SCIENTIFIC DISCUSSION

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

1. Introduction

Parkinson's disease (PD) is a neurodegenerative, slowly progressive disorder characterised by bradykinesia, resting tremor, rigidity and postural reflex impairment with associated characteristic eosinophilic cytoplasmatic inclusions (Lewy bodies). The Lewy bodies are found in specific regions of the CNS including the substantia nigra and locus coeruleus. The neuronal loss results in a significant decrease of the brain dopamine levels which becomes symptomatic over a certain threshold. Severe disability or death may be expected in 25% of the patients within 5 years, in 65% of the patients within 10 years and in 80% of the patients within 15 years of onset.

The incidence of Parkinson's disease is estimated 4.5-16/100.000 persons/year. Parkinson's disease is rare before 50 years of age. Incidence rates increase with age from 5/100.000 in the 45-49 age group up to 90/100.000 in the 75+ age group and, on average, 2 to 3 % of the population in the western world will develop PD.

The cause of the disease is still unknown. PD develops due to loss of neuronal functions within the basal ganglia and the substantia nigra of the brain. Specifically, there is a marked deficiency in the nigrostriatal dopamine (DA) system due to degeneration of nigral DA neurons.

The pharmacological intervention of Parkinson's disease is symptomatic at the moment and the improvement of an impaired dopaminergic neurotransmission forms the central strategy for the treatment of PD. Recently, research has turned to developing neuroprotective therapies in order to reduce the rate of progression of the underlying disease. Non pharmacological interventions such as deep brain structure stimulation and neuronal grafts have an investigational status.

The standard treatment of PD consists of the intake of L-dopa, a dopamine precursor, with carbidopa or benserazide, peripheral aromatic amino-acid decarboxylase inhibitors, to prevent the breakdown of L-dopa to dopamine outside the brain and thereby reducing peripheral unwanted effects, in a fixed combination called L-dopa+. Other treatments include dopamine-agonist to improve neurotransmission at the dopamine receptor level; antimuscarine drugs to reduce the relative excess of striatal cholinergic activity that accompanies dopamine deficiency; monoamine-oxidase-B inhibitors to inhibit breakdown of dopamine and amantadine, which has shown a modest effect on the Parkinson symptoms. Symptomatic relief is often transient as neuronal loss continues or tolerance may develop. Co-medication with other symptomatic drugs is often given to reduce the dose of the L-dopa, thereby increasing treatment tolerability.

The response to L-dopa is generally stable during the initial years of treatment. However, due to the progressive degeneration of the DA system, the neuronal buffer capacity is believed to be reduced. At that stage, the patient may switch within seconds from a state of relatively good mobility to one of severe parkinsonism, giving rise to the term “ON-OFF” phenomenon. This end-of-dose deterioration implies a shortening of the duration of action of L-dopa. OFF periods tend to become longer and to set in abruptly. ON periods are often combined with dyskinesias and/or other movement disorders.

The fixed combination L-dopa+ improves the brain bioavailability of L-dopa, through peripheral dopa-decarboxylase inhibition (DDCI). However, following dopa-decarboxylase inhibition, more L-dopa is metabolised by the enzyme catechol-O-methyl transferase (COMT) in the gastrointestinal tract, liver and kidney, resulting in high circulating levels of 3-O-methyldopa (3-OMD). This metabolite has been reported to accumulate on both sides of the blood-brain barrier during L-dopa+ treatment. Several studies suggest that 3-OMD may reduce the efficacy of L-dopa but this has not been conclusively demonstrated. High erythrocyte COMT activity and high plasma 3-OMD/L-dopa ratio have been reported to be associated with poor response to L-dopa treatment. Thus, concomitant inhibition of COMT will reduce the metabolism of L-dopa, increase the amount of L-dopa available for conversion into DA in the brain and should improve the efficacy of L-dopa+.

Entacapone is an orally active, nitrocathecol derivative with a selective and reversible inhibitory effect on COMT. By inhibition of COMT, the breakdown of L-dopa is decreased and thus, the half life of L-dopa is prolonged. Entacapone is indicated in combination with standard preparations of L-dopa/benserazide or L-dopa/carbidopa for use in patients with Parkinson's disease with end-of-dose motor fluctuations, who cannot be stabilised on L-dopa therapy. The proposed dose in adults is 200 mg with each L-dopa+ dose up to a maximum of 2000 mg/day.

2. Part II: Chemical, pharmaceutical and biological aspects

Entacapone is an orally active nitrocathecol derivative COMT inhibitor, indicated for use as an adjunct in the treatment of PD. It is presented as Comtess film coated tablets 200 mg. Different pack sizes are proposed: 30, 60, 100 and 350 tablets in white HDPE plastic jars with tamper proof HDPE closures.

Composition

The film-coated tablets are made with standard core and film-coat excipients. The active substance comprises 29% of the core weight. The containers proposed are white HD-polyethylene plastic jars with white tamper-proof HD-polyethylene closures. The containers are further packed into cardboard boxes.

Satisfactory detail has been provided on the development of the commercial formulation and bioavailability studies.

Entacapone is "practically insoluble" in water. It exists in two stereoisomeric forms: the (E) = *trans*-isomer and the (Z) = *cis*-isomer. The (E)-isomer was originally chosen because of a more favourable synthetic route. It has been used throughout the clinical and toxicological programme and the amount of (Z)-isomer has been controlled to be less than 0.5%. Both isomers are pharmacologically active as COMT-inhibitor and have an equivalent activity. The acute toxicity of the two isomers seems to be similar.

The specific particle size of the active substance has been chosen because of the low solubility of entacapone in water. The particle size is controlled by the validated laser diffraction method.

All batches have met the acceptable specification limits. For the *in vitro* dissolution testing, the most selective medium was the phosphate buffer pH 5.5, which allows complete dissolution within a reasonable time. The bioequivalence of the products used in the studies has been tested in all significant steps of the product development process. The bioavailability studies proved no marked difference in Cmax, tmax and AUC values between tablets. All preparations behaved as immediate release tablets.

Method of preparation

The batch sizes of industrial scale are 1 000 000 tablets.

The manufacturing process of entacapone 200 mg tablets includes mixing with intra-granular excipients,granulation**,** mixing the granulate with extra-granular excipients compression and film-coating. The in-process controls and limits proposed are satisfactory. The manufacturing process has been adequately validated.

Control of starting materials

The specification of the active substance includes tests for identity by IR, UV and HPLC, related substances, assay, particle size, residual solvents, water, sulphate ash bromide and heavy metals. The impurity profile of entacapone is reviewed in accordance with the ICH guideline CPMP/142/95. The main impurity is Z-isomer of entacapone (impurity A) which has been found 0.04-0.2% in some batches or not detected. Impurity B has been found 0.05-0.24% (three batches) or not detected (14 batches). Impurity C has been found <0.04% (one batch), 0.13% (one batch) or not detected (15 batches). Hydrogen bromide is a potential residual reagent and it has been found <0.01%, which limit is established to ensure that no significant amounts of HBr remains in the product. Acetic acid has been found 0.02-0.2% and toluene <0.01-≤0,07%. No detectable amount of benzene was found in the batches studied, i.e. <0.5 p.p.m.

Entacapone is synthesised in a 3-step process. In the final step crude entacapone, which is a mixture of (E)- and (Z)-isomers, is crystallised from acetic acid and toluene. Details are presented in the DMF.

The structure of entacapone has been proved by elemental analysis and interpreted UV/VIS-, IR-, MS-, ^{1}H- and ^{13}C-NMR spectra. Two polymorphic forms have been found, polyform I and II. The control of polymorphic forms done by x-ray powder diffraction method is considered to be sufficient and no quality or efficacy issues arise from the existence of the two polymorphs. The current manufacturing process yields only the form 1. In general, analytical methods have been well validated.

The excipients comply with PhEur., B.P. or USP-NF requirements. The colorants comply with the EEC requirements.

Standard packaging materials are used, and testing is satisfactory.

Control tests on the finished product

The specification includes standard tests for this type of dosage form. Results of comparative studies of old and new modified dissolution tests and between the automated and manual UV method are presented. The stability of entacapone in the dissolution medium was shown to be good for one hour. Stability of standard solutions has been presented. Batch analytical results provided for three commercial-scale lots comply with the specifications.

Stability

Active substance

Long-term stability studies were performed on 14 lots of entacapone drug substance. Stability data of 60 months for three lots, 48 months for one lot, 36 months for three lots and 18 months for one lot are available (at warehousing temperature). The results show that no special change was noted in the appearance, loss on drying, pH and the content of related substances/(Z)-isomer after 18-60 months. The content of entacapone remained within the limits of specifications. The stability studies for six batches stored at 25°C/60% RH have currently 3-12 months data available depending on the batches. The results show that parameters studied meet the proposed specification of entacapone drug substance. Seven batches were studied for 6 months under the accelerated conditions recommended by ICH and no changes were noted in the parameters studied.

Finished Product

Stability data of 36 months for two lots stored at RT/75% RH, 4 months for four lots stored at +25°C/60% RH and shorter times for eight other lots stored in different storage conditions, are currently available. The results of these studies are within the specifications proposed. Also the results of photostability and repeated freezing-thawing tests show that entacapone tablets are neither light sensitive or sensitive to the repeated freezing thawing. Based on the data provided, a 3-year shelf life for entacapone tablets in white HDPE plastic jars is supported.

During the evaluation phase the applicant submitted additional upon request, which was considered satisfactory by the reviewers. However the applicant should also provide results of the planned stability studies for the drug substance and the finished product according to the agreed timetable.

3. Part III: toxico-pharmacological aspects

Pharmacodynamics

Effects related to proposed indications

In vitro and *ex vivo*, entacapone and its Z-isomer showed a potent inhibitory effect on soluble and membrane bound and COMT with IC50-values *in vitro* ranging from 0.01µM (rat brain) to 0.16µM (rat liver). *Ex vivo* tests, after oral (10 mg/kg) or iv administration of entacapone, confirmed the inhibition of soluble -COMT activity (from 76% in the kidneys to 98% in the duodenum) by the drug with good correlation to the IC 50-values obtained in *in vitro* tests. The only exception was COMT activity in the brain (12%), which reflects poor penetration of entacapone into the CNS.

Entacapone did not inhibit any other enzymes synthesising or metabolising catecholamines. After single oral dose administration in rats (0.3-30 mg/kg) serum L-dopa concentrations were significantly higher than if L-dopa (50 mg/kg)/carbidopa (50 mg/kg) was given alone; the levels of 3-O-methylated

metabolite of L-dopa, 3-OMD, significantly decreased or were almost totally inhibited by the higher entacapone doses. The bioavailability of L-dopa increased to about 190% and the elimination half-life was prolonged from 0.9 h to 2.2 h after oral entacapone 30 mg/kg. The effect of entacapone was dose-dependent and time-dependent. Similarly, oral administration of entacapone increased dose-dependently the concentrations of L-dopa, DA, DOPAC and HVA and decreased those of 3-OMD in rat striatum. The increase of the HVA levels in the brain reflected the inability of the drug to inhibit COMT in the brain in acute experimental conditions.

Data from studies in animal models of PD (MPTP-model, reserpinised mice and turning behaviour in rats lesioned unilaterally with 6-OHDA), supported a potential efficacy in PD when entacapone was co-administered with L-dopa/carbidopa. Taken together, the data indicate that entacapone is a potent, selective and reversible inhibitor of COMT. This may lead to an enhancement of the bioavailability of L-dopa in the brain, as evidenced by changes in the concentrations of its metabolites.

General pharmacology

The applicant has adequately investigated general safety pharmacology.

Entacapone seems to be devoid of any marked central effect, at least in single dose experiments, which is in agreement with its low penetration into the CNS. Entacapone did not change body temperature in rats, after single (400 and 800 mg/kg) or repeated administration (200 mg/kg bid for 7 days) in contrast to tolcapone and dinitrophenol suggesting that under *in vivo* conditions entacapone does not uncouple oxidative phosphorylation.

No adverse effects of clinical relevance were observed with respect to the cardiovascular, respiratory, renal or gastrointestinal systems.

Following intravenous administration (0.003-3 mg/kg) to anaesthetised normotensive rats, no effect on blood pressure, heart rate or ECG was observed. Even high doses of entacapone (300 mg/kg *per os*) had no effects on ECG in dogs when measured 1 and 24 hours after last dose in a 51-week chronic toxicity study.

Pharmacokinetics

The pharmacokinetics of entacapone has been investigated in rats and dogs. A few qualitative and quantitative differences across species were found. However, the pharmacokinetic profile of entacapone is sufficiently similar in animals and humans to allow the animal toxicology studies as a valid exploratory tool for human safety.

Absorption of unchanged entacapone after single oral administration is quite rapid both in rats and in dogs. Two peaks in plasma concentrations, occurring at 5-15 minutes and at 3-5 hours post dose, were found in rats indicating that entacapone is subject to enterohepatic circulation and a single peak at 3 hours was found in dogs. A transformation of entacapone to its (Z)-isomer took place in both species studied, the transformation being minimal in rats but quite noticeable in dogs.

In rats and in humans, the absolute bioavailability was dose-dependent and ranged from 20% to 55%, following single dose of 10, 65 and 400 mg/kg, in rats and from 29% to 49%, following single dose of 5, 25, 50, 100, 200, 400 and 800 mg, in humans.

In vitro, the protein binding of entacapone (5µg/ml) was high with species differences: about 98% in man, rabbit and monkey; 5% in mouse and pig and 10% in dog. Consequently, the extravascular tissue distribution was limited. The binding site was the benzodiazepine binding site, but not the warfarin one. *In vitro*, no displacement was observed with warfarin, salicylic acid, phenylbutazone, diazepam, carbidopa and (Z)-isomer of entacapone.

The overall elimination half-life of entacapone ranged from 30 minutes to 1 hour in dogs and from 1.5 to 3 hours in man. Following repeated administration in rats and in dogs, no accumulation or retention of drug-related material was observed.

Entacapone is extensively metabolised in the liver in all species including humans, the main metabolic pathway being glucuronidation, sulfation and isomerisation from (E)- to (Z)-isomer (active metabolite). Similar pathways across species are the reduction of the C-C double bond of the side chain (less important in rat and in man) and the hydrolysis to 3,4-dihydroxy-5-nitrobenzaldehyde. The dissimilarities consists of amide N-dealkylation, nitro reduction and O-methylation (only in rats),

amide hydrolysis and nitrile hydrolysis (only in dogs) and oxidative hydrolysis of one of the ethyl groups of the diethylamide group (only in man).

In rats and dogs, entacapone metabolites are predominantly excreted in the faeces (two thirds as glucuronide or sulphate conjugates) and one third in the urine with less than 1.5% of the dose as unchanged entacapone. After the first hour 30-45% of the dose was recovered in the bile, with an enterohepatic circulation accounting for about 10% of the given radioactivity.

Toxicology

Single dose toxicity studies were performed in rats and mice. The acute toxicity is low: LD50 being about 2 g/kg p.o. in mice and over 2 g/kg p.o. in rats with no difference between (Z)- and (E)-isomer.

Repeated dose toxicity of entacapone was studied for up to 12 months in rats, with oral doses up to 600 mg/kg (13-week and 28-day toxicity) and up to 400 mg/kg (52-week toxicity), and in dogs with oral doses up to 400-600 mg/kg (28-day toxicity) and up to 300 mg/kg (52-week toxicity). The non toxic effect level (NTEL) was, in rats of both sexes, 65 mg/kg/day in the 13-week studies and 95 mg/kg/day in the 1-year studies. In the 52-week toxicity studies in rats and dogs, the non toxic effect level (NTEL) corresponded to exposures 9 and 15 times higher, respectively, than the average exposure in man AUC_{man} 6x200 mg). No clear signs of organ toxicity were found in the chronic toxicity studies. The only consistent finding was that entacapone induced a slight anaemia. This may be due to iron deficiency, since high doses of entacapone chelate iron.

In chronic toxicity tests in male rats, chronic progressive nephropathy was found. The incidence of chronic myocarditis was also increased, but it was considered not clinically relevant.

The combination of entacapone, L-dopa and decarboxylase inhibitor (carbidopa or benserazide) was studied for up to 28 days in rats. In addition, the effects of the carbidopa combination were studied in monkeys during 13 weeks. Karyomegaly in renal proximal tubule cells was observed in some rats (both females and males) receiving entacapone either alone or in combination with DDCI. As this finding was evenly distributed in males and females and not only in males, such as renal neoplasia, it can be concluded that it is of no clinical relevance.

The applicant was asked to provide information on the toxicity of the combination with L-dopa + DDCI + selegiline. An additional 28-day oral toxicity study in rats has been conducted. The combination of entacapone (120 mg/kg/day), L-dopa (40 mg/kg/day), carbidopa (10 mg/kg/day) and selegiline (2 mg/kg/day) for 28 days was well tolerated. The clinical signs of the combination were mild and they were restricted to signs seen previously with entacapone alone or seen in this study with the combination of L-dopa, carbidopa and selegiline. There were no findings in haematology, clinical chemistry, urine analyses, organ weights or in histopathological evaluation considered related to the combined treatment.

Reproductive toxicity - No effects on fertility and general reproductive performance were observed in the rat with doses up to 700 mg/kg/day of entacapone The exposure factor was calculated to be approximately 50 times higher than the average exposure in man (AUCman 6 x 200 mg).

Embryo-foetal studies were performed in rats (doses up to 1000 mg/kg/day) and in rabbits (doses up to 300 mg/kg/d). Entacapone administered to the pregnant rats during the period of organogenesis produced no significant effects upon survival and development in utero. The exposure factor based on toxicokinetic data was calculated to be 80 times higher in the highest dose group than the average exposure in man (AUCman 6 x 200 mg). Entacapone administered to the pregnant rabbits resulted in an abnomal body weight gain in mother and in an increased incidence of small foetuses. Skeletal examination of foetuses revealed an apparent slight developmental delay in some bones. The exposure factor based on toxicokinetic data was calculated to be approximately 5 times higher than the average exposure in man (AUCman 6 x 200 mg).

Peri/post-natal performance was evaluated in rats with doses up to 700/mg/kg/d. Gestation length and parturition were unaffected by entacapone. Litter size, survival, sex ratio, weight gain and post-natal development was also normal. The fertility and litter responses of the F1-generation were also unaffected by treatment of F0-generation.

Genotoxicity The genotoxicity potential of entacapone was studied in an adequate battery of *in vitro* and *ex vivo* genotoxicity tests, performed according to current requirements. Entacapone was found to be mutagenic in two mammalian cell tests *in vitro*, suggestive of chromosome type damage. However, entacapone has not shown any genotoxicity *in vivo*.

Carcinogenicity - Carcinogenicity studies were performed in rodents with up to 600 mg/kg/day (mice) or 400 mg/kg/day (rats) entacapone administered orally by gavage. The mouse study did not reveal any treatment-related increase of neoplastic findings. The duration of the rat study was 104 weeks.

The major finding was an increased number of adenomas and carcinomas in the kidneys of male rats receiving 400 mg/kg/day of entacapone. No such tumours were observed in females. Additional studies provided evidence that entacapone-induced tumours are related to alpha2μ-globulin. The applicant has conducted several additional studies, which gave further support that the kidney neoplasias found in high dose male rats are connected to male rat specific alpha2μ-globulin nephropathy.

Environmental risk assessment –The applicant provided sufficient information on ecotoxicity and environmental risk associated with the use of entacapone.

In summary, the applicant has conducted appropriate and well-designed series of preclinical experiments, in accordance with GLP, which demonstrate that the COMT inhibitor entacapone, when given together with L-dopa and carbidopa, dose-dependently increases plasma concentration of L-dopa and enhances the availability of L-dopa in the brain. At the same time the amount of the 3-O-methylated metabolite the 3-OMD is reduced. In animal models of PD, entacapone potentiates beneficial effects of L-dopa and enables the reduction of dose of L-dopa. The main effect of entacapone in preclinical studies seems to be a prolongation of action of L-dopa. There is sufficient experimental data, which provides scientific background for clinical testing in the treatment of PD.

The applicant provided, during the assessment procedure, the additional data requested. The potential toxicity of L-dopa/dopamine metabolites, such as dopa quinone and melanin, was investigated in rats (entacapone penetration into CNS) and in monkeys (neurotoxicity): entacapone penetrates the blood brain barrier very poorly and does not seem to induce neurotoxic damage in nigrostriatal dopaminergic neurons when given alone or in combination with L-dopa+carbidopa. Additional studies on the receptor binding profile were also conducted. Entacapone had no significant binding affinity for any of the receptors investigated including adenosine A1 and A2 receptors, adrenoceptors (α1, β1 and β2), dopamine (D1, D2, D3, D4, D5), GABA, glutamate (NMDA), histamine (H1 and H2), muscarinic or nicotinic, opiate, PAF, serotonin (non-selective) or sigma receptors.

4. Part IV: Clinical aspects

The core clinical documentation of entacapone consists of two pivotal phase III double-blind, randomised, placebo-controlled, parallel group studies conducted in 376 idiopathic and end-of-dose fluctuating Parkinson's disease patients. Pharmacodynamics and pharmacokinetics of the product were investigated in 26 pharmacodynamic, 18 pharmacokinetic and 5 pharmacokinetic and pharmacodynamic studies, which involved about 680 subjects.

The clinical studies generally are of good quality and GCP has been adhered to. The pharmacodynamic and the pharmacokinetic studies involved small groups of subjects, making it often difficult to draw conclusions.

Pharmacodynamic studies

The primary pharmacodynamic effect of entacapone, COMT-inhibition, has been demonstrated to be dose-dependent and reversible, in the red blood cells of healthy volunteers. Maximum inhibition (approximately 60%) was reached within 60 min with a single dose of 200 mg. The activity returned to baseline within 8 hours. Reversible inhibition was also observed following repeated dosing for 10 days. However, the percent inhibition was almost statistically significantly lower ($p=0.0586$, paired t-test) on day 10 compared to day 1. The difference might be explained by differences in C_{max} and T_{max} observed in the pharmacokinetic analyses carried out during the study. A study in small number of healthy volunteers investigating the inhibition of COMT activity in the gastrointestinal tract was not conclusive.

In healthy male volunteers, a single dose of entacapone 400 mg alone or together with L-dopa/ carbidopa 300/75 mg did not affect growth hormone and prolactin concentrations to a clinically relevant extent.

Plasma noradrenaline and adrenaline concentrations were not significantly affected by single increasing doses or repeated doses (up to 7 days) of entacapone at rest or during submaximal exercise in healthy volunteers. Plasma catecholamine concentrations were not significantly affected during exercise in PD patients who were concomitantly taking entacapone and levodopa/DDCI.

Haemodynamics, cardiovascular autonomic function and catecholamine metabolism were studied both in healthy volunteers and in PD patients. Blood pressure and heart rate at rest and during exercise were not consistently affected by entacapone in healthy volunteers (single doses up to 200 mg, repeated doses 400 mg or 800 mg t.i.d.). Changes in plasma MHPG, DHPG and DOPAC were consistent with COMT inhibition. Plasma noradrenaline and adrenaline concentrations were not significantly affected.

Exercise capacity, cardiorespiratory function (spiroergometry) and cardiovascular autonomic functions were not clinically significantly affected in PD patients by the combination of entacapone (200 mg per day) and L-dopa/DDCI (300-1000 mg per day). No clinically relevant arrhythmias during normal daily activities (24 h Holter monitoring) or during exercise were found. Plasma catecholamine concentrations were not significantly affected during exercise.

Effect of entacapone in combination with DDCI, mainly L-dopa plus carbidopa, on the motor response to L-dopa in Parkinson's disease has been evaluated in a number of phase II studies. In a single dose crossover study with increasing entacapone doses versus placebo, a statistically significant effect on ON time was observed at 200 mg (mean increase 20.6%), but not at 50, 100 or 400 mg. At 200 mg and 400 mg, the onset of the motor response was delayed. The duration of dyskinesia during a L-dopa test increase at 200 mgfrom 142 minutes during placebo to 187 minutes during entacapone treatment. The duration of faster tapping and increased walking speed were prolonged at 200 mg. An increase in the dose did not enhance the motor response in the L-dopa test. Increased response in the L-dopa test latency was not observed in several other studies. In a double-blind crossover study with repeated dosing (100, 200 or 400 mg with each L-dopa dose), none of the entacapone doses increased ON time compared to placebo. However, daily L-dopa dose was maximally decreased at 200 mg. An increase in the frequency of orthostatic hypotension and increased heart rate in patients treated with entacapone combined with L-dopa+ was observed in several phase II clinical trials.

L-dopa pharmacokinetics and interaction studies

The effect of entacapone on L-dopa pharmacokinetics has been studied in healthy volunteers and PD patients. In healthy volunteers, single doses of entacapone (50, 100, 200 and 400 mg) significantly increased the L-dopa AUC in a dose-dependent way but there did not appear to be an effect on t½ and there was no affect on Cmax and Tmax. A dose-dependent decrease in AUC of 3-OMD was observed as well. In another study entacapone was administered up to 10 times per day along with L-dopa+carbidopa for 7 days in 12 healthy volunteers. There was no evidence of accumulation of entacapone on Days 3, 4 and 5. No accumulation of COMT-inhibition was noted (Days 1 and 6). The plasma levels of L-dopa and carbidopa were almost superimposable on Days 1 and 6 and there were no statistically significant differences in the PK parameters, except for Tmax of L-dopa occurring later on Day 6 (0.8±0.4 vs 1.25±0.5 h, $p<0.05$). The relevance of this study in healthy volunteers for the clinical setting is doubtful.

In PD patients, the effect of entacapone on the AUC of L-dopa, either after a standard or a controlled-release L-dopa/carbidopa formulation (200 mg with each L-dopa dose), consisted of a 20-46% increase, which was fairly consistent across the studies. Cmax of L-dopa was only occasionally affected. Doses of entacapone exceeding 200 mg/L-dopa dose have not consistently been associated with further increases in L-dopa AUC. The AUC of 3-OMD decreased to a similar extent regardless of the L-dopa formulation. However the benefit of combining of entacapone with L-dopa+ controlled release preparations has not been studied sufficiently (2 open studies; 2 cross-over studies which show a moderate prolongation of the ON time versus placebo).

The effect of entacapone on L-dopa pharmacokinetics may substantially depend on the L-dopa/DDCI preparation. In one crossover study in PD patients, entacapone increased L-dopa AUC by 23% when the patients were using standard L-dopa/carbidopa. However, the AUC of L-dopa increased by 50%

when the patients were using standard L-dopa/benserazide. This could differentially affect both the efficacy and tolerability of these preparations.

In positron emission tomography studies employing ^{18}F-6-fluorodopa (6-FD), an analogue of L-dopa, an increase in 6-FD accumulation in the striatum after entacapone administration was observed. This increase was less and the 6-FD uptake lower in advanced PD patients as opposed to *de novo* PD patients or healthy subjects after entacapone. The clinical implication of this finding is uncertain.

Several pharmacodynamic interaction studies have been carried out. In healthy subjects, a single dose of entacapone seemed to increase the arrhythmogenicity of i.v. catecholamines (isoprenaline and adrenaline). When administered with a small dose of moclobemide entacapone did not clearly affect the plasma catecholamine levels. However, the combination of entacapone with MAO-A inhibitors is not recommended.

A single dose of entacapone (200 mg) did not aggravate the haemodynamic responses to, or alter the adverse effects of a single dose of imipramine (75 mg). However, patients with Parkinson's disease are more likely to have autonomic dysfunction and may be more sensitive to the combined haemodynamic effects of L-dopa and antimuscarinic/antiadrenergic effects of imipramine.

In a phase II study in PD patients, selegiline did not affect the haemodynamic effects of entacapone and L-dopa+. There were no differences between the treatments with respect to plasma noradrenaline and dopamine concentrations. The motor response to L-dopa was not significantly different with or without selegiline. Selegiline did not affect the increase in the bioavailability of L-dopa achieved with entacapone. However, the study suggested that dyskinesias may be aggravated by the concomitant use of selegiline, entacapone and L-dopa.

Study ENT-D-01 was a two-way, cross-over study involving 12 healthy males and females. The participants received warfarin until their INR was stable and between 1.4 - 1.8. The individuals were randomised to receive either concomitant entacapone 200mg or placebo, four times a day for 7 days followed by a switch in the treatment for additional 7 days. The mean INR was increased by 13% (CI90 6-19%). The AUC of the R-warfarin increased by 18% and S-warfarin (the more potent isomer) by 5%. The data were reported to CPMP as a response to PSUR 3 and the results and a statement recommending a control of INR when initiating treatment with entacapone in patients receiving warfarin was added to the SPC section 5.2 through a Type II variation.

In section 4.5 of the SPC the text on concomitant use of antidepressants was changed from "Concomitant use of entacapone with these medicinal products is not recommended" to " "Caution should be exercised when these medicinal products are used concomitantly with entacapone" through a Type II variation. In clinical praxis, the concomitant use of antidepressants with entacapone is sometimes necessary. The presented safety data are assuring. However, caution should be exercised because the experience is still limited and very rare effects cannot be ruled out. Thus, the proposed wording is justified.

Dose finding studies

The dose-finding studies did not clearly establish the optimal dose of entacapone. However, doses exceeding 200 mg with each dose of L-dopa may be associated with less benefit regarding motor response and increased dopaminergic adverse events. Moreover, higher doses of entacapone may decrease the bioavailability of L-dopa/carbidopa compared to the 200 mg dose.

Pharmacokinetics

Pharmacokinetic studies were carried-out in healthy volunteers, in PD patients and in special patient groups (elderly, subjects with renal or hepatic impairment). Pharmacokinetic studies in PD patients cover the dosing frequency of 4-6 times/day.

Clinical studies have not been conducted with the formulation intended for marketing. However, a number of bioequivalence studies have been conducted with the formulations used in phase I-III studies. The tablets used in Phase III studies and the market-image tablet were shown to be bioequivalent.

Entacapone is a chiral active drug. The E-isomer is the main product, less than 0.5% of the Z-isomer occurs in the raw material. Isomerisation occurs *in vitro* and *in vivo* with a short half-life. However, the isomers have similar pharmacodynamic and pharmacokinetic characteristics.

Marked intra- and interindividual variation in absorption (T_{max}, C_{max}) is a characteristic feature of the pharmacokinetics of entacapone.

The absorption of oral entacapone is fast. Mean C_{max} and mean $AUC_{0\text{-}inf}$ of entacapone increased linearly with dose (single doses from 5 to 800 mg).

After doses from 100 to 800 mg the disposition was mainly described by two phases, the corresponding half-lives were 0.27-0.37 h ($T½_{alpha}$) and 1.59-3.10 h ($T½_{ß}$). The plasma concentration-time profiles of entacapone and its Z-isomer were similar.

The bioavailability of entacapone and its Z-isomer increased substantially and linearly with increasing doses (36±11% at 200 mg). This could be explained by saturation of first-pass metabolism.

The decay of intravenous ^{13}C-entacapone was tri-exponential with half-lives of 0.05 (α), 0.38 (β) and 2.4 (γ) hours. The first two phases represented 94% of the total AUC. However, dose-standardised AUC values increased more than dose-proportionally. V_c was roughly equal to the blood volume and V_{ss} about the same as the extracellular volume (20 l).

Repeated dose pharmacokinetics of entacapone (100, 200, 400 mg tid for 10 days) showed no evidence of accumulation of the parent compound and its Z-isomer.

The extent of binding to plasma proteins is high (98%) with both isomers. Entacapone is mainly bound to albumin.

The main phase I metabolic reaction was isomerisation from E- to Z-isomer. Free entacapone and its Z-isomer represented 3-4% of all metabolites detected in urine. The main phase II pathway was glucuronidation. Entacapone, Z-isomer and conjugates represented about 98% of all metabolites detected.

The excretion of entacapone and its Z-isomer in urine was studied after single oral doses of entacapone (5, 25, 50, 100, 200, 400 and 800 mg) in 12 healthy volunteers. Eleven of the volunteers also received an intravenous dose of 25 mg. The mean cumulative excretion of entacapone into urine ranged from 0.1±0.1% to 0.2±0.4% during the first 4 hours after an oral dose of 5-800 mg. The cumulative excretion after the intravenous dose was 0.5±0.6% during the first 4 hours. Only traces of the Z-isomer were found. Thirty-eight (±2.5)% of intravenous ^{13}C-entacapone and 13.3 (±1.4)% of the oral dose was excreted in urine during 48 hours.

Biliary excretion has not been studied in man. It is estimated that 80-90% of the dose is excreted in faeces, although this has not been confirmed in man. There is no data on the magnitude of enterohepatic circulation in man.

Food did not affect the bioavailability of entacapone to a significant extent, although absorption was slightly delayed.

The pharmacokinetics of entacapone were not significantly different in elderly and young healthy subjects.

All pharmacokinetic studies in the target population have been carried out in patients receiving either standard or depot/controlled-release L-dopa/DDCI. In patients receiving 4-6 doses of entacapone (200 mg) per day, the AUC of entacapone was significantly higher on day 28 than after the first dose. Six out of 12 patients had measurable entacapone trough concentrations.

Different L-dopa/DDCI formulations have been shown to affect the pharmacokinetics of entacapone. C_{max} and AUC of entacapone were significantly greater after depot than after standard L-dopa + carbidopa. Theoretically, the difference in entacapone absorption and bioavailability may be due to competition between entacapone and carbidopa during the absorption phase. Although differences appear to exist in the interactions between entacapone and L-dopa/DDCI combinations as well as L-dopa/DDCI formulations, entacapone has been consistently shown to increase the bioavailability of L-dopa.

The interaction of entacapone with benserazide has not been studied.

Selegiline did not significantly affect the pharmacokinetics of entacapone. Formal pharmacokinetic studies with other antiparkinson drugs have not been carried out since entacapone penetrates the CNS poorly and various receptor binding and uptake studies suggest that interactions are unlikely. However, since dopaminergic adverse events were more frequently reported in patients who took dopamine agonists with entacapone than with placebo, an appropriate warning is included in the SPC. The same applies combination with amantadine although the safety analysis does not provide reliable information due to the small number of patients involved.

An interaction between entacapone and omeprazole has been demonstrated. Omeprazole significantly decreased the AUC of entacapone. This interaction may be based on inhibition of gastric acid secretion. However, the observed interaction seems not to be of any clinical consequence since daily ON time did not show any difference between entacapone and placebo with or without gastric acid blocking agents and the magnitude of the pharmacokinetic interaction was modest.

Entacapone may displace drugs that bind to the albumin binding site II ("diazepam site" which binds also several NSAID drugs, including ibuprofen). Clinical interactions have not been studied and, hence, cannot be ruled out. However, according to *in vitro* studies, significant displacement is not anticipated at therapeutic concentrations of these drugs.

The potential interaction of entacapone and drugs known to inhibit or induce the hepatic cytochrome P450 system have not been studied. However, the main metabolic pathway of entacapone is conjugation. Interactions based on the induction of glucuronide conjugation reactions have not been formally studied. However, no difference in the AUC of entacapone was observed in smokers versus non-smokers. Following the 3rd PSUR the CPMP requested the MAH to include data from in vitro studies using human liver microsomal preparations indicating that entacapone inhibits cytochrome P450 2C9 (IC_{50} ~ 4 μM). Entacapone showed little or no inhibition of other types of P450 isoenzymes (CYP1A2, CYP2A6, CYP2D6, CYP2E1, CYP3A and CYP2C19). This information was added to section 5.2 of the SPC through a Type II variation.

The C_{max} and AUC of entacapone were higher in patients with moderate renal impairment or who were on renal replacement therapy. The mean elimination T½ varied between 1-2.2 hours. However, the differences are probably not clinically significant. The results suggest that routine dosage adjustment is not necessary for patients with renal impairment. However, for patients who are receiving dialysis treatment, a longer dosing interval may be considered.

The bioavailability of entacapone was substantially higher in subjects with hepatic cirrhosis and mild to moderate liver insufficiency (Child-Pugh Class A and B). The C_{max} and AUC were doubled in these patients compared to healthy subjects. This probably reflects decreased first-pass metabolism. The rate of absorption and elimination were not affected. The dose of entacapone should be reduced by 50% in patients with liver impairment (cirrhosis). However, because the tablets can not be divided, entacapone must not to be used in patients with hepatic impairment, whether mild or moderate.

Efficacy

As Parkinson's disease progresses, control of symptoms, particularly mobility, with L-dopa becomes increasingly difficult due to the ON/OFF fluctuations. Patients experiencing ON/OFF effects are referred to as fluctuating patients, those with a stable response to L-dopa treatment as non-fluctuating patients.

The main clinical documentation of the efficacy of entacapone as an adjunct to L-dopa/DDCI consists of one phase II short-term crossover double-blind study (293930) and two pivotal phase III 6-month double-blind studies (NOMECOMT and SEESAW).

For 'fluctuating' patients, the primary efficacy criterion were ON time and proportion of ON time assessed by patient diary rating during 18 hour and 24 hour recording periods respectively. Secondary criteria (FR) were the Unified Parkinson's Disease Rating Scale (UPDRS), total and cluster scores; global score; daily fluctuations in disability and L-dopa dose, proportion of OFF time.

For non-fluctuating patients, UPDRS motor score was defined as a primary (FR) efficacy variable.

The pivotal studies were well planned and conducted in compliance with GCP.

The phase II study enrolled almost exclusively patients with a long history of idiopathic Parkinson's disease and L-dopa dose-dependent motor fluctuations (wearing off). None of the phase II or III studies enrolled patients with *de novo* Parkinson's disease. Only one of the phase III safety studies (FILOMEN) included non-fluctuating patients. Most of the patients had other concurrent illnesses and medications.

All patients had received previous treatment with L-dopa/DDCI. The majority of patients were concomitantly using other antiparkinsonian medication (up to 65% used selegiline and up to 50% used dopaminergic agonists).

The pivotal phase III studies and the phase II study enrolled a total of 402 patients with idiopathic Parkinson's disease, 214 patients were treated with entacapone. The study populations represent patients with advanced PD.

The efficacy variables used in the pivotal studies are well documented. The endpoints are adequate. Both Intention-To-Treat (ITT) and Per Protocol (PP) analyses have been presented. The statistical analyses are appropriate.

Fluctuating patients

NOMECOMT (2939033): This was a phase III multicentre, randomised, comparative (placebo vs. entacapone 200 mg with each L-dopa+ dose, carbidopa or benserazide), double blind, parallel group study of 6-month duration carried out in 171 patients (85 entacapone and 86 placebo) with `advanced (FR) PD and end-of-dose fluctuations. The primary efficacy criterion was mean daily ON time following the first morning dose of levodopa (Fr). Compared to placebo, entacapone increased the duration of ON time by 1.3 hours ($p<0.001$, 95% CI 0.8-1.9) and decreased OFF time to about the same extent. The proportion of daily ON time increased by 10%. The proportion of OFF time decreased by 24% in the entacapone group and did not change in the placebo group. These results are clinically relevant. However, there was a trend towards increased duration of dyskinesias. The ON time with and without dyskinesias was not evaluated. However, the dyskinesias were less frequent at the end of the study, possibly due to the decrease in daily L-dopa dose. Entacapone slightly decreased the proportion of patients with predictable OFF periods, but did not affect unpredictable or sudden OFF periods. The frequency of wearing off significantly decreased with entacapone. Entacapone did not significantly affect other daily fluctuations in disability. The global evaluation by patient and investigator favoured entacapone over placebo (percentage improved according to the investigators was 56.5% in the entacapone and 27.9% in placebo group). The mean L-dopa dose and dosing frequency decreased significantly with entacapone (dose decrease was 102 mg in the entacapone group, $p<0.001$, 95% CI from -137 to -67). The clear withdrawal effects which were observed following discontinuation of entacapone after 24 weeks of treatment also support its efficacy.

The data indicate that the increase in bioavailability of L-dopa from immediate release tablets of L-dopa/benserazide during entacapone treatment is more pronounced than from immediate release tablets of L-dopa/carbidopa.

SEESAW (2939044): This was a phase III multicentre, randomised, comparative (placebo vs. entacapone 200 mg with each L-dopa+ dose, carbidopa), double blind, parallel group study of 6-month duration carried out in 205 patients (103 entacapone and 102 placebo) with advanced PD and end-of-dose fluctuations. The primary efficacy criteria was mean daily ON time during an 18hr recording period.(Fr) The study consisted of a L-dopa dose-adjusting period (weeks 1-8) and a period of fixed L-dopa dosing (weeks 9-24). This study also included a staggered withdrawal period. A 6% increase in the proportion of daily ON time was observed with entacapone. The benefit from entacapone in this study was not as clear-cut as in the former study. However, the proportion of ON time was already about 60% at baseline and the assumed increase of 10% or more may have been optimistic. The increase in ON time was 0.58 hours compared to placebo in the whole study population and 0.75 hours in patients who were OFF at least 3 hours at baseline. A significant and proportional decrease in OFF time was observed. UPDRS scores were not different between placebo and entacapone. Mean daily L-dopa dose decreased significantly. The duration of dyskinesias increased with entacapone. Global evaluation by patient and investigator favoured entacapone over placebo. Entacapone was not significantly different from placebo with respect to occurrence and severity of daily fluctuations in disability. However, clear withdrawal effects were observed after entacapone treatment was discontinued. The difference in the magnitude of effect of entacapone between NOMECOMT and

SEESAW studies may partly be explained by the fact that, in the former study, the majority of patients were on L-dopa/benserazide treatment.

Study 293930: This was a phase II randomised, comparative (placebo or entacapone 200 mg with each L-dopa+ dose, carbidopa or benserazide), double blind crossover (2x2) study of two 4-week periods without washout, carried out in 26 patients. The primary efficacy criterion was the duration of motor response during an L-dopa test. A clear sequence effect concerning the primary variable was shown. However, the mean duration of ON time increased significantly with entacapone: the difference between placebo and entacapone was 49 min.

The latency of onset of the motor response was not affected. The duration of dyskinesias increased significantly. Excluding nocturnal akinesia (frequency was decreased by entacapone), there were no obvious differences in the numbers of patients experiencing daily fluctuations in disability. The mean daily dose of L-dopa decreased significantly during entacapone (from 860±320 mg to 720±250 mg, p=0.0011) treatment.

A *post hoc* analysis was performed by the applicant on the data of phase III pivotal efficacy studies, which showed that baseline severity of the disease had no significant influence on the response to entacapone.

Non-fluctuating patients

FILOMEN (2939052): This is an ongoing long-term phase III multicentre safety study of entacapone in patients with Parkinson's disease. A six-month interim report has been submitted. Study design is comparative, randomised (2:1 entacapone:placebo), double blind, parallel group comparison. The treatment consisted of 200 mg entacapone or placebo with each L-dopa+ dose (maximum daily dose of entacapone 2000 mg). The total study duration for each patient was 6.5-7 months including a 2-4-week run-in period and a 6 month double-blind treatment period.

This was the only study, which enrolled non-fluctuating PD patients. However, the study was designed to primarily assess the long-term safety of entacapone. Analysis of ON time, OFF time and fluctuations in disability were not included. The only efficacy parameters that were significantly different from placebo were total levodopa dose/day and the number of levodopa doses/day.

Efficacy conclusion

The placebo-controlled pivotal studies support the efficacy of entacapone as an adjunct to standard L-dopa/DDCI preparations in the treatment of idiopathic Parkinson's disease in patients with end-of-dose motor fluctuations. The documentation does not support efficacy in non-fluctuating patients or in patients who are on controlled-release L-dopa+.

Long-term efficacy of entacapone has been demonstrated up to 6 months in double-blind studies.

Safety

Safety data from each of the phase I-III studies have been reviewed separately for this AR.

The phase II and III studies (including on-going phase III long-term studies) include 925 patients who have been exposed to entacapone. The phase III 6-month studies included 188 patients who were allocated to entacapone treatment. Altogether 198 patients have received entacapone for 6 months in an ongoing double-blind study (FILOMEN), 96 patients have received entacapone for 12 months in an open on-going safety study (NOMESAFE) and 106 patients have been exposed for at least 48 weeks in the on-going open follow-up study (SEESAFE).

In the phase III studies, 8-11% of patients discontinued entacapone due to adverse events.

Dopaminergic adverse events have been clearly more frequent after entacapone than after placebo (hyperkinesia, dyskinesia, nausea). The dopaminergic adverse events have been dose-dependent.

Entacapone may cause urine discoloration. However, the most prominent adverse events have been addominal pain(7.1%)and diarrhoea (8.4% of patients, severe in 1%).

Diarrhoea has also been the most frequent cause for discontinuation of entacapone (2.5% of the cases). The mechanism of diarrhoea is unclear. It may be a class effect of nitrocatechol-structured COMT

inhibitors. It was not clearly dose- or age-dependent; its incidence does not appear to increase during long-term treatment and it seems not to be associated with malabsorption.

Entacapone treatment has not been found to be associated with clinically important ECG changes. Changes in supine and standing blood pressured have shown a slight trend towards lower values on entacapone than on placebo treatment. However, by enhancing levodopa effects entacapone may aggravate orthostatic hypotension.

The frequencies of adverse events have been analysed according to the L-dopa+ medication (L-dopa + carbidopa or benserazide) in NOMECOMT study. Dyskinesia and postural hypotension were more frequent in patients who were using L-dopa/benserazide.

This could have a pharmacokinetic background (entacapone increases the bioavailability of L-dopa/benserazide 5-10% more than that of L-dopa/carbidopa). In fact, the mean reduction in L-dopa daily dose is greater in patients taking entacapone/benserazide than in patients taking entacapone/carbidopa.

Adverse events have been analysed separately in patients who concomitantly received selegiline or dopamine agonists (FILOMEN). The results should be interpreted cautiously, since the analyses did not separate the effects of individual drugs (both selegiline and dopamine agonists probably were used by a substantial proportion of patients). Selegiline and dopaminergic drugs may increase the frequency of dopaminergic adverse events, including postural hypotension and dyskinesias. The frequencies of other adverse events did not appear to have been affected.

Decreases in haemoglobin (1.5% with entacapone and 0.3% with placebo after 6 months), erythrocytes and haematocrit have been a consistent finding in the clinical studies. This phenomenon was also observed in animal toxicity studies. In addition, in the open label extension studies the frequency of clinically relevant decrease in haemoglobin increased to 5.8%. The decreases in red blood cell parameters are probably due to iron deficiency anaemia (Fe-chelation). Slight, but significant decreases in serum iron, MCHC, MCH and MCV over 6 months have been observed. However, the changes in iron binding capacity do not conclusively support iron deficiency.

Decreases in the mean leukocyte and platelet counts have been observed (not consistently). The mean changes observed in these parameters are not clinically relevant. One case of clinically significant thrombocytopenia and epistaxis has been reported from a one-year long-term open study (causality unlikely). This patient had had slightly lowered platelet counts previously during double-blind entacapone. Similarly, one case of leucopenia and eosinophilia has been reported from an on-going long-term safety study. This patient had had slightly lowered WBC counts previously during double-blind entacapone. The follow-up confirmed that the causality relationship is unlikely. Low WBC counts have been detected in at least three other patients (FILOMEN). However, WBC abnormalities were not more frequent with entacapone than with placebo in this study.

In both the SEESAW study as well as in the combined population of the three phase III double blind studies, the incidence of dyspnoea, abnormal vision and purpura increased dose-dependently in the entacapone group. No consistent dose-dependency was observed in the placebo group (L-dopa+). However, the overall incidence was similar in the entacapone and in the placebo group. Hence, a clear relationship could not be established.

The mean changes in clinical chemistry parameters generally have been slight and not clinically relevant. However, slight decreases in serum calcium (and in some studies, phosphate), serum albumin and potassium have been observed.

Increases in serum glucose have been observed. The increases in the mean values were not clinically significant, and a further analysis conducted by the applicant suggested that entacapone does not adversely affect glucose tolerance.

Abnormal ALT/AST/GGT values have been observed in up to approximately 5-15% of patients during long-term treatment (12 months) in both entacapone and placebo groups. However, clinically significant increases have been rare.

Post Marketing experience

Following the 4th PSUR the CPMP requested the MAH to include the increase in transaminases in the table of labelled adverse effects. The cumulative rate of increase in transaminases is < 1:1000 and > 1:10 000 and abnormal liver function tests have been included in section 4.8 of the SPC with the frequency 'rare' through a Type II variation.

The adverse event agitation was reported seven times (four of which with possible relatedness to treatment) during the reporting period of the 4th PSUR. This emotional and behavioural symptom may be part of confusion, but could also be a separate phenomenon. Agitation as a very rare event was included in section 4.8 through a Type II variation.

Four cases of hepatitis have been reported. In one of these four cases biopsy results revealed severe cholestasis. In the other three cases an arbitrary ALT/ALP ratio below 2 was indicative of cholestatic nature. The text 'Isolated cases of hepatitis with cholestatic features have been reported' has been added to section 4.8 through a Type II variation.

In the assessment of the fifth PSUR for Comtess, it was concluded that, as regards the review of sudden sleep attacks and somnolence submitted in the PSUR and the class-review of dopaminergic substances including levodopa combinations, that the PSUR included data that justified a request for an amendment of the current Comtess SPC. Entacapone enhances the effects of levodopa and is administered concomitantly with levodopa and a DDC inhibitor. Possible effects of entacapone on alertness can not be reliably separated from the effects of levodopa in clinical use. However, there is evidence that concomitant use of entacapone + levodopa was associated with somnolence or sudden onset of sleep in isolated cases. As a consequence sections 4.4, 4.7 and 4.8 of the SPC and corresponding sections of the Package Leaflet were updated through a Type II variation.

First 5 year renewal

During the period of the seventh PSUR, a total of 6 reports including weight decrease, anorexia, or both these adverse drug reactions, were received. No clear pattern of AE is evident at present. Both weight loss and anorexia are often associated with other gastro-intestinal disorders and underlying medical conditions. In the past clinical trials, there was no significant difference in the incidence of anorexia or weight decrease reported as an adverse event or as actual weight decrease in the controlled clinical studies in patients receiving entacapone compared to those receiving placebo. A total of 35 reports including weight decrease and/or anorexia have been received since the first marketing authorisation of entacapone. Weight decrease has been included altogether in 26 and anorexia in 15 reports, 6 reports included both ADRs. Most of the reports including weight decrease or anorexia included one or more additional ADRs. The MAH proposed to add a precaution to section 4.4 and both weight loss and anorexia to section 4.8. of the SPC were endorsed by the CPMP. These changes were also reflected in the Package Leaflet. These changes were accepted by the CPMP.

A follow up of certain issues, such as liver disorders, NMS and rhabdomyolysis, anorexia and weight loss, as well as anaemia and gastro-intestinal complications, was requested. Since there were still several issues to be followed up, the submission of an additional 1 year PSUR was considered necessary.

Benefit/risk assessment

The efficacy of entacapone as an adjunct to standard levodopa/DDCI preparations has been demonstrated in double-blind placebo-controlled studies (up to 6 months) in PD patients with end-of-dose motor fluctuations. Efficacy has not been established in non-fluctuating PD or in *de novo* PD. The most important undesirable effects due to the product itself are abdominal pain and diarrhoea. In the majority of cases these undesirable effects were graded mild or moderate. By adding entacapone to L-dopa therapy the dopaminergic side effects, especially dyskinesia, are increased during on time.

Risk/benefit in the treatment of patients with Parkinson's disease and end-of-dose motor fluctuations is considered to be positive.

5. Conclusion

Entacapone has been demonstrated in *in vitro* and *ex vivo* pharmacological studies to be a reversible inhibitor of COMT. Entacapone increases levels of L-dopa in the blood when co-administered with L-dopa and a peripheral decarboxylase inhibitor. Entacapone acts peripherally, but does not inhibit COMT centrally.

The quality of Comtess 200 mg film coated tablets has been demonstrated, allowing 3-year shelf life.

The applicant has adequately investigated the general safety pharmacology.

No adverse effects of clinical relevance were observed with respect to the cardiovascular, respiratory, renal or gastrointestinal systems in animal studies.

As to the clinical pharmacology and the efficacy of the drug in patients suffering from fluctuating PD, the following issues needed clarification during an oral explanation before granting a marketing authorisation:

- The reasons for inconsistency in efficacy between the two pivotal trials.
- The clinical benefit of adding entacapone to controlled released L-dopa.
- Data from clinical studies strongly suggested that during entacapone treatment the increase in bioavailability of levodopa from standard levodopa/benserazide tablets is more pronounced than from standard levodopa/carbidopa tablets. The clinical relevance of this difference in terms of efficacy and safety need clarification.
- Though an effect on on/off time was seen, entacapone did not clearly increase the apparent t½ of L-dopa.

The CPMP concluded that the reasons for the inconsistency in the magnitude of the effect of entacapone on efficacy variables in the two phase III pivotal studies (NOMECOMT and SEESAW) were not fully clarified. However, the CPMP noted that in the SEESAW study, all patients were taking levodopa/carbidopa whereas in the NOMECOMT study, the majority of patients were taking levodopa/benserazide.

The observed differences in the effect of entacapone on the pharmacokinetics of levodopa depending on the dopa decarboxylase inhibitor may partially explain the differences in clinical effect in the two pivotal phase III studies. The difference in the effect of entacapone on levodopa pharmacokinetics depending on the levodopa/DDCI preparation is stated in the SPC.

The CPMP concluded that the efficacy of entacapone as an adjunct to controlled release levodopa/dopa decarboxylase inhibitor preparations has not been proven. Therefore, the SPC was amended accordingly.

A positive Opinion was adopted by majority vote (17 out of 24 CPMP members, no abstention). Some CPMP members considered the benefit/ratio of the product to be negative and expressed the following divergent view:

“The concept behind using a COMT inhibitor in addition to L-dopa/DDCI is to smooth the L-dopa plasma levels by increasing the apparent t1/2 of L-dopa. The pharmacokinetic data showed an increase in AUC of L-dopa but there did not appear to be an effect on t1/2. The clinical effects were studied in the two pivotal trials of 6 months duration versus placebo.

The results were inconsistent as in one study the mean difference in on time between placebo and entacapone was 1.20 min and in the other 35 min. The effect of entacapone appears to be dependent on the dopa decarboxylase inhibitor used”.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by majority that the benefit/risk profile of COMTESS was favourable in the indication as an adjunct to standard preparations of levodopa/benserazide or levodopa/carbidopa for use in patients with Parkinson’s disease and end-of-dose motor fluctuations, who cannot be stabilised on those combinations.

Based on the CPMP review of the available information at the time of the first 5 year renewal, the CPMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered by consensus that the

benefit/risk profile of COMTESS remains favourable in the indication as an adjunct to standard preparations of levodopa/benserazide or levodopa/carbidopa for use in patients with Parkinson's disease and end-of-dose motor fluctuations, who cannot be stabilised on those combinations.