SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Prometax. This scientific discussion has been updated until 1 April 2004. For information on changes after this date please refer to module 8B.

All doses quoted refer to rivastigmine base.

1. Introduction

Alzheimer's Disease (AD) is 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 AD. It is not only a heavy burden for the patient but is also responsible for making the patient dependent on his family or the community.

Dementia is characterised by dysmnesia, intellectual deterioration, and changes in personality, and behavioural abnormalities. Dementia of the Alzheimer type is the most common cause of dementia. The prevalence of this disease, which mainly occurs from the sixth decade of life increases gradually with age to reach about 30% by the end of a century of life.

The cause of the disease remains unknown. Its diagnosis is an exclusion diagnosis in the face of a dementia with insidious onset, a gradual progression, and no sign of another cause of dementia. The neuropathology of AD is characterised by extensive neuronal cell loss, deposition of numerous senile plaques and neurofibrillary tangles in the cerebral cortex. Early neurochemical studies suggested that there is a specific loss of cholinergic neurones and/or acetyltransferase activity in AD. This led to the development of acetylcholinesterase inhibiting drugs for treatment of AD.

Tacrine was the first acetylcholinesterase (AChE) inhibitor to obtain a marketing authorisation in symptomatic treatment of Alzheimer's Disease in the USA (1993) and in some European countries. Another AChE inhibitor, donepezil, has been recently authorised in 14 EU Member States.

Rivastigmine is a non-competitive acetylcholinesterase inhibitor of the carbamate type. It has been shown, in animal and man, to inhibit central and peripheral acetylcholinesterases and butyrylcholinesterases, proportionally with the dose. Animal studies indicate a weak specificity for the cortex within the CNS.

PROMETAX is indicated for symptomatic treatment of patients with mild to moderately severe Alzheimer's dementia.

Doses of rivastigmine should be titrated to achieve an individual optimal therapeutic response; the recommended starting dose is 1.5 mg twice a day. The daily dose may be increased up to 6 mg twice a day, after a minimum of two weeks treatment between each increase. The effective dose is 3 to 6 mg twice a day; to achieve maximum therapeutic benefit patients should be maintained on their highest well-tolerated dose.

2. Chemical, pharmaceutical and biological aspects

PROMETAX hard capsules:

Composition

PROMETAX hard gelatin capsules contain rivastigmine hydrogen tartrate. There are four capsule strengths containing 2.4 mg, 4.8 mg, 7.2 mg, and 9.6 mg of rivastigmine hydrogen tartrate, corresponding respectively to 1.5 mg, 3.0 mg, 4.5 mg, and 6.0 mg of rivastigmine. The 4 strengths are differentiated by colour or colour combination and imprint. The various strengths are not homothetic. The primary packaging material is composed of a clear PVC film and coated hard aluminium foil or a clear polypropylene film and coated soft aluminium foil. Each blister contains 14 capsules and there are 3 package sizes: 28, 56, and 112 capsules.

Other ingredients

The capsules contain microcrystalline cellulose as disintegrant/filler, colloidal anhydrous silica as flow regulator, methylhydroxypropylcellulose as binder, and magnesium stearate as lubricant. All excipients are commonly used in many other authorised pharmaceuticals and meet European Pharmacopoeial requirements.

Active substance

Rivastigmine hydrogen tartrate is a white to off-white, fine crystalline powder that is very soluble in water, soluble in ethanol and acetonitrile, slightly soluble in n-octanol and very slightly soluble in ethyl acetate. The pKa is 8.85. The distribution coefficient at 37°C in n-octanol/phosphate buffer solution pH 7 is 3.0. Forced degradation experiments have revealed the potential degradation pathways of the active ingredient, and the main degradation products have been identified. The active substance is not sensitive to light. Rivastigmine hydrogen tartrate is very hygroscopic and is deliquescent. At a relative humidity above 55% it should, therefore, be stored in packaging that is impermeable to moisture.

The rivastigmine base is chiral, containing one optical active centre and is used as a single stereo-isomer (the S-isomer). The active substance is a (R,R)-hydrogentartrate salt that has an overall positive rotation. The racemate separation provides active substance with high optical purity. No polymorphism was observed.

Rivastigmine hydrogen tartrate is manufactured in a synthesis using well-established chemical reactions.

The chemical structure of rivastigmine has been confirmed by elemental analysis, interpreted infra red (IR)-, ultra violet (UV)-, mass spectroscopy-, and nuclear magnetic resonance spectra. The absolute configuration of the chiral centre was determined by single crystal x-ray diffraction. For identification thin layer chromatography is used in comparison with a reference substance. The purity is checked by high performance liquid chromatography (HPLC) and UV. The proportion of the (+)-antipode in the drug substance is routinely determined by a separate HPLC method using a chiral stationary phase. All methods have been adequately validated.

Fifteen potential impurities are described for the active substance, but only nine have been observed. The (S)-3-(1-dimethylaminoethyl) phenol was the only impurity detected above 0.1%. It is the main by-product, the main metabolite and a possible hydrolysis product. The proposed limit is ≤ 0.3%. The R-enantiomer is present as an impurity at levels below the limit of quantitation (<0.2%), with a specification limit at ≤ 0.3%. The level of total related compounds in the active ingredient is limited to 0.5% by HPLC. Batch results indicate that lower limit levels of total and individual impurities are possible, and further tightening may be considered after sufficient experience in chemical production has been gathered.

In the solid state, the active substance was tested under accelerated and normal conditions. A re-test period of 5 years for the active substance is acceptable.

Product Development and Finished product

The pharmaceutical development conducted by the company resulted in the production of conventional capsules for immediate release. The compatibility of the active ingredient with various excipients was demonstrated in a pre-formulation programme from which the optimum formulation was selected. In order to guarantee content uniformity at low strengths a wet granulation was the selected process.

The manufacturing process is a conventional process for oral solid capsules consisting of 4 principle steps: aqueous wet granulation, fluidised bed drying, final blending and capsule filling. Validation of the process was carried out with industrial sized batches particularly with regard to uniformity of content of active substance in the resulting product, bearing in mind the low dose. In-process controls are performed and have been validated.

Control tests on the finished product use adequately validated methods, including identification of active substance, quantitative determination of active substance, determination of degradation products, uniformity of mass, content uniformity, disintegration testing, dissolution testing and

identification of colouring material. Results from batch analyses showed that all batches complied with release specifications and demonstrated acceptable batch to batch consistency.

In the finished product specification (release) the main impurity, the main metabolite of the active substance, is limited at ≤ 0.4% in the specification. Other identified impurities are limited to ≤ 0.3% and unidentified impurities to ≤ 0.2%. The limit for total impurities is 0.5%.

For the finished product stability data support the storage conditions "storage at below 30°C". A shelf life of 5 years is supported by real time stability data and acceptable when the hard capsules are stored under these conditions.

PROMETAX oral solution:

Composition

PROMETAX oral solution contains rivastigmine hydrogen tartrate. There is one strength containing 3.2 mg of rivastigmine hydrogen tartrate, corresponding to 2 mg of rivastigmine base per ml. The oral solution contains sodium benzoate, citric acid, sodium citrate, quinoline yellow (E104) and purified water. The primary packaging material is composed of a USP Type III amber glass bottle with a child-resistant cap, dip tube and self-aligning plug. Each bottle contains 120 ml.

Active substance

Rivastigmine hydrogen tartrate is the same active substance as that used in the hard capsule dosage form described above.

Other ingredients

The oral solution contains sodium benzoate as antimicrobial preservative, anhydrous citric acid and sodium citrate as buffers, quinoline yellow (E104) as colouring agent and purified water as solvent. All excipients are commonly used in many other authorised pharmaceuticals and meet European Pharmacopoeial requirements, with the exception of quinoline yellow, which is tested according to French Pharmacopoeial procedures.

Product development and finished product

The objective of the pharmaceutical development was to obtain a flavourless, unsweetened solution. An existing injectable solution of rivastigmine, developed as a clinical service form, was the starting point for the development of the oral solution. An oral solution was developed with the same aqueous solvent and at the same pH (3.5-4.5) as the injectable dosage form. Sodium benzoate was selected as an antimicrobial preservative. Quinoline yellow WS was used as a colouring agent to make the clear solution more visible in the dispensing syringe. An amber glass bottle was chosen for the packaging because of its known inertness to liquid pharmaceutical products.

The manufacturing process is conventional. No overages are included in the manufacturing formula. The critical process parameters are adequately controlled during manufacture and have been validated. Batch analyses show that the manufacturing process results in a uniform product which conforms to specifications.

The finished product specification includes tests to identify and assay the active substance and preservative, identification of the colourant, and tests for density, refractive index, pH, determination of degradation products, deliverable volume, leakage and microbial limits. Adequately validated methods are employed. The same assay limits and purity specifications as the hard capsule formulation are used.

The finished product is packed in 120 ml USP type III amber glass bottles with a child resistant cap. The specifications and tests for the packaging materials are satisfactory.

The finished product showed good stability both during long term and accelerated stability studies. The data, therefore, support a shelf life of 3 years for the oral solution when stored below 30ºC and in an upright position. The oral solution should be protected from freezing.

3. Toxico-pharmacological aspects

Pharmacodynamics

The pharmacodynamic action of rivastigmine has been studied *in vitro* and *in vivo*.

The inhibition of acetylcholinesterase (AChE) leads to an increased availability of acetylcholine (ACh) in cholinergic neurones of the brain assumed to ameliorate cognitive deficits associated with Alzheimer's disease. The active site of AChE comprises two distinct regions: an anionic site and an esteratic site. Anti-cholinesterase drugs fall into different categories according to the nature of their interaction with the active site. Rivastigmine, like physostigmine, interacts with the catalytic site resulting in a carbamylated enzyme that slowly breaks down to generate free-enzyme, resulting in a "pseudo-irreversible action". Short acting AChE inhibitors such as tacrine bind to the anionic site of the enzyme.

The effect of rivastigmine on the electrically evoked release of [^{3}H]-ACh from rat hippocampal slices was studied *in vitro* and showed that the decrease in the release of ACh was due to an increased accumulation of endogenous ACh which triggers the negative feed-back mechanism via the muscarinic autoreceptor. This effect on auto-receptor is expected with AChE inhibitors.

The ability of rivastigmine to inhibit the activity of AChE in different rat brain regions (cortex, hippocampus, striatum and pons/meddulla), heart, and blood was measured *in vitro* and *ex vivo*. Short-term exposure showed that rivastigmine was 4-17 times more specific for inhibition of brain AChE compared to heart and blood AChE. However, sub-chronic treatment with rivastigmine over 14 days resulted in similar AChE inhibition in brain, heart and blood, indicating that any possible regional selectivity of rivastigmine was lost during subchronic treatment. Following chronic administration, rivastigmine increased acetylcholine levels. The ACh increase was in the range of that observed with physostigmine or tacrine.

In *in vitro* studies, the major metabolite of rivastigmine, ZNS 114-666 (also known as NAP 226-90), caused a dose-dependent inhibition of AChE activity. No inhibition of AChE by ZNS 114-666 was detected *ex vivo*, which might be due to poor blood-brain-barrier penetration.

In radioligand binding studies, rivastigmine displayed no affinity for muscarinic, α- and β- adrenergic, dopaminergic, serotoninergic or opiate binding sites.

A study of behavioural effects in mice, aimed at studying AChE inhibition, showed the lowest active oral dose to be 0.5-1 mg/kg. In a study examining the effects of the hippocampal EEG in the rat, the lowest active dose was 0.075 mg/kg. A study of salivation in anaesthetised mice showed that the peripheral effects appeared at higher doses than the central effects.

A water maze test, conducted to study memory activity in rats, suggested that rivastigmine may reverse short-term scopolamine-induced amnesia with no effect on long term memory. The short-term activity weakly increased with dose (1 to 10 mg/kg). Although this model of scopolamine induced amnesia is probably not the best animal model for Alzheimer's disease available, given the clinical efficacy studies, no further preclinical studies were considered necessary.

General pharmacology studies showed effects expected from a cholinomimetic agent: stimulation of smooth muscle fibres inducing an increase in enteral peristaltism and bronchoconstriction, a negative chronotropic effect (slight bradycardia) and hypertension of central origin.

Pharmacokinetics

The pharmacokinetic profile of rivastigmine was studied in the mouse, rat, rabbit and dog, the main species used in the preclinical program. Plasma protein binding was low, < 20% in the animals as compared to approximately 40% in humans. Rivastigmine was mostly distributed within the blood compartment, while drug-related radioactivity was rapidly distributed into tissues. The highest levels were observed in the liver, kidney and salivary gland. Rivastigmine was found to penetrate easily into the brain when investigated *in situ* using a rat brain perfusion/ capillary depletion method, with a brain extraction of 70% and 19%, respectively for rivastigmine and the metabolite ZNS 115-666. In pregnant rabbits, moderate transfer of drug–related material across the placenta was seen. In lactating rabbits, rapid distribution of radioactivity into milk was observed. After oral administration, absorption

was rapid in all species. The oral bioavailability increased with dose, due to saturable first pass metabolism. At high dose levels, it ranged from 3% (rat) to 43% (dog). In humans the absolute bioavailability is approximately 36%.

The metabolic pattern of rivastigmine was qualitatively similar in all species studied including humans. The main metabolic pathways were decarbamylation, conjugation and N-dealkylation. The main product of esterase metabolism was the phenol ZNS 114-666 in all species (also known as NAP 226-90). *In vitro* studies indicated that the liver is the main organ for rivastigmine metabolism, with up to 5 times faster metabolism in rat than in human liver. The major route of excretion was via the kidney, with >75% (except mouse 51-66%) of the radioactivity recovered in urine. The urinary excretion was rapid and nearly complete within 24 hours of dosing.

Based on pharmacokinetic comparisons, the dog was considered the most relevant species for the assessment of safety. Based on toxicokinetic data, the systemic exposure of animals in the toxicity studies was usually lower than that in patients on recommended doses. Only at higher doses tested in mice and dogs did systemic exposure in the toxicity studies approach that found in AD patients receiving 6 mg twice a day.

Toxicology

Single dose toxicity of rivastigmine after oral administration was studied in rodents and dogs. These studies showed that rivastigmine had relatively low LD_{50} values. All deaths and symptoms observed including clonic convulsions, tremors, decreased activity, ataxia and effects on respiration, were associated with the pharmacological action of rivastigmine.

Repeated dose toxicity of rivastigmine after oral administration was studied in mice (13 weeks), rat (up to 52 weeks), mini pigs (4 weeks), dog (up to 52 weeks) and monkeys (2 weeks). All species showed signs of toxicity related to exaggerated pharmacodynamic responses to rivastigmine, i.e. an excessive cholinergic stimulation as a result of AChE-inhibition. Dose dependent clinical signs, which diminished over time in dogs, included effects on the gastrointestinal (e.g. diarrhoea) and respiratory systems. At high doses, reduced food intake and reduced body weight gain were observed. Nevertheless, neither unexpected toxicological findings nor specific target organs were found in the studies. The dog was the most sensitive species. The No Observed Adverse Effect Level in rodents and dogs was around 0.11 mg/kg, i.e. less than the maximum recommended human dose (0.2 mg/kg for a 60kg patient).

Toxicity to reproduction was studied in rats and rabbits at dose levels inducing excessive cholinergic stimulation**.** In a rat study of fertility and general reproductive function, a reduced weight of offsprings was seen at the end of the lactation period. Administration during organogenesis resulted in increased embryonic resorptions and post implantation loss (rabbit only) but there were no signs of teratogenic effects. The peri/post natal study showed increased neonatal mortality and reduced post natal body weights. All these findings were possibly consequences of AChE inhibition/maternal toxicity. In the peri/post natal study, a slight increase in gestation time (about 0.5 days) was also observed.

The genotoxic potential of rivastigmine was studied *in vitro* and *in vivo*. Overall, it was not genotoxic, although a slight increase of chromosomal aberrations was observed in human peripheral blood lymphocyte test at a very high concentration. Chromosomal damage was not seen in the *in vivo* micronucleus test in mice. Consequently, these observations were not considered to raise toxicological concerns for the dose levels used in man.

Carcinogenicity was studied in mice and rats following 2 years administration. In general, symptoms related to excessive cholinergic stimulation were observed but there was no indication of specific target organs of toxicity or of carcinogenic effects.

Rivastigmine showed no local irritancy or antigenicity.

Impurities

Single dose toxicity studies were conducted on several impurities. Results did not show any toxicological effect of significance.

The genotoxic potential was also evaluated for 226-90 and 541-87. Results were negative for 226-90 and slightly positive for 541-87.

4. Clinical aspects

The clinical program was aimed at evaluating the efficacy and safety of rivastigmine for the symptomatic treatment of mild to moderately severe Alzheimer's disease. The clinical documentation, contained in the application for marketing authorisation for rivastigmine hard capsules, consisted of a total of 39 studies. In phase I and II there were 17 clinical pharmacology and 6 therapeutic studies, and there were 16 studies in the phase III programme.

The oral solution was developed to allow patients dose flexibility during both the titration and maintenance phases, which are necessary to optimise dose. In addition the oral solution addresses the need of patients who may have difficulty swallowing hard capsules. Although this formulation has not been used during clinical trials, it has been shown to be bioequivalent to the existing hard capsule by means of a standard single dose crossover study in humans described in this section.

Pharmacodynamics and pharmacokinetics

Following single and repeated administration, rivastigmine was shown to inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) in the central nervous system (in cerebrospinal fluid, CSF) and in the periphery (in erythrocytes or plasma). Central effects were moderately greater than peripheral effects. In Alzheimer's patients significant dose-dependent inhibition of CSF AChE was observed by 1.2 hours post-dose, and was maintained for up to 11.6 hours. The maximum CSF AChE and BChE inhibition was comparable (62% and 77% respectively). Significant BChE inhibition was also observed in plasma with a maximum observed inhibition of 51% at 5 mg b.i.d. significant inhibition was generally observed from 1.5 hours post-dose up to 8 hours post-dose. Through a Type II variation the Marketing Authorisation Holder submitted new information on the pharmacodynamic properties of rivastigmine as a BChE inhibitor. The application was a bibliographic application referencing three studies. The studies showed that inhibition of BChE activity in CSF of 14 Alzheimer's disease patients by rivastigmine was similar to that of AchE.

Pharmacokinetic profile: The pharmacokinetic profile of rivastigmine and its decarbamylated metabolite ZNS 114-666 has been well documented both in healthy volunteers and the target patient population. Rivastigmine demonstrates non-linear kinetics, with variable bioavailability. It is well absorbed, but a first-pass metabolism results in a bioavailability of approximately 36% for a 3mg oral dose. It is extensively metabolised, principally via cholinesterase-mediated hydrolysis. A higher than proportional increase with dose in C_{max} and AUC of rivastigmine was seen both after oral and i.v. administration, while the exposure of the phenolic metabolite is dose proportional. The dose disproportionality for the parent drug may be due to binding to the target enzyme. The plasma protein binding of rivastigmine is in the range 35-45%.

Elimination: Plasma clearance of rivastigmine is 130 l/h at a dose of 0.2mg and it is decreased to 70 l/h for a 2.7 mg dose. The half-life was approximately 1 hour following a 3 mg oral dose. No accumulation is expected. Rivastigmine derived material is predominantly (about 90%) excreted via the kidney.

No study specifically investigating the effect of gender on the pharmacokinetics of rivastigmine has been conducted. However, in the population analysis, females were found to have lower renal clearance compared to males (98 vs 149 l/h) resulting in a greater exposure.

Interactions: Food delays the absorption and decreases C_{max} while the extent of absorption is slightly increased. Drug interaction studies were performed with digoxin, warfarin, diazepam, and fluoxetine. No pharmacokinetic interactions were demonstrated, and no effects on the dynamic properties of warfarin (as measured by prothrombin time and complex activity) and digoxin (as measured by blood pressure, pulse rate and PR interval) were demonstrated. Metabolic interactions are not expected as rivastigmine is minimally metabolised by cytochrome P450 isoforms, although rivastigmine may inhibit the BChE mediated metabolism of other drugs.

Special populations: Healthy elderly subjects and Alzheimer patients appeared to have higher plasma levels of rivastigmine than young healthy subjects. However, in Alzheimer patients aged between 50 and 92 years no change in bioavailability was found with age. Gender and body surface area were found to be two factors contributing to the variability in plasma levels of rivastigmine. No prolonged elimination or accumulation was observed.

Although no unchanged parent drug is excreted renally, C_{max} and AUC of rivastigmine were twice as high in subjects with moderate renal impairment compared to healthy subjects. A slight increase in exposure was also seen in severely impaired renal function, but not as much as in moderate impairment.

In cirrhotic patients, the conversion of rivastigmine to ZNS 114-666 was decreased. The AUC ratio of rivastigmine to ZNS 114-666 was 1.8 in cirrhotics compared to 0.7 in normal subjects.

A statement is included in the SPC advising that, due to increased exposure in renal and mild to moderate hepatic impairment, dosing recommendations to titrate according to individual tolerability should be closely followed in these patient groups.

Bioequivalence

The clinical development of the oral solution formulation of rivastigmine focused on demonstrating the bioequivalence between the new formulation and the hard capsule formulation. Three open pharmacokinetic studies were conducted with various formulations. These included two pilot pharmacokinetic studies (B353-Amendment 1 and study W251) which were carried out with a primary drink solution (2 mg/5 ml intravenous solution diluted in water), not the proposed formulation, and one study (B153) with the proposed formulation. Details of study B153 are provided below. The pilot studies will not be further discussed here.

Study B153 was an open-label, randomised, cross-over study comparing single doses of 3 and 6 mg rivastigmine oral solution (formulation proposed for marketing) with rivastigmine capsules in patients with probable Alzheimer's disease. To eliminate the need for dose titration patients who tolerated doses of rivastigmine at or above the doses to be used in the study were recruited from other ongoing rivastigmine studies (B353, B355 and B357). Patients fasted for 10 hours prior to dosing and 2 hours after dosing.

A total of 27 patients taking doses of 3-5 mg (bid) were assigned to the 3-mg cohort and 26 patients taking doses of 6 mg bid were assigned to the 6-mg cohort. One patient in the 3-mg cohort was excluded from the statistical analyses because of an incomplete PK profile. The patients stopped taking rivastigmine three days before the first intake in this study and there was a 3-day interval between the cross-over of doses.

The relative bioavailability of the capsules compared to the solution ranged from 101 to 111 %. Consistent with the non-linear pharmacokinetics of rivastigmine, a more than proportional increase in AUC and C_{max} was observed with a doubling of the dose from 3 mg to 6 mg given either as solution or capsule. However, as the intra-subject variability for rivastigmine has been found to be low, and based on the results for AUC_{0-t},AUC_{0-8} and C_{max} of both rivastigmine and metabolite, the 3 mg and 6 mg doses of the oral solution proposed for marketing were bioequivalent to the 3 mg and 6 mg capsule forms respectively.

As rivastigmine displays non-linear pharmacokinetics and a food interaction (delayed absorption, increased AUC and decreased C_{max}) had previously been shown with the hard capsule formulation, the CPMP requested further information on the effect of food with the oral solution. In view of the narrow therapeutic margin from both the efficacy and safety viewpoints, the CPMP considered that it was neither possible nor acceptable to extrapolate the pharmacokinetic data obtained with the capsule formulation to the oral solution in the fed state. Although this is not a common requirement, the CPMP requested that food interaction be studied with the oral solution as a post-marketing commitment. Results of that study evidenced the effect of food on the bioavailability of rivastigmnine oral solution (T_{max} delayed and AUC increased). Following the recommendation of the CPMP, the MAH included through a Type II variation information on the interaction with food in section 5.2 of the SPC and added in the package leaflet the instruction to take PROMETAX with breakfast and with the evening meal.

Therapeutic efficacy

Phase II: Three phase II studies in 566 patients have been carried out, as summarised in Table 1 below. In addition, three Japanese studies have been carried out (2 open and 1 double-blind study with 2, 4 mg/day for 12 weeks) which will not be further commented upon.

Table 1: Phase II studies with rivastigmine and study extensions (rndomised, double-blind studies in parallel groups)

Study	Description *Extensions*	Doses	Duration	No. of patients
B103	Placebo-controlled, three-arm, multicentre study to evaluate the efficacy, tolerability and pharmacology of rivastigmine. *Double-blind extension (B103-01/04) followed by open long-term extension (B103-06).*	2 mg or 3 mg b.i.d	13 weeks (2 week washout)	402
B104	Placebo-controlled, multicentre study to assess the maximum tolerated dose (MTD) and efficacy of b.i.d or t.i.d rivastigmine. Efficacy of concomitant anti-emetic therapy was also studied. *Open extension (B104-01/02)*	Titration up to 12 mg daily (b.i.d or t.i.d)	10-week titration period, followed by 8 weeks of maintenance therapy	114
B105	Placebo controlled, single centre, study to assess the MTD of b.i.d or t.i.d rivastigmine.	Titration up to 12 mg daily (b.i.d or t.i.d)	9 week titration period, followed by a one week washout period	50

Results from these studies suggested that the maximum tolerated dose was 12 mg/day. In study B103, statistically significant efficacy versus placebo was observed for the CGIC primary endpoint and efficacy was shown on secondary criteria (Mini Mental State Examination, Fuld object memory evaluation, Digit symbol substitution test, Benton visual retention test, Trial making test, Nurse observation scale for geriatric patient). The Clinician Interview Based Impression of Change-Plus (CIBIC-Plus) analysis of study B104 revealed a statistically significant improvement in the b.i.d group when compared with placebo (56% vs 16% respectively).

In study B104, there is a trend suggesting that t.i.d administration could be better tolerated than b.i.d. This is being further investigated in an ongoing phase III study, B304, the results of which will be submitted when finalised.

Phase III*:* sixteen phases III trials were conducted, of which four randomised, placebo-controlled, multicentre studies (B303, B304, B351, and B352) with duration of 26 weeks were regarded as the main efficacy studies, see table 2 below. For study B304 efficacy data were not yet available, only interim safety data. Overall, efficacy data were evaluated from more than 2100 patients.

Table 2: Main Phase III placebo-controlled studies (radomised, multicentre, double-blind studies in parallel groups)

Study	Description	Treatment (mg/day) *Fastest titration rate*	Duration (weeks)	No. of patients randomised	
				rivastigmine	placebo
B351	Study comparing the efficacy and safety of three doses of rivastigmine (3 mg/day, 6 mg/day, 9 mg/day) with placebo.	Fixed dose: 3, 6 and 9 (b.i.d) *1mg/day/week*	26	529 (175/176/178)	173
B352	Study to compare the efficacy and safety of 1-4 mg/day rivastigmine with 6-12 mg/day rivastigmine with placebo.	Individual MTD, 1-4 and 6-12 (b.i.d) *1-1.5mg/day/week*	26	434 (233/231)	235
B303	Study to compare the efficacy and safety of 1-4 mg/day rivastigmine with 6-12 mg/day rivastigmine with placebo.	Individual MTD, 1-4 and 6-12 (b.i.d) *1-1.5mg/day/week*	26	486 (243/243)	239
B304 **Interim Safety Report**	Study comparing rivastigmine 2-12 mg/day, given in a tid or bid regimen, with placebo.	Individual MTD, 2-12 (b.i.d or t.i.d) *1-1.5mg/day/week*	26	229 (118/111)	117

Two open extension phases have followed these trials, to provide an additional two years of treatment for B303 (US centres only), B351 and B352 and an additional 6 months in study B303 and B304.

Phase III patient population: Patients of both sexes, who were at least 50 years old (mean age was 73 years)–and fulfilled the DSM-IV criteria for Alzheimer's type dementia, having probable AD according to NINCDS-ADRDA criteria, and having MMSE score between 10 and 26 (both included), participated in the trials. The Global Deterioration Scale (GDS) of Reisberg evaluated the severity of the disease. The mean duration of dementia in patients treated with rivastigmine was 39.4 months (placebo 39.3 months). Exclusion criteria included severe progressive illness, and clinically significant laboratory abnormalities indicative of impaired renal or hepatic function. In the phase III controlled trials, 86% of the patients were experiencing concurrent medical conditions with cardiovascular disorders (31%) being most frequent (primarily hypertension 27%). Concomitant administration of medication known to influence the assessment of efficacy was not permitted, except chloral hydrate for occasional insomnia or agitation (and short-acting benzodiazepines and haloperidol in studies B303 and B304).

Efficacy parameters: Improvement of symptoms was assessed in the following three domains: cognition as measured by objective tests (cognitive endpoint), activities of daily living (functional endpoint) and overall clinical response as reflected by global assessment (global endpoint). In all phase III studies, the primary efficacy measures were the cognitive and global endpoints: Alzheimer's Disease Assessment Scale-Cognitive sub-scale (ADAS-Cog) and the Clinician Interview Based Impression of Change-Plus (CIBIC-Plus). A number of secondary endpoints were also assessed, e.g. the Progressive Deterioration Scale (PDS) a functional endpoint, Mini-Mental State Examination (MMSE), and Global Deterioration Scale (GDS).

Multiple definitions of responders, which combined cognitive, functional and global efficacy measures (ADAS-Cog, PDS, and CIBIC-Plus) were investigated for the pooled studies. For ADAS-Cog and

CIBIC Plus a lower rating is in the direction of improvement. In the PDS, positive changes are in the direction of improvement.

The number of patients entered, completed, discontinued and drop-outs due to adverse events in the three main efficacy studies according to dose group are shown in Table 3 below:

Table 3: Number of patients, entered, completed and withdrawn in studies B303, B351, and B303

Study	B351				B352			B303		
Groups mg/day	9	6	3	Pbo	6-12	1-4	Pbo	6-12	1-4	Pbo
No. entered	178	176	175	173	231	233	235	243	243	239
No. Completed	91	111	130	130	149	199	197	164	209	208
Discontinued	49%*	37%*	26%	25%	35%*	15%	16%	33%*	14%	13%
Adverse event drop outs	34%*	21%*	10%	12%	29%*	8%	7%	23%*	7%	7%

* significantly different from placebo

Efficacy results from B303, B351, and B352:

The efficacy results of the three main efficacy studies are provided in table 4 on the next page (ITT analysis at week 26 for each treatment group and with a pooled analysis of the three clinical trials).

Results indicated that doses of rivastigmine in the range of 1 to 4 mg/day failed to confer statistically significant differences in efficacy in some trials with a small effect overall. With regard to ADAS-Cog and CIBIC-Plus, at these doses, statistically significant differences were only demonstrated versus placebo in study B352 and in the pooled analysis, but not in studies B303 and B351. Results of the analyses of various definitions of responders, for the dose range 1 to 4 mg/day, showed only a significant greater number of responders for one of the definitions (i.e. any improvement in ADAS-Cog, CIBIC-Plus or PDS).

Doses of 6 to 12 mg/day rivastigmine demonstrated consistent statistical differences in efficacy versus placebo. With regard to ADAS-Cog, a statistically significant difference was demonstrated versus placebo in all groups, and for CIBIC-Plus in the [6-12 mg] groups of B303 and B352 but not the 6 or 9 mg groups of study B351. The mean difference versus placebo in the pooled analysis was 2.4 points for ADAS-Cog and 0.3 point for CIBIC-Plus (table 4). For ADAS-Cog a significantly greater proportion of patients were improved by at least 4 points in study B352 and B303, as well as in the pooled analysis (16% versus 10% in the placebo group). Similarly for CIBIC-Plus a significantly greater proportion of patients improved (score <4) in studies B352 and B303, and in the pooled analysis (28% versus 20% in the placebo group).

Table 4: Efficacy results from study B351, B352, B303 (ITT analysis at week 26) and pooled analysis of three studies

STUDY	B351				B352			B303			Pooled Studies		
Groups mg/day	9	6	3	Pbo	6-12	1-4	Pbo	6-12	1-4	Pbo	6-12	1-4	Pbo
ADAS-Cog Baseline	21.5	21.7	22.0	21.7	22.6	22.2	22.1	23.6	23.9	23.3	22.9	22.9	22.5
Change from baseline	+1.2	+0.9	+1.7	+2.4	+0.3	+2.4	+4.1	-0.3	+1.4	+1.3	+0.2	+1.8	+2.6
p vs placebo	***0.018***	***0.004***	*0.17*		***<0.001***	***0.002***		***0.011***	*0.97*		***<0.001***	***0.02***	
CIBIC-Plus Rating	4.1	4.2	4.2	4.2	4.2	4.2	4.5	3.9	4.2	4.4	4.1	4.2	4.4
p vs placebo	*0.24*	*0.86*	*0.84*		***0.01***	***0.02***		*0.012*	*0.36*		***<0.001***	***0.02***	
PDS Baseline	54.9	57.0	55.9	54.0	52.0	54.7	53.7	55.2	53.8	54.8	53.6	54.6	53.8
Change from baseline	-2.2	-2.5	-2.9	-3.1	-1.5	-5.2	-4.9	0.1	-3.4	-2.2	-1.1	-3.9	-3.4
p vs placebo	*0.37*	*0.58*	*0.85*		***<0.001***	*0.77*		***0.07***	*0.33*		***<0.001***	*0.46*	
MMSE Baseline	20.2	19.9	20.0	19.8	19.7	19.5	20.0	20.1	19.7	19.9	19.9	19.7	19.9
Change from baseline	-0.11	0.04	0.2	-0.7	0.2	-0.4	-0.9	0.2	-0.6	-0.5	0.2	-0.3	-0.7
p vs placebo	***0.054***	***0.018***	***0.003***		***<0.001***	***0.07***		***0.04***	*0.66*		***<0.001***	***0.04***	
GDS Baseline	3.9	3.8	3.8	3.9	4.0	4.0	3.9	4.0	4.1	4.0	4.0	4.0	4.0
Change from baseline	-0.1	-0.1	-0.1	-0.2	-0.1	-0.2	-0.3	-0.1	-0.2	-0.3	-0.1	-0.2	-0.3
p vs placebo	*0.40*	*0.47*	*0.25*		***0.003***	***0.014***		***0.006***	*0.63*		***<0.001***	***0.04***	

Post-hoc analyses:

At the request of the CPMP the effect of rivastigmine was analysed with a responder definition of at least 4-point improvement in ADAS-Cog and an improvement (score <4) on CIBIC-Plus. The results are provided in Table 5 below:

Table 5: Patients with clinically significant response (%) from pooled studies B351, B352 and B303

	ITT		
Improvement from baseline	**Rivastigmine 6-12 mg N=749**	**Placebo N=619**	**Rivastigmine 6-12 mg vs placebo**
At least 4 points improvement on ADAS-Cog and an improvement (score < 4) on CIBIC-Plus	8%	4%	4%***

*** p<0.001

For the 6-12mg/day-dose range, an analysis pooling only two out of the three pivotal 26-week multicentre which were dose titration studies (B352 and B303) was also carried out, excluding the fixed dose pivotal study (B351). Clinically relevant improvement in these two studies was defined a priori as at least 4-point improvement on the ADAS-Cog, improvement on the CIBIC-Plus, or at least a 10% improvement on the PDS. Table 6 shows the results of the analyses for this definition of response, together with a post-hoc definition of response requiring a combination of a 4-point or greater improvement on the ADAS-Cog, no worsening on the CIBIC-Plus, and no worsening on the PDS. The mean actual daily dose for responders in the 6-12 mg group, corresponding to the post-hoc definition, was 9.3 mg. This information has been provided in section 5.1 of the SPC.

Table 6: Patients (%) with clinically significant response from pooled studies B352 and B303

	ITT		LOCF	
Response Measure	**Rivastigmine 6-12 mg N=473**	**Placebo N=472**	**Rivastigmine 6-12 mg N=379**	**Placebo N=444**
ADAS-Cog: improvement of at least 4 points	21***	12	25***	12
CIBIC-Plus: improvement	29***	18	32***	19
PDS: improvement of at least 10%	26***	17	30***	18
At least 4 points improvement on ADAS-Cog with no worsening on CIBIC-Plus and PDS	10*	6	12**	6

* p<0.05, **p<0.01, ***p<0.001

Safety

The assessment of safety of rivastigmine is based on data from 3006 patients who received treatment with rivastigmine in all therapeutic studies. All patients who received at least one dose of study medication and had a subsequent safety evaluation were included in the safety database. In total, 1249 patients were treated with rivastigmine for more than 6 months (128 patients with a mean daily dose $\leq$ 3mg, 513 with a dose of 3-6 mg/day, 248 with a dose of 6-9 mg/day, 360 with a dose of 9-12 mg/day). In total, 220 patients were treated with rivastigmine for more than a year.

There is no statistically significant increase in the risk for mortality or in the incidence of serious adverse events in patients treated with rivastigmine compared to placebo. Up to 31 March 1997, 57 deaths (55 rivastigmine, 2 placebo) had been reported in clinical trials with rivastigmine worldwide.

Data from patients were entered into an analysable data-base based on 2 criteria: cut-off date and a patient's opportunity for meeting the designated exposure. In the analysed safety data-base (cut-off 31 December 1996) a total of 35 deaths (33 rivastigmine, 2 placebo) occurred in patients whose data were included. Of the 33 deaths of patients receiving rivastigmine, 15 occurred in long-term extension studies that have no placebo control and a further 6 occurred in study B355 which also had no placebo group. The data available do not indicate an increased mortality rate with rivastigmine.

In phase III controlled clinical trials, of the patients withdrawn for adverse events, 17% of the patients treated with rivastigmine had at least one adverse event compared to 8% in the placebo group. The highest proportion of withdrawals for adverse events were for gastro-intestinal disorders, in particular for nausea and vomiting. The percentage of withdrawals appeared to decrease with the duration of exposure and the cumulative hazard seemed to reach a plateau after 3 months of treatment.

About the same frequency of patients (82% for rivastigmine and 72% for placebo) experienced at least one adverse event in both groups. There was a high incidence of side-effects by body system for gastro-intestinal disorders (57% rivastigmine, 31% placebo), central and peripheral nervous system disorders (36% rivastigmine, 24% placebo), psychiatric disorders (30% rivastigmine, 24% placebo). The most frequent adverse events were nausea (38% rivastigmine, 10% placebo) and vomiting (23% rivastigmine, 5% placebo).

Following the review of the 1st PSUR the MAH included the events 'seizures' and 'gastric and duodenal ulcers' to section 4.8 (Undesirable effects) through a Type II variation. Twenty serious cases of gastrointestinal ulcers, including 15 cases of gastric or duodenal ulcers have been received for rivastigmine.

Nausea seemed more frequent in females, in patients treated with doses higher than 6-9 mg/day, and at the start of treatment (weeks 1-12). This information has been reflected in the SPC. Most of the nausea episodes were mild to moderate in severity. In each dose group, about half of the patients with nausea experienced only one episode of nausea. Nausea associated with vomiting seemed more frequent in patients treated with doses over 6-9 mg/day and some of the patients experienced multiple episodes of nausea/vomiting in these dose ranges.

The gastro-intestinal side effects of rivastigmine were reflected in body weight decreases, especially in female patients. In patients treated with rivastigmine, 13% of patients had a weight decrease versus 5% in the placebo group, and 6% of the patients had a weight increase versus 12% in the placebo group. A warning that patient's weight should be monitored has been included in the SPC accordingly.

Following one published case of spontaneous rupture of the oesophagus the MAH submitted a Type II variation to include a recommendation on re-initiation of therapy following treatment interruption. The proportion of patients reporting adverse events within 7 days following re-initiation of treatment had been analysed by duration of treatment interruption and restarting dose. The percentage of vomiting and any serious adverse events were higher at restarting doses above 3 mg/day than at a restarting dose of 3 mg/day. Sections 4.2 (Posology and method of administration) and 4.4 (Special warnings and special precautions for use) of the SPC were amended to specify that re-initiation after treatment interruption for more than several days should start at 1.5 mg twice daily to reduce the possibility of adverse reactions (e.g. vomiting).

During long term treatment gastro-intestinal side effects predominated. The gastro-intestinal symptoms often responded to dose reduction. No clinically important effects on laboratory parameters, ECGs or cardio-respiratory vital signs were observed in rivastigmine treated patients. However, the CPMP requested, following the review of the 1st PSUR that bradycardia and following the review of the fourth and fifth PSUR that the wording "Very rare cases of atrio-ventricular block" be included in section 4.8 of the SPC (Undesirable effects). Consequently, the MAH submitted a Type II variation.

The bioequivalence studies conducted with the oral solution formulation did not raise any specific safety concerns. No deaths, discontinuations, severe, serious or unexpected adverse events were reported. The oral solution and hard capsule formulations were considered to be equally tolerated.

Further to the assessment of the 6th PSUR, which covered the period from 01 February 2000 to 31 January 2001, the MAH was requested to submit safety reviews on myocardial infarction, heart rate and rhythm disorders, hypertension and hallucinations.

In the majority of the cases of hypertension reviewed, the causal relationship between PROMETAX and hypertension was doubtful and the pharmacological effect of PROMETAX is increase of acetylcholine, which can be expected to induce vessel relaxation. However, in 19 cases, the responsibility of PROMETAX could not be definitely ruled out and as the initial pre-clinical assessment report application mentioned cardiovascular effects, such as hypertension of central origin, the term hypertension was added through a Type II variation to the Product Information.A total of 95 reports of atrial fibrillation and flutter and 66 reports of tachycardia had been received. Given that in rare cases, the responsibility of PROMETAX could not be ruled out the terms 'atrial fibrillation' and tachycardia were added to the Product Information through a Type II variation.

As of 30 June 2001**,** 98 cases of hallucinations with rivastigmine have been reported to the Marketing Authorisation Holder. The hallucinations were mainly visual hallucinations. Hallucination may be a symptom of Alzheimer's disease, and may be an intermittent symptom. Therefore, the responsibility of PROMETAX is difficult to assess. However, the reports of hallucinations after a drug overdose, shortly after a dose increase or PROMETAX initiation, the occurrence of positive dechallenges justified the inclusion of the term 'hallucination' to the Product Information through a Type II variation.

Pancreatitis was reviewed in the assessment of the 7th PSUR. Until the 7th PSUR, the analysis of all reported cases of pancreatitis did not suggest strong evidence of PROMETAX responsibility. However, in the seventh PSUR, 20 additional cases were reported and in half of these cases, responsibility of PROMETAX could not be ruled out (chronology, positive dechallenge). In some cases, patients had predisposing factors (past history of pancreatitis, drug-induced pancreatitis). It cannot be excluded that PROMETAX may play a part, especially in these patients and the term 'pancreatitis' was added to the Product Information through a Type II variation.

During post-marketing surveillance, PROMETAX has been associated with elevation of liver enzymes. In some cases, the data are too scarce to allow an accurate assessment and some details are lacking such as the outcome, the result of a dechallenge, the time to onset, the history of the patient. In some cases, confounding factors have been identified such as concomitant medications, underlying diseases (cholelithiasis..) or a negative dechallenge has been observed. However, in other cases, the responsibility of PROMETAX cannot be ruled out due to the chronology, the positive dechallenge or the absence of risk factors. In a few cases, liver disorders occurred shortly after dose increase of rivastigmine. Therefore, following the assessment of the Renewal dossier in which the 8th PSUR was reviewed the MAH updated section 4.8 of the SPC to include elevated liver function tests.Sections 4.4 and 4.8 of the SPC were also amended during the renewal procedure to take into account that like other cholinomimetics rivastigmine may exacerbate or induce extrapyramidal symptoms, including worsening symptoms in patients with Parkinson's disease.

5. Overall Conclusions and benefit/risk assessment

Quality

The quality of PROMETAX capsules and oral solution is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physiochemical and biological aspects relevant to the uniform clinical performance of these products have been investigated and controlled in a satisfactory way.

Preclinical pharmacology and toxicology

Overall, the primary pharmacodynamic studies provided adequate evidence of the ability of rivastigmine to inhibit AChE activity. Furthermore, rivastigmine dose-dependently reversed scopolamine induced amnesia in the rat during behavioural testing in a water maze, indicating a positive effect on memory dysfunction. The general pharmacology studies showed effects expected from a cholinomimetic agent.

From the pharmacokinetic point of view, the dog was the most relevant species for preclinical efficacy and safety studies. Overall, the toxicology program revealed mainly effects related to exaggerated pharmacodynamic responses to rivastigmine. Exposure levels in toxicity studies were in general lower than those observed in patients on recommended doses. This information has been included in the SPC.

Efficacy

Overall, the clinical programme for rivastigmine was well conducted. The patients studied were representative of the target population i.e. patients with mild to moderately severe dementia of Alzheimer type, at inclusion MMSE was 20, GDS 4 and ADAS-Cog 22-23. The primary efficacy criteria were acceptable. The applicant performed analyses on various definitions of responders in order to demonstrate a clinically relevant effect of the product.

In clinical use, doses of rivastigmine are titrated to achieve an individual optimal therapeutic response, and doses ranging from 1 to 12 mg were tested in clinical trials. The results of the analyses of various definitions of responders showed a statistically significant larger number of responders with PROMETAX (6-12 mg/day). According to the various definitions of responders there was from 2 to 12% more responders in 6-12 mg group than in the placebo group. According to the responder definition requested by the CPMP, combining at least 4 points improvement on ADAS-Cog with no worsening on CIBIC-Plus and PDS, there was a statistically significant difference in the percentage of responders on rivastigmine (8%) compared to placebo (4%).

The proposed maintenance dose of 3 to 6 mg twice a day is supported by the clinical results. The recommended starting dose is 1.5 mg twice a day, with dose titration at 2 weekly intervals to a maximum of 6 mg twice a day. In order to achieve maximum therapeutic benefit it is recommended that patients be maintained on their highest well-tolerated dose.

Safety

On the basis of the data provided, the overall safety profile of rivastigmine is considered acceptable. The main safety concerns raised were gastro-intestinal disorders, such as nausea and vomiting, and dizziness. There were concerns about the odds of experiencing weight decrease, it was therefore recommended that patient's weight be monitored during treatment with rivastigmine.

Benefit/risk assessment

In patients with mild to moderately severe Alzheimer's disease, the high dose group of rivastigmine (6-12 mg/day) demonstrated a statistically significant effect in comparison to placebo for cognitive function, global function and activities of daily living. Although the benefit at doses of 6 to 12 mg/day was considered modest and its clinical relevance in some patients may be questioned, as the differences on the ADAS-Cog and CIBIC-Plus scores are lower than 4 points and 1 point respectively, in the overall population analyses of various responders suggest that a clinically relevant benefit does exist in some patients (2-12%).

The CPMP agreed that the mean effect of rivastigmine is modest. Some CPMP members held a divergent view and moreover considered that the dose of 6-12mg/day might be too low to achieve clinically relevant benefit, whereas at higher doses it may not be well tolerated. The majority of the CPMP considered that, although modest, it is clinically relevant.

Although no active comparator trials have been performed, the effects observed with other AChE inhibitors appear to be of similar size. It is important to note that the scales used in this indication vary and direct comparisons of results for different therapeutic agents are not valid.

The main safety concerns raised were gastro-intestinal side effects, in particular nausea and vomiting, and dizziness. The gastro-intestinal side effects were also reflected in body weight decreases. To address these concerns appropriate warnings and precautions have been included in the SPC together with recommendations regarding weight monitoring. Taking these measures into account, the potential safety concerns were considered to be adequately addressed.

Based on the CPMP review of the data on quality, safety and efficacy, the CPMP considered by majority decision that the overall benefit/risk profile of rivastigmine in the symptomatic treatment of mild to moderately severe Alzheimer's dementia was favourable.