac arrhythmia (e.g. atrio-ventricular block, atrial fibrillation and tachycardia)* **as very rare Adverse Drug Reactions observed with oral formulations only. The SmPC/PIL maybe updated if new patterns develop during ongoing review)**
Exacerbation of Asthma and COPD	• **Routine pharmacovigilance** • **Detailed review in PSUR**	• **Routine risk minimization (Identified in the SmPC Section 4.4 as warning:** *…to patients with a history of asthma or obstructive pulmonary disease.* **The SmPC/PIL maybe updated if patterns develop during ongoing review)**
Cardiac disorders (Myocardial infarction)	• **Routine pharmacovigilance** • **Detailed review in PSUR**	• **Routine risk minimization (***Angina pectoris* **is identified in the transdermal patch SmPC Section 4.8. as rare Adverse Drug Reaction observed with oral formulations only. The SmPC/PIL maybe updated if new patterns develop**

Safety concern	Proposed Pharmacovigilance activities (routine and additional)	Proposed Risk Minimization activities (routine and additional)
		during ongoing review)
Liver disorders (hepatitis)	• **Routine pharmacovigilance** • **Detailed review in PSUR**	• **Routine risk minimization (***Elevated liver function tests* **are identified in the transdermal patch SmPC Section 4.8 as uncommon Adverse Drug Reaction observed with oral formulations only. The SmPC/PIL maybe updated if new patterns develop during ongoing review)**
Hematuria	• **Routine pharmacovigilance** • **Detailed review in PSUR**	• **Routine risk minimization (SmPC/PIL maybe updated if patterns develop during ongoing review)**
Hypertension	• **Routine pharmacovigilance** • **Detailed review in PSUR**	• **Routine risk minimization (***Hypertension* **is identified in the transdermal patch SmPC Section 4.8 as very rare Adverse Drug Reaction observed with oral formulations only. The SmPC/PIL maybe updated if new patterns develop during ongoing review)**
Cerebrovascular accidents	• **Routine pharmacovigilance** • **Detailed review in PSUR**	• **Routine risk minimization (SmPC/PIL maybe updated as appropriate based on ongoing review)**
Urinary tract obstruction	• **Routine pharmacovigilance** • **Detailed review in PSUR**	• **Routine risk minimization (Identified in the transdermal patch SmPC Section 4.4 as warning:** *to patients predisposed to urinary obstruction … because cholinomimetics may induce or exacerbate these diseases.* **The SmPC/PIL maybe further updated if new patterns develop during ongoing review)**
Gastric ulcer	• **Routine pharmacovigilance** • **Detailed review in PSUR**	• **Routine risk minimization (Identified in the transdermal patch SmPC Section 4.4 as warning:** *to patients with active gastric or duodenal ulcers or patients predisposed to these conditions because rivastigmine may cause increased gastric secretions* **and in Section 4.8 as uncommon Adverse Drug Reaction. The SmPC/PIL maybe updated if new patterns develop during ongoing review)**
Death	• **Routine pharmacovigilance** • **Detailed review in PSUR**	• **Routine risk minimization (SmPC/PIL maybe updated as appropriate based on ongoing review)**

Safety concern	Proposed Pharmacovigilance activities (routine and additional)	Proposed Risk Minimization activities (routine and additional)
Bullous reactions	• **Routine pharmacovigilance** • **Detailed review in PSUR**	• **Routine risk minimization (SmPC/PIL maybe updated as appropriate based on ongoing review)**
Seizures	• **Routine pharmacovigilance** • **Detailed review in PSUR**	• **Routine risk minimization (Identified in the transdermal patch SmPC Section 4.4 as warning:** *to patients predisposed to … seizures because cholinomimetics may induce or exacerbate these diseases* **and in Section 4.8 as Adverse Drug Reactions observed with oral formulations only. The SmPC/PIL maybe further updated if new patterns develop during ongoing review**

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

6. OVERALL CONCLUSIONS, RISK/BENEFIT ASSESSMENT AND RECOMMENDATION

Quality

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

Non-clinical pharmacology and toxicology

No studies on the pharmacodynamic action of rivastigmine were included in the dossier as rivastigmine is considered a well known inhibitor of AChE and BChE. The non-clinical pharmacokinetic and toxicology development program to support the patch formulation was considered adequate.

Efficacy

Prometax 5 cm^2 patch was considered acceptable as the initial treatment dose.

Prometax 10 cm^2 patch showed statistical superiority versus placebo at Week 24 as demonstrated by simultaneous testing of ADAS-Cog and ADCS-CGIC, with respective p-values of 0.005 and 0.010.

An overall responder analysis based on patients with ADAS-Cog improvement of at least 4 points and ADCS-CGIC categories 1-4 (any improvement or no change) and ADCS-ADL change ≥ 0 points (no change or improvement) showed that at Week 24, a statistically significant greater proportion of patients responded to Prometax patch 10 cm^2 than to placebo.

Thus, efficacy of Prometax patch 5 cm^2 and 10 cm^2 was considered acceptable.

Safety

All the adverse reactions reported in clinical trials and post-marketing experience have been included in the Summary of Product Characteristics

Overall, these data do not highlight new or unexpected adverse events, in association with Prometax patch administration, which were not already known for Prometax capsule.

The 20 cm^2 patch was overall associated with a higher incidence of adverse effects compared to the equivalent Prometax 12 mg capsule. In particular, gastrointestinal disorders (such as diarrhea, vomiting, abdominal pain), and other disorders such as decreased appetite, weight decreased, insomnia and anxiety, were more frequently observed. Discontinuation due to gastrointestinal disorders was higher in the Prometax 20 cm^2 patch and Prometax capsules groups. The safety profile of the 20 cm^2 patch formulation constituted an area of concern for the CHMP and the MAH agreed to continue to evaluate the safety of this dose before a new application for its approval can be re-submitted. The safety profile of the 15 cm^2 patch needs to be further addressed.

The 10 cm^2 patch is better tolerated than the Prometax capsule (except for diarrhea, abdominal pain and anxiety, which were more frequent in the 10 cm^2 patch group) and than the 20 cm^2 patch (particularly regarding nausea, vomiting, decreased weight, anorexia, dizziness).

Skin reactions are expected side-effects associated with the use of patch. Patients treated with Prometax patches experienced more frequently slight or mild skin irritation, compared to placebo group.

The safety of Prometax 5 cm^2 patch was considered acceptable as the initial treatment dose.
The MAH agreed that Prometax 15 cm^2 patch may provide additional efficacy benefits over Prometax 10 cm^2 patch with fewer tolerability concerns than those associated with Prometax 20 cm^2 patch. However, the clinical program for the Prometax transdermal patch was not designed to answer this question. Without additional data, the MAH was unable to provide sufficient information on the relative efficacy, tolerability and safety profile of the Prometax 15 cm^2 patch size to the CHMP.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 5 adequately addressed these concerns.

Risk-benefit assessment

The efficacy and safety of rivastigmine patches has been investigated in patients with AD in one pivotal study. Supportive data were provided from 3 further uncontrolled studies in AD patients and 9 studies in healthy volunteers.

Considering the physicochemical (relatively low molecular weight, lipophilicity and lack of polymorphic forms) and pharmacokinetic (hepatic first-pass metabolism generating inactive metabolite) properties of rivastigmine, the claimed use of this drug by trans-dermal route appears to be potentially a suitable alternative to the current oral route.

Prometax transdermal patches, with once-a-day dosing and without the need for oral administration with food, might offer the advantage of improved caregiver and patient convenience which may lead to improved patient compliance. In addition this formulation might be useful for patients with swallowing difficulties who are unable or refuse to take oral medication. Nevertheless, available data from clinical studies on this specific topic should be provided with the comparison between Prometax patch and capsules. This will be addressed in the phase IV and drug utilization study that the MAH is planing.

The superiority of Prometax 10 cm^2 patch versus placebo has been demonstrated and there are no findings as regards safety as compared to Prometax 12 mg capsules. The overall benefit/risk of

Prometax patches 5 cm^2 and 10 cm^2 is positive for the "symptomatic treatment of mild to moderately severe Alzheimer's dementia".

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- no additional risk minimisation activities were required beyond those included in the product information.