SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 1 September 2004. For scientific information on procedures after this date please refer to module 8B

1.   Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterised by bradykinesia, rigidity, postural imbalance and tremor. The incidence of PD is estimated to 4.5-16/100,000 persons per year and on average, 2 to 3 % of the population in the western world will develop PD. The disease is rare before the age of 50 years, and incidence rates increase with age. 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. Thus, restoration of the dopaminergic transmission forms the central strategy for the treatment of PD.

The standard treatment of PD consists of levodopa (L-dopa, a dopamine precursor) in combination with a peripheral aromatic amino-acid decarboxylase (AADC) inhibitor (carbidopa or benserazide). Other treatments include DA agonists and anticholinergic drugs. Such compounds are often given in combination with L-dopa to reduce the dose of the latter thereby increasing treatment tolerance. 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.

To improve the brain bioavailability of L-dopa, its metabolism via decarboxylation is prevented by the co-administration of peripherally active AADC inhibitors. When peripheral dopa-decarboxylase is inhibited, the main catabolic pathway of L-dopa is the conversion into 3-OMD (3-methoxy-dopa) by the enzyme catechol-*O*-methyl transferase (COMT). Thus, concomitant inhibition of COMT should reduce the metabolism of L-dopa and increase the amount of L-dopa available for conversion into DA in the brain.

Tolcapone is an orally active, selective and reversible COMT inhibitor. By inhibition of COMT, the breakdown of L-dopa is decreased and thus, the half life of L-dopa is prolonged. Tasmar is indicated in combination with levodopa/benserazide or levodopa/carbidopa for use in patients with Parkinson's disease, who cannot be stabilised on levodopa therapy, especially fluctuating patients with end-of-dose phenomena. The recommended starting dose is 100 mg orally t.i.d. The dose can be increased to 200 mg t.i.d.

2.   Overview of Part II of the dossier: chemical, pharmaceutical and biological aspects

Tolcapone is an orally active benzophenone derivative COMT inhibitor, indicated for use as an adjunct in the treatment of PD. It is presented as Tasmar tablets 100 and 200 mg. Different pack sizes are proposed: 30 and 60 tablets in blisters, or 100 tablets in glass bottles.

Composition

The film-coated tablets are made with standard core and film-coat excipients; the core formulations are dose proportional. The active substance comprises 57% of the core weight. The containers proposed are PVC/PE/PVDC blister packs and amber glass bottles.

Satisfactory detail has been provided on the development of the marketing formulation. Particle size is controlled because of the low solubility of tolcapone in water and in acidic solution. All batches have met the acceptable specification limits. For the *in vitro* dissolution testing, an alkaline medium of borate buffer pH 8.5 was finally chosen to allow complete dissolution within a reasonable time.

Method of preparation

Tablet core batch sizes of 410 kg are proposed, equivalent to 2 million of the 100 mg tablets or 1 million of the 200 mg tablets.

The manufacturing process involves granulation, mixing with extra-granular excipients, compression and film-coating. The in-process controls and limits proposed are satisfactory. The manufacturing process has been adequately validated on both pilot-scale and production-scale batches.

Control of starting materials

The drug substances specification includes tests for identity by IR, UV and HPLC, related substances, assay, particle size, residual solvents, water, sulphate ash and heavy metals. Only two impurities are named in the specification, Ro 40-7591 (the precursor of tolcapone) and Ro 44-1446 (a by-product); the limits proposed are acceptable. In the related-substances HPLC tests, three impurities (Ro 44-1446, Ro 48-6830 and Ro 61-4977) co-elute at the same retention time. However, as very low amounts of the three impurities have been found, the designation of them as Ro 44-1446, is acceptable.

Satisfactory limits are proposed for the solvents tested (methylene chloride and ethanol) and for other tests in the specification.

Tolcapone is synthesised in a 3-step process. Pre-clinical and clinical studies were performed with tolcapone made by a 6-step process. However, with regard to related substances, no significant differences were shown between batches synthesised from the two processes. Batch analytical data confirm their equivalent quality.

The structure of tolcapone has been proved by elementary analysis and interpreted UV, IR, MS, ^{1}H- and ^{13}C-NMR spectra. Two polymorphic forms have been found, modification A and B. The control of polymorphic form by IR is considered to be sufficient and no quality or efficacy issues arise from the existence of the two polymorphs. The analytical methods have been well validated.

All potential impurities arising from synthesis and all organic solvents used during synthesis have been tested for, but only those related substances named in the specification have been detected.

The excipients comply with Ph. Eur., B.P. or U.S.P. requirements. The colourants 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. The dissolution specification limit is 70% (Q) in 30 minutes, which means that the dissolution result of individual tablets is equal or higher than 75%. The degradation product limits are less than the proposed ICH threshold limits for identification. The HPLC method used for determination of content of tolcapone and degradation products is adequately validated. Batch analytical results provided for five batches of each strength, including one production batch, comply with the specifications.

Stability

Four batches have been stored for up to one year at different temperatures and relative humidity. No degradation was detected using the validated routine methods. Further stability data showed that the particle size distribution does not change on storage. The results support the proposed two-year retest date. Stress testing has shown tolcapone to be degraded in alkaline solutions, with a very slight degradation in hydrogen peroxide conditions. No degradation occurs under other stress conditions.

Three tablet batches of each strength have been stored in both amber glass bottles and blister packs for up to 18 months at different temperatures and relative humidity; both pilot and production scale batches were included. The results showed good stability, with no evidence of degradation using the routine stability-indicating HPLC method. The results also demonstrated the suitability of the proposed packaging materials. Stress testing under light, humidity and in-use conditions confirmed the good stability of the product. Based on these data, a 2 year shelf life was supported when the product was centrally authorised. The shelf life was then extended to 3 years, in accordance to the data

presented after the Marketing Authorisation by the MAH to the EMEA and to the subsequent positive notification issued on 28 October 1997.

3. Overview of Part III of the dossier: toxico-pharmacological aspects

Pharmacodynamics

Effects related to proposed indications

In vitro, tolcapone showed a high affinity for COMT with onset of action within 10 minutes and duration of inhibition of up to 8 hours. In *ex vivo* rat preparations, the doses required to reduce COMT activity to 50% of baseline values ranged from 1.2 mg/kg to 28 mg/kg depending on the organ system studied. After oral administration in rats, a dose dependent inhibition of COMT activity was observed both in peripheral organs and the CNS. Maximal inhibition was reached within 15-60 minutes after dosing, and complete recovery was observed after 8 to 16 hours. *In vivo* microdialysis studies in rats indicated that tolcapone when given in combination with L-dopa and benserazide, increased L-dopa levels in the CNS. Tolcapone did not inhibit any other enzymes or show affinity to neurotransmitter binding sites. Data from studies in animal models of PD, supported a potential efficacy in humans PD when tolcapone was co-administered with L-dopa. Taken together, the data indicate that tolcapone 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 flux of its metabolites.

General pharmacodynamics

An antidepressant effect of tolcapone was demonstrated in a rat model of depression, probably by enhancing brain levels of catecholamines. Tolcapone did not induce physical or psychological dependence. No adverse effects of clinical relevance were observed with respect to the respiratory, renal, or gastrointestinal systems.

Following intravenous administration in anaestethised dogs, a dose dependent decrease of blood pressure was observed. In rabbits, an intravenous bolus of a high dose caused cardiac arrhythmias and death while no cardiac effects were observed following intravenous infusion. The systemic exposure (C_{max}) was 9-17 fold (dogs) and 20-40 fold (rabbits) higher than that of humans given clinical therapy. Based on these safety margins and the fact that tolcapone is intended for oral use only, the clinical relevance of these findings was regarded as minor.

Pharmacokinetics

The pharmacokinetics of tolcapone have been investigated in the rat, dog and rabbit. Modest quantitative differences across species were found. However, the pharmacokinetic profile of tolcapone is sufficiently similar in animals and humans to allow the animal toxicology studies to be considered as a valid exploratory tool for human safety.

Absorption after oral administration is rapid with peak plasma concentrations occurring within 30 minutes post dose. In rat, dog and human, the oral bioavailability was 60-80%. The protein binding of tolcapone was similarly high, around 99.9%, in rat, dog and human. Consequently, the extravascular tissue distribution was limited. The overall elimination half-life of tolcapone ranged from 30 minutes to 2 hours, depending on species and route of administration. Following repeated administration in rats, no accumulation or retention of drug-related material was observed.

Tolcapone is extensively metabolised in all species including human, the main metabolic pathway being glucuronidation to the 3-O-methylglucuronide. In addition, oxidation to the alcohol derivative and methylation are significant routes. In rat and dog, tolcapone metabolites are predominantly excreted in bile, while in humans, urinary excretion was predominant. Tolcapone is excreted in high concentration in rat milk.

Toxicology

Single dose toxicity studies were performed in rodents and a pyramidal dose toxicity study in dogs. Sudden deaths occurred in rats after oral tolcapone doses $\geq$ 300 mg/kg or plasma concentrations of > 100 µg/ml (C_{max} in patients is about 6 µg/ml). No mortality occurred in dogs up to the top dose of

300 mg/kg. In rodents, single dose toxicity was similar when tolcapone was given alone or in combination with L-dopa (1000 mg/kg) and decarboxylase inhibitor (carbidopa or benserazide).

Repeat dose toxicity of tolcapone was studied for up to 12 months in rats dosed via feed-admix with up to 500 mg/kg/d (6 month) or 450 mg/kg/d (12 month) and in dogs given capsules with up to 2x90 mg/kg/d (12 month). In rats, the kidney was the target organ of toxicity. Degeneration of proximal tubular epithelium with atypical nuclei was observed in the 12 month study at plasma AUC (based on unbound concentrations) about 10 times greater than those in patients. The same type of lesion, with single cell necrosis and regenerative hyperplasia was seen in the 2 year carcinogenicity study (see further below). At the no adverse effect levels (NOAEL) for these findings, the systemic exposure of rats was equivalent to at least two times the therapeutic AUC. In dogs, vomiting and occasional phases of soft stool were the most prominent signs and occurred at the top dose.

The combination of tolcapone, L-dopa and decarboxylase inhibitor (carbidopa or benserazide) was studied for up to 13 weeks in rats and dogs. In addition, the effects of the carbidopa combination were studied in monkeys during 4 weeks. Not unexpectedly, these studies showed a slight enhancement of some L-dopa related effects, e.g. hyperactivity in rats and monkeys, increased salivation in dogs. However, overall, it was concluded that no interactions resulting in new unexpected findings were revealed.

Reproductive toxicity - No effects on fertility and general reproductive performance of doses up to 300 mg/kg/d of tolcapone were observed in the rat. Segment II studies were performed in rats (doses up to 300 mg/kg/d) and rabbits (doses up to 400 mg/kg/d). In the rat study, some fetal abnormalities and variations were observed in the tolcapone groups, but the findings were isolated and the relation to treatment was considered questionable. In the rabbit study, an abortive potential was observed at doses ≥ 100 mg/kg/d. Peri/post-natal performance was evaluated in rats with doses up to 250/150 mg/kg/d (the high dose was reduced due to high maternal mortality). In the high dose group, resorptions and litter size were slightly affected, as well as learning performance of female pups. The NOAEL correspondent to exposures at least 3 times higher than estimated therapeutic exposure. Segment II studies of the combination of tolcapone, L-dopa/carbidopa were performed in rats and rabbits. A non-significant increase of fetotoxicity and some skeletal defects were observed with L-dopa/carbidopa alone and in combination with tolcapone. Possibly, these effects were related to L-dopa which is known to induce skeletal defects in rabbits. The findings in the reproductive studies are addressed in section 4.6 of the Summary of Product Characteristics.

Genotoxicity - The genotoxicity potential of tolcapone alone and in combination with L-dopa/carbidopa was studied in an adequate battery of genotoxicity tests, performed according to current requirements. Based on these studies, it was concluded that tolcapone did not exert any clinically relevant genotoxic effects.

Carcinogenicity - Carcinogenicity studies were performed in rodents administered up to 800 mg/kg/d (mice) or 450 mg/kg/d (rats) tolcapone in the diet. The mouse study was terminated after 80 (females) or 95 (males) weeks at a mortality rate of about 50%. There were no treatment-related increases of neoplastic findings. The duration of the rat study was 104 weeks as planned. Three and five percent of the rats in the mid- and high-dose groups, respectively, were shown to have renal epithelial tumours (adenomas or carcinomas). The tumours were considered to be due to cell necrosis and consequent repair due to chronic epithelial cell damage in the proximal tubule. No evidence of renal toxicity was observed in the low-dose group, equivalent to at least two times the therapeutic AUC. Based on comparisons of plasma levels, a safety factor of 2-5 (or 4-10 based on unbound tolcapone concentrations) was established. These data were incorporated in the SPC at the time of first approval.

Uterine carcinomas were present in 0/100 control rats, 2/49 low dose, 3/50 intermediate, 7/50 high dose animals. The uterine carcinomas were considered to be secondary to a tolcapone-induced imbalance in the dopamine-prolactin-oestrogen-progestagen axis, and to be species specific to the rat.

Environmental risk assessment - Although tolcapone is classified as harmful for the environment, the solubility of the compound would be sufficient to result in a rapid and high degree dilution yielding concentrations below levels that would cause adverse effects.

In summary, the pre-clinical documentation of tolcapone is of good quality. Tolcapone has been demonstrated to be a selective, potent and reversible inhibitor of COMT which enhances brain levels

of L-dopa when co-administered with L-dopa and a peripheral decarboxylase inhibitor. Based on findings in long-term toxicity studies, the main preclinical concern with respect to human safety is the nephrotoxic potential of tolcapone. This together with findings in reproductive toxicity studies has been addressed in the relevant sections of the SPC.

4. Overview of Part IV of the dossier: clinical aspects

In addition to the studies related to pharmacodynamics/pharmacokinetics, the core clinical documentation of tolcapone consists of 6 trials (5 placebo controlled and 1 open-label) conducted in fluctuating PD patients and 2 trials (placebo-controlled) in non-fluctuating patients.

Pharmacodynamics

The pharmacodynamic effect of tolcapone was studied in 13 phase I trials. Inhibition of erythrocyte COMT activity was monitored as a measure of tolcapone effect. There was a close, inverse, relationship between rising plasma tolcapone levels and falling erythrocyte COMT activity. After withdrawal, a moderate 'rebound' effect with erythrocyte COMT activity rising above baseline was observed. A dose response study in healthy volunteers, indicated a steep increase in maximum COMT inhibition for doses up to 50 mg, a slower rise between 50 and 200 mg, and a plateau thereafter.

When tolcapone was co-administered with L-dopa + decarboxylase inhibitor, the plasma levels of L-dopa were dose-dependently increased up to a tolcapone dose of 200 mg. Following this tolcapone dose (200 mg t.i.d), together with L-dopa plus carbidopa or benserazide (100 mg + 25 mg), $t_{1/2}$ of L-dopa was prolonged 1.1-1.9 times that of placebo, and the L-dopa AUC was doubled. The peak plasma concentration remained unchanged. Higher tolcapone doses did not improve the L-dopa pharmacokinetics. The doses selected for phase II trials were based on the effects of tolcapone on L-dopa pharmacokinetics.

Pharmacokinetics

The pharmacokinetic documentation consists of 15 clinical trials in healthy volunteers, PD patients and patients with hepatic disease. The pharmacokinetics of tolcapone and its main metabolite RO 40-7591 were studied after administration of tolcapone alone or in combination with L-dopa/carbidopa and L-dopa/benserazide. Furthermore, the pharmacokinetics of L-dopa and its metabolites were investigated when L-dopa was co-administered with tolcapone. Both compartmental and non-compartmental pharmacokinetic methods were used and based on data from phase III trials, 2 population pharmacokinetic analyses were submitted.

The absolute bioavailability after oral administration was 65%. In the presence of food, the bioavailability was reduced but it was concluded that because adjustment of the dose of both tolcapone and L-dopa will be necessary to achieve optimal therapeutic effect, tolcapone may be administered with or without concomitant food intake. After a single oral dose of tolcapone alone or together with L-dopa + decarboxylase inhibitor, t_{max} was 1.4-1.8 h. The plasma protein binding was high, the unbound fraction in healthy volunteers was $0.12 \pm 0.01\%$. The volume of distribution at steady state was small (9 l). At recommended therapeutic doses, no accumulation of tolcapone was observed following repeated administration.

Tolcapone is almost completely metabolised prior to excretion, with less than 1% of the parent compound excreted unchanged. Following administration of a radiolabelled dose, 60% of radioactivity was recovered in urine and 40% in faeces. In plasma, most radioactivity up to 12 hours post dose corresponded to tolcapone and its main metabolite the glucuronide. The total clearance was 7-8 l/h, of which renal clearance was 0.02 l/h. The estimated terminal half life was 1-4 hours. The population analyses based on data from phase III trials, indicated a slightly lower clearance (4.5-5.5 l/h) and bigger volume of distribution (15-35 l) and thus, a slightly longer half life in PD patients.

The main metabolic pathway of tolcapone is conjugation via glucuronyl transferase. Tolcapone is also methylated by COMT to 3-O-methyl-tolcapone which has a half-life of 55 h after oral administration. Metabolism via CYP 3A4 and CYP 2A6 to a primary alcohol which is subsequently oxidised by an unknown enzyme to the carboxylic acid has also been demonstrated.

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The pharmacokinetics of tolcapone were studied in subjects with non-cirrhotic or cirrhotic liver disease. It was shown that liver disease resulted in a 50% reduction of the clearance of unbound drug. Thus, increased plasma levels of unbound drug can be expected. This was addressed in the SPC, which recommended that patients with moderate liver impairment should not be escalated to 200 mg t.i.d.

A special study in patients with renal impairment has not been performed. Data from clinical trials indicated that the tolcapone does not accumulate in Parkinson's disease patients with creatinine clearances varying from 30-130 ml/min.

In *in vivo* interaction studies, tolcapone did not affect the pharmacokinetics of desipramine (glucuronidation as main metabolic pathway), tolbutamide, (CYP 2C9) or carbidopa (COMT). A number of catecholamines are metabolised via COMT and potentially, COMT inhibition could affect their elimination. However, no significant pharmacodynamic or pharmacokinetic interactions were seen when ephedrine was given together with tolcapone + L-dopa/carbidopa. Interaction with benserazide was observed, which may lead to increased levels of benserazide and its active metabolite. This is referred to in the SPC.

A number of tablet formulations have been used in clinical trials. Bioequivalence has been shown between the different formulations.

Efficacy at the time of granting of the EU Marketing Authorisation

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

For 'fluctuating' patients, the primary efficacy criterion was ON/OFF time assessed by patient diary rating. For non-fluctuating patients, the primary criterion was the Unified Parkinson's Disease Rating Scale (UPDRS), and the Assessment of Daily Living (ADL) scale. Secondary criteria were; for fluctuating patients ADL, and for both fluctuators and non-fluctuators global investigators scales, UPDRS motor scale and reduction of the L-dopa dose.

In fluctuating PD patients, 2 Phase II and 3 Phase III placebo controlled trials were performed. Two of the Phase III trials were long-term (up to 12 months), the others were 6 week studies with open-label extensions. These 5 studies were multiple-dose, multicentre, randomised, double-blind and parallel-group in design, and were of adequate size (number of patients between 154 and 215). All patients included had been diagnosed as idiopathic PD and had completed three ON/OFF self-rating charts before randomisation.

NZ14316 was a US Phase II dose finding and efficacy study. Patients received placebo (n=42) or tolcapone 50 mg (n=41), 200 mg (n=40), 400 mg (n=36) t.i.d. in addition to their normal L-dopa/carbidopa treatment (total doses of L-dopa were 982 mg, 916 mg, 771 and 775 mg respectively). Efficacy was based on a physician's examination and ON time with dyskinesia was formally recorded. The OFF time was significantly reduced in all tolcapone groups compared to placebo (p ‹ 0.001) but the improvements in ON time without dyskinesia were not significant. Particularly, for the 200 mg dose, the reduction in OFF time seemed to be on the basis of increased ON time with dyskinesia.

BZ14114 was an European/Australian Phase II study comparing placebo (n=42) and tolcapone 50 mg (n=37), 200 mg (n=38), 400 mg (n=37) t.i.d. in addition to their normal L-dopa/carbidopa or L-dopa/benserazide treatment. ON time was significantly increased for all tolcapone groups compared to placebo (p ≈ 0.01), but reduction in OFF time was only significant for the tolcapone 200 mg group. Improvements in UPDRS total and sub-scales showed non-significant trends in a non-dose related manner.

NZ14654 was a US/Canadian, 13 week Phase III efficacy study, with an extension phase of 9 months. Patients received placebo (n=66) or tolcapone 100 mg (n=69) or 200 mg (n=67) t.i.d. in addition to their normal L-dopa/carbidopa treatment (total doses of L-dopa were 948, 789, and 866 mg/day respectively). The placebo improvement of about 8% was larger than that seen in other studies. The

reduction in OFF time and increase in ON time were significantly better for tolcapone 200 mg (p ‹ 0.01 and 0.05 respectively) compared to placebo. Neither change was statistically significant for tolcapone 100 mg. Results of other indices were discordant, the investigator's global assessment of severity showed a significant improvement but the UPDRS and its sub-scales did not. Analysis of 12 month data showed that the reduction in L-dopa dosage and in OFF time were maintained for 12 months.

NZ14655 was an European, 13 week Phase III trial, with an extension phase of 9 months. Patients received placebo (n=58) or tolcapone 100 mg (n=60) or 200 mg (n=59) t.i.d. in addition to their normal L-dopa/benserazide treatment. This study demonstrated that both doses of tolcapone were superior to placebo in producing a L-dopa dose reduction. Tolcapone 100 mg produced the largest decrease in OFF time (p ‹ 0.05), but OFF time reduction was not significant for 200 mg group. Increases in ON time were greater than placebo for both tolcapone doses (p ‹ 0.01). A significant improvement in the quality of life measurement (Sickness Impact Profile/Psychosocial dimension) from the 200 mg group was also observed. Changes recorded at month 3 were generally maintained at the end of the study (months 6 and 12). An exception was the 100 mg tolcapone effect on L-dopa dosing, which was gradually approaching the placebo level (from weeks 13 to 39).

NN14971 was a US/Canadian, six-week Phase III study. Patients received placebo (n=72) or tolcapone 100 mg (n=69) or 200 mg (n=74) t.i.d. in addition to their normal L-dopa/carbidopa treatment. For both doses, the increase in ON time and reduction in OFF time, estimated by self-rating, were significantly better than those of the placebo group. There were minor, non-significant, improvements in UPDRS.

In addition to the above pivotal trials, NZ14656 was a supportive, open-label, active-controlled study for 8 weeks, comparing tolcapone 200 mg t.i.d. and bromocriptine as add-on therapy in PD patients receiving L-dopa/carbidopa or L-dopa/benserazide. Differences between treatments were not statistically significant.

Safety at the time of granting of the EU Marketing Authorisation

Altogether 1934 patients participated in 13 clinical trials, 1536 of which received tolcapone and 1378 received at least 6 weeks of treatment, 222 for more than a year.

Deaths - Thirty nine deaths occurred during or after clinical trials, including the extension phases of the studies. Fifteen deaths occurred during the clinical trials, 11 patients had received tolcapone and 4 were in the placebo treatment group. Given the age of the population studied (range 66 - 84 years), a causative relationship between treatment and death is unlikely. However, two deaths in the tolcapone-treated group were rated as possibly due to treatment, a 55 year old women who had diarrhoea and jaundice before her sudden death. The death was attributed to possible cardiac causes. A second case was a patient who died of respiratory failure after discontinuing tolcapone treatment, this event was assessed as probably neuroleptic malignant syndrome.

Adverse Events - The incidence of adverse events was higher in 50, 100 and 200 mg tolcapone treated than placebo patients. The incidence for all adverse events in the 400 mg tolcapone treated group was lower than in the placebo group, it is probably due to the lack of long-term exposure (> 13 weeks) in the 400 mg tolcapone groups.

As might be expected from a compound which raises L-dopa levels, the most frequent adverse events were of a dopaminergic nature, with dyskinesia as the most frequent side-effect. However, the population which experienced increased dyskinesia did not withdraw from clinical trials in large numbers.

Nausea was the second most commonly reported adverse event and was more common in females than males. Other dopaminergic adverse events reported were sleep disorder, anorexia, orthostatism, somnolence, hallucination and vomiting.

The following adverse events occurred with an incidence above 2% for both tolcapone doses compared with placebo: diarrhoea, headache, increased sweating, xerostomia and abdominal pain. Diarrhoea was the most commonly reported non-dopaminergic adverse event, and was often

associated with discontinuation of tolcapone. In clinical trials, diarrhoea developed in 16% and 18% of patients receiving tolcapone 100 and 200 mg respectively, compared to 8% of patients receiving placebo. It usually began 2 to 6 months after therapy initiation. Cases of respiratory tract infections and influenza were also reported.

Three cases of Neuroleptic Malignant Syndrome have been reported during tolcapone treatment, following reduction or discontinuation of tolcapone and other concomitant dopaminergic medications.

As tolcapone and its metabolites are yellow, they can cause a harmless intensification in the colour of the patient's urine.

Laboratory Abnormalities - The only relevant laboratory adverse events occurring during tolcapone treatment was elevation of liver transaminases. Increases to more than 3 times the upper limit for alanine aminotransferase occurred in 1% of patients receiving tolcapone 100 mg and 3% of patients at 200 mg. The increases usually appeared within 6 weeks to 6 months of starting tolcapone treatment but were transient and reversible. Thus, it was originally recommended that transaminases had to be monitored when starting tolcapone treatment and monthly for the first 6 months. This frequency has subsequently been increased. The current SPC recommends that liver function tests (SGPT/ALT and SGOT/AST measurements) are to be carried out on alternate weeks for the first year of treatment, four weekly for the following six months and eight weekly thereafter (See 'Discussion on benefit/risk).

Withdrawal Rates - Review of the data suggests a dose response relationship for withdrawals due to diarrhoea, nausea, raised hepatic transaminases, dyskinesia, headache. In clinical trials, diarrhoea lead to withdrawal of 5% and 6% of patients receiving tolcapone 100 and 200 mg respectively, compared to 1% of patients receiving placebo.

In summary - In 5 well conducted double-blind clinical trials in fluctuating patients, tolcapone consistently showed efficacy superior to placebo in reducing the proportion of OFF time and increasing the proportion of ON time experienced by PD patients. In a single open-label comparative study, it was shown that efficacy of tolcapone and bromocriptine did not differ. Patients with unpredictable ON/OFF events have not been studied. The Efficacy seemed to be maintained throughout 52 weeks. The increase in ON time was gained at the price of increasing dyskinesia.

In non-fluctuating PD patients, study BZ14115 resulted in wide and to some extent non-conclusive confidence intervals. However the point estimates of the effect sizes were similar to study NZ14653 for Motor, ADL-ON and Total score, thus demonstrating consistency between the 2 studies.

Analysis of the frequency of adverse events and withdrawals from clinical trials according to dose of tolcapone showed that dyskinesia, nausea, sleep disorder, anorexia, abnormal dreaming, somnolence and orthostatic complaints were frequent, treatment related and probably mediated through dopaminergic mechanism. Diarrhoea was frequent. The occurrence of a significant rise in liver enzymes in some patients indicates the need for hepatic safety monitoring for the first 6 months of treatment.

5. Benefit/Risk Assessment at the time of granting of the EU Marketing Authorisation

Acknowledging the pre-clinical evidence that tolcapone caused renal tumors in rats, with a narrow safety margin, the information on BUN, creatinine and proteinuria available from approximately 600 patients treated for 12 months showed no indication of any kidney toxicity.

Tolcapone demonstrated efficacy in fluctuating L-dopa/carbidopa and L-dopa/benserazide treated PD patients. Adverse events associated with its use include dopaminergic effects which can be reduced by lowering the L-dopa dose, diarrhoea which should be clinically monitored, and elevated liver transaminases which should be monitored during the first 6 months of treatment. The discrepancy between the frequency of dyskinesia observed in clinical trials and the infrequency of withdrawal due to this effect, suggests that patients may take it as an acceptable trade-off for increased mobility.

Although the small size and short duration of the pivotal trial, consistent results seems to foresee efficacy in non-fluctuating patients.

Tolcapone demonstrated to be a selective, potent and reversible inhibitor of COMT, which enhances the bioavailability of L-dopa when co-administered with L-dopa and a peripheral decarboxylase inhibitor.

Based on findings in long-term toxicity studies, the main preclinical concern with respect to human safety was the nephrotoxic potential of tolcapone. This was addressed in the relevant sections of the SPC.

Tasmar improves symptom control in PD patients with some forms of ON/OFF phenomena. The clinical data supported efficacy in fluctuating patients, especially those with the end of dose wearing off effect.

6. POST-MARKETING EXPERIENCE

On the grounds of the above described favourable CPMP Opinion on the benefit/risk balance, on 27 August 1997, the European Commission granted Roche Registration Limited a marketing authorisation for Tasmar.

In November 1998, however, the European Commission requested the Opinion of the EMEA on cases of hepatotoxicity and neuroleptic malignant-like syndrome that had been reported in the post-marketing authorization phase. On 10 November 1998, the CPMP convened an extraordinary meeting to review the cases. Following that meeting, the CPMP adopted, on 12 November 1998, an Opinion recommending the suspension of the marketing authorisation for Tasmar, for a period of one year renewable, due to increasing concerns over reports of severe hepatotoxicity, three with a fatal outcome.

Background of the suspension
The CPMP initial Opinion (12 November 1998, CPMP/2481/98) recommending the suspension of the Marketing Authorisation for Tasmar, was adopted for the following reasons:

− serious hepatic reactions occur unpredictably and liver monitoring does not seem able to predict the development of severe, sometimes fatal, hepatic disease;

− taking into consideration this hepatotoxicity, as well as the possible occurrence of rhabdomyolysis and neuroleptic malignant-like syndrome, the overall benefit/risk balance of tolcapone was considered to be unfavourable in the authorised indication and it was not felt possible to restrict the indications sufficiently to permit safe use.

In October 1999 (CPMP/2685/99), the CPMP agreed on a further year of suspension. In this context, the CPMP agreed that a decision in lifting the suspension of the Tasmar marketing authorisation could be considered, for a restricted indication, if the following conditions were fulfilled:

1. Evidence of therapeutic benefit in patients being switched to tolcapone from other COMT-inhibitors is provided.
2. A better insight and understanding of the safety concerns, hepatitis and Neuroleptic Malignant–like Syndrome, is gained with respect to their incidence, mechanism and the means to prevent their occurrence.
3. The possibility of establishing a system of patient undertaking informed consent in the EU Member States is explored and outlined by the MAH.

On 14 January 2000, the MAH Roche Registration Ltd. requested Scientific Advice for Tasmar in order to best address the points above. The view of CPMP was that if tolcapone was to be reinstated via a positive risk/benefit assessment, then an efficacy advantage over comparable treatments should be demonstrated in a prospective study - the 'switch study'. In addition, certain safety measures would be required together with extensive re-writing of the SPC. Moreover, as the new efficacy data which had been submitted by the MAH did not sufficiently improve or expand the efficacy profile of tolcapone, the CPMP recommended on 19 October 2000 (CPMP/2717/00) that:

- The suspension of the marketing authorisation should be renewed for a further year.
- The suspension could be re-evaluated after the provision of the final report of the "switch study".
- The monthly reporting requirement for the review entitled "Review on Spontaneous hepatobiliary Adverse Events Associated with Tolcapone" should be set back to a three monthly basis.

On 19 September 2001, having reviewed the evidence submitted by the MAH, re-assessed the risk/benefit profile of the medicinal product, and considering that a prospective trial against comparable treatments was in progress, the CPMP recommended the renewal of the suspension of the marketing authorisation for a further year, which could be re-evaluated when the results of the prospective study would become available.

On 19 September 2002, on the basis of data provided by the MAH and considering the fact that the "switch study" was in progress but still incomplete, the CPMP concluded that the suspension of the marketing authorisation should be renewed for a further year.

On 22 October 2003, the CPMP adopted an Opinion, recommending the renewal of the suspension of the marketing authorisation for Tasmar, for a further year. However, the CPMP agreed on a list of outstanding issues to be addressed by the MAH focussing on the submission of revised product information and proposals for safety measures relating to the possible re-introduction of Tasmar into the EU market.

Lifting of the suspension
On 16 February 2004, the MAH submitted documentation to support the lifting of the suspension of the Marketing Authorisation for Tasmar, addressing the issues raised by CPMP during its October 2003 plenary meeting, including a proposal to ensure safe use of Tasmar, a communication plan to prescribers and revised Product Information.

The above information complemented the bulk of the safety and clinical data submitted by the MAH on 15 July 2003 to support the review of the suspension of the marketing authorisation. This request was based on new data from the now completed Switch study and information on safety data. These data included a comprehensive safety update report with a critical review of all hepatotoxicity data; an update of the ongoing and completed clinical trials since the granting of the marketing authorisation (including a study report on the "switch study", entitled *"Entacapone to Tolcapone switch study to determine whether Tolcapone can improve patients receiving optimal treatment with Entacapone"*) and analysis of the overall benefit/risk profile.

Clinical aspects

The CPMP had indicated in January 2000 that in order to reinstate tolcapone via a positive risk/benefit assessment, an efficacy advantage over similar treatments should be demonstrated to offset the possible higher risk attached to the use of tolcapone. As entacapone was at the time the only other COMT inhibitor authorised in the EU, the MAH was asked to perform a comparative study of tolcapone and entacapone (Switch study).

Method

The 'Switch study" is a multicentre, randomised, double-blind, active-controlled study with an open optimisation phase. It was conducted between July 2000 and December 2002.

1   Inclusion/Exclusion criteria

Patients with idiopathic Parkinson's disease of at least five years duration were eligible for inclusion if they continued to experience significant fluctuations and impairment of activities of daily living despite being on optimal medical therapy. At entry, patients were to be on levodopa at a daily dose of 400 - 3000 mg and entacapone 200 mg co-administered with each dose of levodopa, with a maximum of ten daily doses. Exclusion criteria were a history of liver disease or other concurrent serious illness.

2   Study design

Eligible patients entered an initial open treatment optimisation phase with entacapone, during which their levodopa dose was adjusted in order to achieve the best balance between efficacy and tolerability (see Table 1).

Following treatment optimisation (at least ten days), if patients had at least 3 hours OFF-time while on the optimal levodopa regimen, they were randomised to a three week double blind phase in which they would either continue entacapone or switch to tolcapone. Treatments were one tablet (100 mg tolcapone) with the first morning dose of levodopa and subsequently with the dose nearest to six and twelve hours later or one capsule (200 mg entacapone) with each dose of levodopa. While on double-blind treatment, the levodopa dose was again adjusted in order to optimize the levodopa regimen for use with the randomized treatment.

Table 1 - Overview of study design

Screening	Open Optimisation Phase	Randomisation	Double-Blind Phase
	≥ 10 days	Day –1/1	Week 1 Week 2 Week 3
	Entacapone*	Group 1 (n = 80**)	Tolcapone 100 mg (t.i.d.)
	Entacapone*	Group 2 (n = 80**)	Entacapone 200 mg (with each levodopa administration)*

*In combination with levodopa and other existing anti-Parkinson's agents.
**Planned sample size.

3   Efficacy parameters

The primary efficacy parameter was the proportion of responders in each group. A response was defined as an increase in ON-time (without disabling dyskinesias) of at least one hour per day. ON and OFF-times were taken as an average over the last three days of each study week and were recorded by means of a patient diary.

The secondary efficacy parameter was the proportion of patients experiencing a moderate to marked improvement as judged by the investigator's clinical impression at the final visit.

Tertiary efficacy parameters were the change in the Unified Parkinson's Disease Rating Scale (UPDRS) and the change in total daily levodopa dose during the double-blind period. These were to be analysed if the analyses of the first and secondary parameters led to inconclusive results.

4   Statistical hypothesis and analytical plan

The power calculation was based on a projected response rate of 5% in the entacapone group and 25% in the tolcapone group. This required 80 patients per treatment to give a power of 92% with two-way $\alpha = 5\%$. In fact, the proportion of responders in the entacapone group was almost 47%. Thus, in retrospect the study was considerably underpowered.

Efficacy parameters were analysed as 'all patients treated' (APT) and 'per protocol' (PP) populations. The APT population included all patients who were randomised to drug and received at least one dose of study medication. The PP population included all patients who were randomised to drug and completed the study in accordance with the protocol. The primary analyses were based on the APT population.

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5   Results

One hundred and seventy-eight patients were enrolled in the study, of whom 150 were randomised into two groups of 75 each, either on talcapone or entacapone treatment. In each group 71 patients completed the study; reasons for exclusion and non-completion were very similar between groups.

There were 4 premature withdrawals from the study in each group. Of these, 2 in the entacapone group and one in the tolcapone group were due to safety reasons. The remaining withdrawals were due to violation of selection criteria at entry and other non-safety reasons.

Efficacy results (Table 2 – Figure 1)

Table 2 – Efficacy results -all patients treated population

	Entacapone n=75	Tolcapone n=75	p value	95% CI
Number (proportion) Of responders	32 (42.7%)	40 (53.3)	p = 0.191	-5.2; 26.6
Number (proportion) with moderate or marked improvement	19 (25.3%)	29 (38.7%)	p = 0.08	-1.4; 28.1
Percentage change in levodopa dose In double blind phase (s.d.)	-0.39 (9.3) (n=64)	-2.26 (13.2) (n=65)	NA	
Mean change UPDRS – ADL ON phase (s.d.)*	-0.34 (3.09)	-0.90 (2.87)	NA	
Mean change UPDRS – ON motor examination**	-1.29 (9.32)	-2.99 (6.05)	NA	

*13 category (speech, dressing etc.) inventory

** 14 category (tremor rigidity gait etc.) inventory; for both lower scores denote better condition. ADL=Activities of daily living.

Figure 1 Patient's individual change in ON time ranked according to benefit
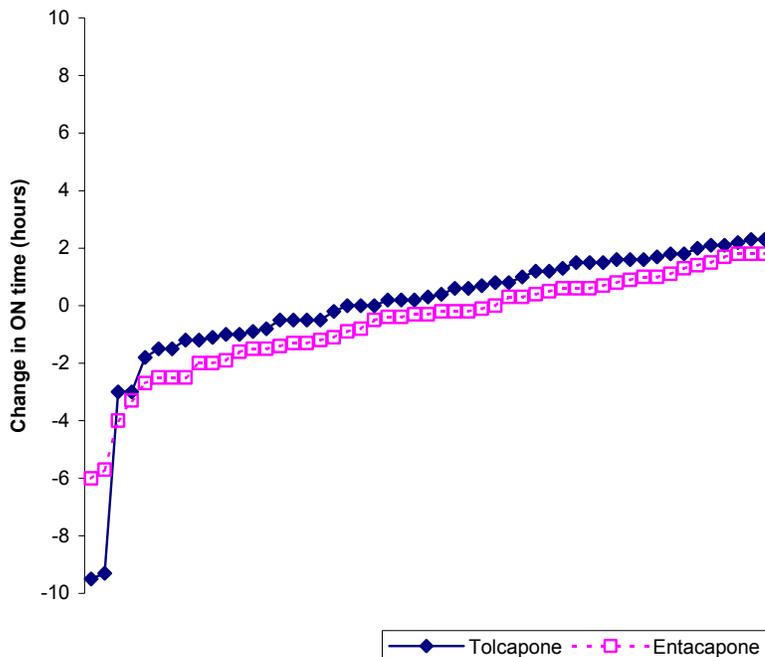
Primary efficacy parameter – For the APT population, a higher proportion of patients in the tolcapone group (53%) experienced an average increase in ON-time of ≥ 1 hour per day than in the entacapone

group (43%), but the difference between groups was not statistically significant (p=0.191). Similar results were seen in the PP population, with approximately 58% of the tolcapone group and 47% of the entacapone group classified as responders.

Secondary efficacy parameter – For the APT population, a higher proportion of patients in the tolcapone group (39%) than in the entacapone group (25%) were judged by the investigator to have shown a marked or moderate global improvement in their Parkinson's disease at the end of the study, but the difference between groups was not statistically significant. Similar results were seen in the PP population, with approximately 40% of the tolcapone group and 27% of the entacapone group showing marked or moderate improvement.

Tertiary efficacy parameters – Mean changes in total daily levodopa dose during the double-blind phase were minimal in both the tolcapone (-2.26%) and the entacapone (-0.39%) groups. Slight improvements in mean UPDRS scores were seen between the beginning and end of the double-blind phase in both treatment groups (APT population). The tolcapone-treated patients showed the largest improvements for both subscales, with the greatest difference between groups seen in the motor examination subscale.

Conclusions on the "Switch Study"

Efficacy

The study shows a modest but consistent efficacy advantage for tolcapone over entacapone.

Although none of the efficacy criteria demonstrated a statistically significant advantage for tolcapone over entacapone, all criteria (four in total) showed a trend or numerical advantage, suggesting that the outcome was more likely to be due to a therapeutic advantage than to a chance finding.

Due to the unexpectedly high response rate (43%) in the entacapone group, the MAH's statistical power calculation was, in retrospect, ill founded, and the study was not sufficiently powered to detect statistically significant difference between the groups.

Safety conclusions of the Switch study

Fifty-three percent of patients in the tolcapone group and 57 % in the entacapone group experienced at least one adverse event (AE) during the study. The most common event was dyskinesia, which occurred in 29% of the entacapone group and 31% of the tolcapone group. All other AEs reported were experienced by less than 5% of patients. A slightly higher number of AEs were reported for the tolcapone group overall, but there were no marked differences between groups in the number of patients reporting AEs or in the types of AE experienced. No hepatobiliary AEs were reported for either treatment group.

The majority of AEs in both treatment groups were considered by the investigator to be either mild or moderate in intensity. One adverse event in the entacapone group (dyskinesia) and 6 adverse events in the tolcapone group (dyskinesia, anxiety, and gastrointestinal disorders) were classified as severe.

There was one serious adverse event (SAE) in the tolcapone group reported during the study. A 68-year old man experienced three episodes with abdominal pain and was hospitalised for 7 days. The event resolved without sequelae following treatment. The SAE was judged to be remotely related to study treatment.

One patient in the tolcapone group had a marked laboratory test value abnormality and was subsequently withdrawn from the study. This 51-year-old male patient had a prior history of alcoholism that had been resolved for 3 months. Aspartate aminotransferase (AST) levels were normal at screening, randomisation and week 1 visits. However, at the week 2 visit, he had an elevated AST level of 55 U/L (reference range, 0-25 U/L). When retested the following day, the AST level had reduced to 28 U/L, but was still outside the standard reference range. Thus, in accordance with the protocol, this patient was withdrawn from the study on day 14.

There were no deaths reported during the study.

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OVERALL SAFETY

In accordance with their letter of undertaking to CPMP dated 21 October 1998, a total of 36 reports entitled "Review on Spontaneous hepatobiliary Adverse Events Associated with Tolcapone" were produced by the MAH, the last of which was received by the EMEA on 10 March 2004.

Since the International Birthday, nine Periodic Safety Update Reports have been submitted. The conclusions of the assessment of the latest PSUR were that no new information arose to alter the CPMP opinion that the suspension of the marketing authorisation could be lifted given agreement between CPMP and the MAH about appropriate controls of use.

In the US, the marketing authorisation was not suspended, but the FDA revised the prescribing information to recommend more stringent monitoring of potential hepatotoxicity and restricted availability. Similar actions were taken in Switzerland.

The safety picture is therefore completed by the fact that experience with tolcapone where it has remained available has shown that there was a significant decline of the incidence of reported cases of acute hepatitis or massive liver injury after the introduction of more stringent liver function monitoring and closer attention to the monitoring of possible signs and symptoms of underlying liver disease.

DISCUSSION ON BENEFIT/RISK

The "Switch" study showed a trend towards efficacy. This modest efficacy advantage for tolcapone over entacapone suggests that Tasmar could offer an alternative treatment to patients not adequately responding to available medications.

Two restrictions to the prescribing information were introduced:

- the indication is being restricted to "patients failing to respond to or intolerant of other COMT inhibitors", in line with the principles of the US and Swiss labelling texts, that have demonstrated to ensure sufficiently safe use of Tasmar;

- the duration of treatment in case of failure of the therapy to show clinical benefits is being limited to three weeks. The new wording for the sections 4.1 and 4.2 of the SPC is as follows "*If substantial clinical benefits are not seen within 3 weeks of the initiation of the treatment, Tasmar should be discontinued.*"

Additionally, a further restriction in the prescription of Tasmar was agreed, in the form of the following sentence in section 4.2 of the SPC: "*The administration of Tasmar is restricted to prescription and supervision by physicians experienced in the management of advanced Parkinson's disease*". This wording entailed a change in the legal status of the product. As a consequence, Annex II to the Commission Decision has been revised to list the legal status as *"Medicinal product subject to restricted medical prescription"*.

The restriction to specialist use is similar to the practice in the US and Switzerland. In the US, Tasmar may be used only by physicians who are thoroughly familiar with the prescribing information and the safety warnings that it contains, and can not be used without written informed consent from the patient. In Switzerland, Tasmar use must be initiated and supervised by a consultant neurologist.

Specific wording has also been introduced in the SPC to instruct prescribers that liver function tests (SGPT/ALT and SGOT/AST measurements) are to be carried out on alternate weeks for the first year of treatment, four weekly for the following six months and eight weekly thereafter. The SPC also indicates that, if the dose is raised to 200 mg t.i.d. the physician should check liver enzymes prior to initiating the higher dose and the monitoring scheme should be re-set from the beginning, as above.

A revised section on contraindications was also required to ensure a safe use of the product. The onset of severe hepatic injury has never been observed during the first three weeks of treatment. Therefore physicians are able to identify the individual benefit of Tasmar during this period. Thus, dosage limitations have also been introduced to limit (to three weeks) the time period between initiation of therapy with Tasmar and its discontinuation in case it fails to show clinical benefits (See sections 4.3 and 4.1 of the SPC, respectively).

Other SPC modifications to incorporate thorough instructions on liver function checks prior to commencing the therapy and its monitoring during the treatment satisfactorily address the safety concerns over hepatic reactions. In Switzerland and the US, where Tasmar has been on the market throughout the EU suspension, liver function monitoring is recommended as it is now done in the EU SPC. Having monitoring recommendations in the European Union mirroring these successfully tested measures is considered to enable sufficiently safe reintroduction of Tasmar in the EU.

In addition to the major changes made to ensure safe use, described above, the SPC underwent extensive re-writing (with corresponding changes to the Package Leaflet), and almost all of its sections are affected by changes.

It was considered that the revision that the SPC underwent, satisfactorily addresses the concerns of neuroleptic malignant-like syndrome (NMS) and rhabdomyolysis and should minimise the risk of new cases of NMS. The basis for the revision focussed mainly on three points:
- Contraindication in patients with a previous history of Neuroleptic Malignant Syndrome Symptom Complex (NMS) and /or non-traumatic Rhabdomyolysis or hyperthermia;
- Introduction of contraindications in patients with severe dyskinesia. Warnings were also introduced to state that patients receiving multiple medications with effects on different CNS pathways
(e.g. antidepressants, neuroleptics, anticholinergics) may be at greater risk of developing NMS);
- Consider increasing the patient's levodopa dose on Tasmar discontinuation.

In order to follow the spontaneous reports following re-introduction of Tasmar to the EU, it was considered appropriate to re-set the PSUR cycle as described in Council Regulation (EEC) No 2309/93, article 22(2).

The MAH will expedite all serious hepatic reactions and NMS occurring outside the EU to the EMEA (Eudravigilance System) and all EU National Competent Authorities.

The MAH will carry out targeted follow up of case reports of hepatic adverse reactions including LFT values, values registered and dates in which tests were performed, liver biopsy if available, relevant past medical history and concomitant medication or alcohol use.

CONCLUSIONS ON BENEFIT / RISK
Having reviewed the data submitted by the MAH in the context of the suspension and having re-assessed the benefit/risk profile of the medicinal product, it was considered that:

- More stringent liver function monitoring and closer attention to the monitoring of possible signs and symptoms of underlying liver disease will be introduced;

- Introduction of contraindications that Tasmar should not be prescribed for patients with severe dyskinesia or with a previous history of Neuroleptic Malignant Syndrome Symptom Complex (NMS) and /or non-traumatic Rhabdomyolysis and hyperthermia;

- Based on accumulating data, there is better insight and understanding of safety concerns, hepatitis and neuroleptic malignant–like syndrome, with respect to their incidence and the means to prevent their occurrence;

- In a short duration (three week) study there was limited evidence of a modest efficacy advantage for tolcapone over entacapone in the control of motor fluctuations in patients with advanced Parkinson's disease;

- The legal status of Tasmar will change to be restricted to prescription by physicians experienced in the management of advanced Parkinson's disease;

- The product information has been revised to introduce a restricted therapeutic indication as well as contraindications and additional warnings and precautions.

OVERALL CONCLUSIONS

Based on review of the newly available information, it was considered that the safety and the efficacy of Tasmar is adequately and sufficiently demonstrated and therefore, after re-evaluation, the benefit/risk profile of Tasmar is now favourable for the treatment of levodopa-responsive patients with idiopathic Parkinson's disease and motor fluctuations, who failed to respond to or are intolerant of other COMT inhibitors.

The lifting of the suspension of the Marketing Authorisation for Tasmar was therefore agreed, on the following conditions:

- The Periodic Safety Update Reports cycle will be re-set as for newly approved products as described Council Regulation (EEC) No 2309/93.

The lifting of the Marketing Authorisation suspension required amendments to the terms of the Community Marketing Authorisation. The following annexes were amended: I, II and IIIB.