ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tasmar 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg tolcapone.

Excipients with known effect
Each film-coated tablet contains 7.5 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pale to light yellow, hexagonal, biconvex, film-coated tablet. “TASMAR” and “100” are engraved on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tasmar is indicated in combination with levodopa/benserazide or levodopa/carbidopa for use in patients with levodopa-responsive idiopathic Parkinson’s disease and motor fluctuations, who failed to respond to or are intolerant of other catechol-*O*-methyltransferase (COMT) inhibitors (see section 5.1). Because of the risk of potentially fatal, acute liver injury, Tasmar should not be considered as a firstline adjunct therapy to levodopa/benserazide or levodopa/carbidopa (see sections 4.4 and 4.8).

Since Tasmar should be used only in combination with levodopa/benserazide and levodopa/carbidopa, the prescribing information for these levodopa preparations is also applicable to their concomitant use with Tasmar.

4.2 Posology and method of administration

Posology

Paediatric population
Tasmar is not recommended for use in children below the age of 18 due to insufficient data on safety or efficacy. There is no relevant indication for use in children and adolescents.

Elderly
No dose adjustment of Tasmar is recommended for elderly patients.

Hepatic impairment (see section 4.3)
Tasmar is contraindicated for patients with liver disease or increased liver enzymes.

Renal impairment (see section 5.2)
No dose adjustment of Tasmar is recommended for patients with mild or moderate renal impairment

(creatinine clearance of 30 ml/min or greater). Patients with severe renal impairment (creatinine clearance <30 ml/min) should be treated with caution. No information on the tolerability of tolcapone in these populations is available (see section 5.2)

Method of administration

The administration of Tasmar is restricted to prescription and supervision by physicians experienced in the management of advanced Parkinson's disease.

Tasmar is administered orally three times daily.
Tasmar may be taken with or without food (see section 5.2).
Tasmar tablets are film-coated and should be swallowed whole because tolcapone has a bitter taste.

Tasmar can be combined with all pharmaceutical formulations of levodopa/benserazide and levodopa/carbidopa (see also section 4.5).

The first dose of the day of Tasmar should be taken together the first dose of the day of a levodopa preparation, and the subsequent doses should be given approximately 6 and 12 hours later. Tasmar may be taken with or without food (see section 5.2).
The recommended dose of Tasmar is 100 mg three times daily, always as an adjunct to levodopa/benserazide or levodopa/carbidopa therapy. Only in exceptional circumstances, when the anticipated incremental clinical benefit justifies the increased risk of hepatic reactions, should the dose be increased to 200 mg three times daily (see sections 4.4 and 4.8). If substantial clinical benefits are not seen within 3 weeks of the initiation of the treatment (regardless of dose) Tasmar should be discontinued.
The maximum therapeutic dose of 200 mg three times daily should not be exceeded, as there is no evidence of additional efficacy at higher doses.

Liver function should be checked before starting treatment with Tasmar and then monitored every 2 weeks for the first year of therapy, every 4 weeks for the next 6 months and every 8 weeks thereafter. If the dose is increased to 200 mg tid, liver enzyme monitoring should take place before increasing the dose and then be reinitiated following the same sequence of frequencies as above (see sections 4.4 and 4.8).

Tasmar treatment should also be discontinued if ALT (alanine amino transferase) and/or AST (aspartate amino transferase) exceed the upper limit of normal or symptoms or signs suggest the onset of hepatic failure (see section 4.4).

Levodopa adjustments during Tasmar treatment

As Tasmar decreases the breakdown of levodopa in the body, side effects due to increased levodopa concentrations may occur when beginning Tasmar treatment. In clinical trials, more than 70 % of patients required a decrease in their daily levodopa dose if their daily dose of levodopa was >600 mg or if patients had moderate or severe dyskinesias before beginning treatment.

The average reduction in daily levodopa dose was about 30 % in those patients requiring a levodopa dose reduction. When beginning Tasmar, all patients should be informed of the symptoms of excessive levodopa dose and what to do if it occurs.

Levodopa adjustments when Tasmar is discontinued

The following suggestions are based on pharmacological considerations and have not been evaluated in clinical trials. Levodopa dose should not be decreased when Tasmar therapy is being discontinued due to side effects related to too much levodopa. However, when Tasmar therapy is being discontinued for reasons other than too much levodopa, levodopa dose may have to be increased to levels equal to or greater than before initiation of Tasmar therapy, especially if the patient had large decreases in levodopa when starting Tasmar. In all cases, patients should be educated on the symptoms of levodopa under-dose

and what to do if it occurs. Adjustments in levodopa are most likely to be required within 1-2 days of Tasmar discontinuation.

4.3 Contraindications

- Hypersensitivity to tolcapone or any of its other ingredients listed in section 6.1.
- Evidence of liver disease or increased liver enzymes.
- Severe dyskinesia.
- A previous history of Neuroleptic Malignant Syndrome (NMS) Symptom Complex and/or nontraumatic rhabdomyolysis or hyperthermia.
- Phaeochromocytoma.
- Treatment with non-selective mono amino oxidase (MAO) inhibitors.

4.4 Special warnings and precautions for use

Tasmar therapy should only be initiated by physicians experienced in the management of advanced Parkinson's disease, to ensure an appropriate risk-benefit assessment. Tasmar should not be prescribed until there has been a complete informative discussion of the risks with the patient.

Tasmar should be discontinued if substantial clinical benefits are not seen within 3 weeks of the initiation of the treatment regardless of dose.

Liver injury

Because of the risk of rare but potentially fatal acute liver injury, Tasmar is only indicated for use in patients with levodopa-responsive idiopathic Parkinson's disease and motor fluctuations, who failed to respond to or are intolerant of other COMT inhibitors. Periodic monitoring of liver enzymes cannot reliably predict the occurrence of fulminant hepatitis. However, it is generally believed that early detection of medicine-induced hepatic injury along with immediate withdrawal of the suspect medication enhances the likelihood for recovery. Liver injury has most often occurred between 1 month and 6 months after starting treatment with Tasmar. Additionally late onset hepatitis after approximately 18 months of treatment has been reported rarely.
It should also be noted that female patients may have a higher risk of liver injury (see section 4.8).

Before starting treatment: If liver function tests are abnormal or there are signs of impaired liver function, Tasmar should not be prescribed. If Tasmar is to be prescribed, the patient should be informed about the signs and symptoms which may indicate liver injury, and to contact the physician immediately.

During treatment: Liver function should be monitored every 2 weeks for the first year of therapy, every 4 weeks for the next 6 months and every 8 weeks thereafter. If the dose is increased to 200 mg tid, liver enzyme monitoring should take place before increasing the dose and then be re-initiated following the sequence of frequencies as above. Treatment should be immediately discontinued if ALT and/or AST exceed the upper limit of normal or if symptoms or signs suggesting the onset of hepatic failure (persistent nausea, fatigue, lethargy, anorexia, jaundice, dark urine, pruritus, right upper quadrant tenderness) develop.

If treatment is discontinued: Patients who show evidence of acute liver injury while on Tasmar and are withdrawn from the medicinal product may be at increased risk for liver injury if Tasmar is reintroduced. Accordingly, such patients should not be considered for re-treatment.

Neuroleptic Malignant Syndrome (NMS)

In Parkinson`s patients, NMS tends to occur when discontinuing or stopping dopaminergic-enhancing medications. Therefore, if symptoms occur after discontinuing Tasmar, physicians should consider increasing the patient's levodopa dose (see section 4.2).

Isolated cases consistent with NMS have been associated with Tasmar treatment. Symptoms have usually onset during Tasmar treatment or shortly after Tasmar has been discontinued. NMS is characterised by motor symptoms (rigidity, myoclonus and tremor), mental status changes (agitation, confusion, stupor and coma), elevated temperature, autonomic dysfunction (labile blood pressure, tachycardia) and elevated serum creatine phosphokinase (CPK) which may be a consequence of myolysis. A diagnosis of NMS should be considered even if not all the above findings are present. Under such a diagnosis Tasmar should be immediately discontinued and the patient should be followed up closely.

Before starting treatment: To reduce the risk of NMS, Tasmar should not be prescribed for patients with severe dyskinesia or a previous history of NMS including rhabdomyolysis or hyperthermia (see section 4.3). Patients receiving multiple medications with effects on different central nervous system (CNS) pathways (e.g. antidepressants, neuroleptics, anticholinergics) may be at greater risk of developing NMS.

Impulse control disorders

Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments such as Tasmar in association with levodopa. Review of treatment is recommended if such symptoms develop.

Dyskinesia, nausea and other levodopa-associated adverse reactions

Patients may experience an increase in levodopa-associated adverse reactions. Reducing the dose of levodopa (see section 4.2) may often mitigate these adverse reactions.

Diarrhoea

In clinical trials, diarrhoea developed in 16 % and 18 % of patients receiving Tasmar 100 mg tid and 200 mg tid respectively, compared to 8 % of patients receiving placebo. Diarrhoea associated with Tasmar usually began 2 to 4 months after initiation of therapy. Diarrhoea led to withdrawal of 5% and 6% of patients receiving Tasmar 100 mg tid and 200 mg tid respectively, compared to 1 % of patients receiving placebo.

Benserazide interaction

Due to the interaction between high dose benserazide and tolcapone (resulting in increased levels of benserazide), the prescriber should, until more experience has been gained, be observant of doserelated adverse reactions (see section 4.5).

MAO inhibitors

Tasmar should not be given in conjunction with non-selective monoamine oxidase (MAO) inhibitors (e.g. phenelzine and tranylcypromine). The combination of MAO-A and MAO-B inhibitors is equivalent to non-selective MAO-inhibition, therefore they should not both be given concomitantly with Tasmar and levodopa preparations (see also section 4.5). Selective MAO-B inhibitors should not be used at higher than recommended doses (e.g. selegiline 10 mg/day) when co-administered with Tasmar.

Warfarin

Since clinical information is limited regarding the combination of warfarin and tolcapone, coagulation parameters should be monitored when these drugs are co-administered.

Special populations
Patients with severe renal impairment (creatinine clearance <30 ml/min) should be treated with caution. No information on the tolerability of tolcapone in these populations is available (see section 5.2).

Tasmar contains lactose and sodium
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take this medicine.
This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Tasmar, as a COMT inhibitor, is known to increase the bioavailability of the co-administered levodopa. The consequent increase in dopaminergic stimulation can lead to the dopaminergic adverse reactions observed after treatment with COMT inhibitors. The most common of these are increased dyskinesia, nausea, vomiting, abdominal pain, syncope, orthostatic complains, constipation, sleep disorders, somnolence, hallucination.

Levodopa has been associated with somnolence and episodes of sudden sleep onset. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with levodopa. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines (see section 4.7). Furthermore a reduction of levodopa dose or termination of therapy may be considered.

Catechols and other drugs metabolised by catechol-*O*-methyltransferase (COMT)
Tolcapone may influence the pharmacokinetics of drugs metabolised by COMT. No effects were seen on the pharmacokinetics of the COMT substrate carbidopa. An interaction was observed with benserazide, which may lead to increased levels of benserazide and its active metabolite. The magnitude of the effect was dependent on the dose of benserazide. The plasma concentrations of benserazide observed after co-administration of tolcapone and benserazide-25 mg/levodopa were still within the range of values observed with levodopa/benserazide alone. On the other hand, after coadministration of tolcapone and benserazide-50 mg/levodopa the benserazide plasma concentrations could be increased above the levels usually observed with levodopa/benserazide alone. The effect of tolcapone on the pharmacokinetics of other drugs metabolised by COMT such as □-methyldopa, dobutamine, apomorphine, adrenaline and isoprenaline have not been evaluated. The prescriber should be observant of adverse reactions caused by putative increased plasma levels of these drugs when combined with Tasmar.

Effect of tolcapone on the metabolism of other drugs
Due to its affinity for cytochrome *CYP2C9 in vitro,* tolcapone may interfere with drugs whose clearance is dependent on this metabolic pathway, such as tolbutamide and warfarin. In an interaction study, tolcapone did not change the pharmacokinetics of tolbutamide. Therefore, clinically relevant interactions involving cytochrome *CYP2C9* appear unlikely.

Since clinical information is limited regarding the combination of warfarin and tolcapone, coagulation parameters should be monitored when these drugs are co-administered.

Drugs that increase catecholamines
Since tolcapone interferes with the metabolism of catecholamines, interactions with other drugs affecting catecholamine levels are theoretically possible.

When Tasmar was given together with levodopa/carbidopa and desipramine, there was no significant change in blood pressure, pulse rate and plasma concentrations of desipramine. Overall, the frequency of adverse reactions increased slightly. These adverse reactions were predictable based on the known adverse reactions to each of the three drugs individually. Therefore, caution should be exercised when potent noradrenaline uptake inhibitors such as desipramine, maprotiline, or venlafaxine are administered to Parkinson's disease patients being treated with Tasmar and levodopa preparations.

In clinical trials, patients receiving Tasmar/levodopa preparations reported a similar adverse reaction profile independent of whether or not they were also concomitantly administered selegiline (a MAO-B inhibitor).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of tolcapone in pregnant women. Therefore, Tasmar should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding
In animal studies, tolcapone was excreted into maternal milk.

The safety of tolcapone in infants is unknown; therefore, women should not breast-feed during treatment with Tasmar.

Fertility
In rats and rabbits, embryo-foetal toxicity was observed after tolcapone administration (see section 5.3). The potential risk for humans is unknown.

4.7 Effects on ability to drive and use machines

No studies on the effects of Tasmar on the ability to drive and use machines have been performed.
There is no evidence from clinical studies that Tasmar adversely influences a patient's ability to drive and use machines. However patients should be advised that their ability to drive and operate machines may be compromised due to their Parkinson's disease symptoms.

Tasmar, as a COMT inhibitor, is known to increase the bioavailability of the co-administered levodopa. The consequent increase in dopaminergic stimulation can lead to the dopaminergic side effects observed after treatment with COMT inhibitors. Patients being treated with Levodopa and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also section 4.4)

4.8 Undesirable effects

The most commonly observed adverse reactions associated with the use of Tasmar, occurring more frequently than in placebo-treated patients are listed in the table below. However, Tasmar, as a COMT inhibitor, is known to increase the bioavailability of the co-administered levodopa. The consequent increase in dopaminergic stimulation can lead to the dopaminergic side effects observed after treatment with COMT inhibitors. The most common of these are increased dyskinesia, nausea, vomiting, abdominal pain, syncope, orthostatic complains, constipation, sleep disorders, somnolence, hallucination.

The only adverse reaction commonly leading to discontinuation of Tasmar in clinical trials was diarrhoea (see section 4.4).

Very common (≥1/10)
Common (≥1/100 to < 1/10)
Uncommon (≥1/1,000 to < 1/100)
Rare (≥1/10,000 to < 1/1,000)
Very rare (<1/10,000)
Not known (frequency cannot be estimated from the available data)

Experience with Tasmar obtained in parallel placebo-controlled randomised studies in patients with Parkinson's disease is shown in the following table, which lists adverse reactions with a potential relationship to Tasmar.

Summary of potentially Tasmar-related adverse reactions, with crude incidence rates for the phase III placebo-controlled studies:

System organ class	**Incidence**	**Adverse Events**
Infections and infestations	Common	Upper respiratory tract infection
Psychiatric disorders	Very common	Sleep disorder
		Dreaming excessive
		Somnolence
		Confusion
		Hallucination
	Rare	Impulse control disorders* (Libido increased, hypersexuality, pathological gambling, compulsive spending or buying, binge eating, compulsive eating (see section 4.4))
Nervous system disorders	Very common	Dyskinesia
		Dystonia
		Headache
		Dizziness
		Somnolence
		Orthostatic complaints
	Rare	Neuroleptic Malignant Syndrome Symptom Complex (see section 4.4)
	Common	Hypokinesia
		Syncope
Gastrointestinal disorders	Very common	Nausea
		Diarrhoea
	Common	Vomiting
		Constipation
		Xerostomia
		Abdominal pain
		Dyspepsia
Metabolism and nutrition disorders	Very common	Anorexia
Skin and subcutaneous tissue disorders	Common	Sweating increased
Renal and urinary disorders	Common	Urine discoloration

General disorders and administration site conditions	Common	Chest pain
		Influenza like illness
Hepatobiliary disorders	Uncommon	Hepatocellular injury, in rare cases with fatal outcome* (see section 4.4)
Investigations	Common	Increase of alanine aminotransferase (ALT)

**** Adverse reactions for which no frequency could be derived from clinical studies (i.e. where a specific adverse reaction was not observed in clinical trials but was reported post-marketing only) are indicated by an asterisk (*), and the frequency category has been calculated according to EU Guideline.***

Increase of alanine aminotransferase
Increases to more than three times the upper limit of normal (ULN) in alanine aminotransferase (ALT) occurred in 1 % of patients receiving Tasmar 100 mg three times daily, and 3 % of patients at 200 mg three times daily. Increases were approximately two times more likely in females. The increases usually appeared within 6 to 12 weeks of starting treatment, and were not associated with any clinical signs or symptoms. In about half the cases, transaminase levels returned spontaneously to baseline values whilst patients continued Tasmar treatment. For the remainder, when treatment was discontinued, transaminase levels returned to pre-treatment levels.

Hepatocellular injury
Rare cases of severe hepatocellular injury resulting in death have been reported during marketed use (see section 4.4).

Neuroleptic Malignant Syndrome Symptom Complex
Isolated cases of patients with symptoms suggestive of Neuroleptic Malignant Syndrome Symptom Complex (see section 4.4) have been reported following reduction or discontinuation of Tasmar and following introduction of Tasmar when this was accompanied by a significant reduction in other concomitant dopaminergic medications. In addition, rhabdomyolysis, secondary to NMS or severe dyskinesia, has been observed.

Urine discolouration
Tolcapone and its metabolites are yellow and can cause a harmless intensification in the colour of the patient's urine.

Impulse control disorders
Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments such as Tasmar in association with Levodopa (see section 4.4 `special warnings and precautions for use´).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

4.9 Overdose

Isolated cases of either accidental or intentional overdose with tolcapone tablets have been reported. However clinical circumstances of these cases were so diverse, that no general conclusions can be drawn from the cases.

The highest dose of tolcapone administered to humans was 800 mg three times daily, with and without levodopa coadministration, in a one week study in healthy elderly volunteers. The peak plasma concentrations of tolcapone at this dose were on average 30 µg/ml (compared to 3 and 6 µg/ml with 100 mg tid and 200 mg tid of tolcapone respectively). Nausea, vomiting and dizziness were observed, particularly in combination with levodopa.

Management of overdose
Hospitalisation is advised. General supportive care is indicated. Based on the physicochemical properties of the compound, hemodialysis is unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Anti-Parkinson drugs, other dopaminergic agents, ATC code: NO4BX01

Mechanism of action
Tolcapone is an orally active, selective and reversible catechol-*O*-methyltransferase (COMT) inhibitor. Administered concomitantly with levodopa and an aromatic amino acid decarboxylase inhibitor (AADC-I), it leads to more stable plasma levels of levodopa by reducing metabolism of levodopa to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD).

High levels of plasma 3-OMD have been associated with poor response to levodopa in Parkinson's disease patients. Tolcapone markedly reduces the formation of 3-OMD.

Pharmacodynamic effects
Studies in healthy volunteers have shown that tolcapone reversibly inhibits human erythrocyte COMT activity after oral administration. The inhibition is closely related to plasma tolcapone concentration. With 200 mg tolcapone, maximum inhibition of erythrocyte COMT activity is, on average, greater than 80 %. During dosing with Tasmar 200 mg three times daily, erythrocyte COMT inhibition at trough is 30 % to 45 %, with no development of tolerance.

Transient elevation above pretreatment levels of erythrocyte COMT activity was observed after withdrawal of tolcapone. However, a study in Parkinson's patients confirmed that after treatment discontinuation there was no significant change in levodopa pharmacokinetics or in patient response to levodopa compared to pretreatment levels.

When Tasmar is administered together with levodopa, it increases the relative bioavailability (AUC) of levodopa approximately twofold. This is due to a decrease in clearance in L-dopa resulting in a prolongation of the terminal elimination half-life ($t_{1/2}$) of levodopa. In general, the average peak levodopa plasma concentration (C_{max}) and the time of its occurrence (t_{max}) were unaffected. The onset of effect occurs after the first administration. Studies in healthy volunteers and parkinsonian patients have confirmed that the maximum effect occurs with 100 – 200 mg tolcapone. Plasma levels of 3OMD were markedly and dose-dependently decreased by tolcapone when given with levodopa/AADC-I (aromatic amino acid decarboxylase - inhibitor) (benserazide or carbidopa).

Tolcapone's effect on levodopa pharmacokinetics is similar with all pharmaceutical formulations of levodopa/benserazide and levodopa/carbidopa; it is independent of levodopa dose, levodopa/AADC-I (benserazide or carbidopa) ratio and the use of sustained-release formulations.

Clinical Efficacy and Safety
Double blind placebo controlled clinical studies have shown a significant reduction of approximately 20 % to 30 % in OFF time and a similar increase in ON time, accompanied by reduced severity of

symptoms in fluctuating patients receiving Tasmar. Investigator's global assessments of efficacy also showed significant improvement.

A double-blind trial compared Tasmar with entacapone in Parkinson's disease patients who had at least three hours of OFF time per day while receiving optimised levodopa therapy. The primary outcome was the proportion of patients with a 1 or more hour increase in ON time (see Table 1).

Tab. 1 Primary and Secondary Outcome of double-blind Trial

	Entacapone N=75	Tolcapone N=75	p value	95 % CI
Primary Outcome				
Number (proportion) with ≥1 hour ON time response	32 (43 %)	40 (53 %)	p=0.191	-5.2;26.6
Secondary Outcome				
Number (proportion) with moderate or marked improvement	19 (25 %)	29 (39 %)	p=0.080	-1.4;28.1
Number (proportion) improved on both primary and secondary outcome	13 (17 %)	24 (32 %)	NA	NA

5.2 Pharmacokinetic properties

In the therapeutic range, tolcapone pharmacokinetics are linear and independent of levodopa/AADC-I (benserazide or carbidopa) coadministration.

Absorption

Tolcapone is rapidly absorbed with a t_{max} of approximately 2 hours. The absolute bioavailability of an oral administration is around 65 %. Tolcapone does not accumulate with three times daily dosing of 100 or 200 mg. At these doses, C_{max} is approximately 3 and 6 µg/ml, respectively. Food delays and decreases the absorption of tolcapone, but the relative bioavailability of a dose of tolcapone taken with a meal is still 80 % to 90 %.

Distribution

The volume of distribution (V_{ss}) of tolcapone is small (9 l). Tolcapone does not distribute widely into tissues due to its high plasma protein binding (>99.9 %). *In vitro* experiments have shown that tolcapone binds mainly to serum albumin.

Biotransformation/Elimination

Tolcapone is almost completely metabolised prior to excretion, with only a very small amount (0.5 % of dose) found unchanged in urine. The main metabolic pathway of tolcapone is conjugation to its inactive glucuronide. In addition, the compound is methylated by COMT to 3-O-methyl-tolcapone and metabolised by cytochromes *P*450 3A4 and *P*450 2A6 to a primary alcohol (hydroxylation of the methyl group), which is subsequently oxidised to the carboxylic acid. The reduction to a putative amine, as well as the subsequent *N*-acetylation, occurs to a minor extent. After oral administration, 60 % of drug-related material is excreted into urine and 40 % into faeces.

Tolcapone is a low-extraction-ratio drug (extraction ratio = 0.15), with a moderate systemic clearance of about 7 L/h. The $t_{1/2}$ of tolcapone is approximately 2 hours.

Hepatic impairment

Because of the risk of liver injury observed during post-marketing use, Tasmar is contraindicated in patients with liver disease or increased liver enzymes. A study in patients with hepatic impairment has shown that moderate non-cirrhotic liver disease had no impact on the pharmacokinetics of tolcapone.

However, in patients with moderate cirrhotic liver disease, clearance of unbound tolcapone was reduced by almost 50 %. This reduction may increase the average concentration of unbound drug twofold.

Renal impairment
The pharmacokinetics of tolcapone have not been investigated in patients with renal impairment. However, the relationship of renal function and tolcapone pharmacokinetics has been investigated using population pharmacokinetics during clinical trials. The data of more than 400 patients have confirmed that over a wide range of creatinine clearance values (30-130 mL/min) the pharmacokinetics of tolcapone are unaffected by renal function. This could be explained by the fact that only a negligible amount of unchanged tolcapone is excreted in the urine, and the main metabolite, tolcapone-glucuronide, is excreted both in urine and in bile (faeces).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

Carcinogenesis, mutagenesis
3 % and 5 % of rats in the mid- and high- dose groups, respectively, of the 24-month carcinogenicity study were shown to have renal epithelial tumours (adenomas or carcinomas). However, no evidence of renal toxicity was observed in the low-dose group. An increased incidence of uterine adenocarcinomas was seen in the high-dose group of the rat carcinogenicity study. There were no similar renal findings in the mouse or dogs carcinogenicity studies.

Mutagenesis
Tolcapone was shown not to be genotoxic in a complete series of mutagenicity studies.

Toxicity to reproduction
Tolcapone, when administered alone, was shown to be neither teratogenic nor to have any relevant effects on fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Calcium hydrogen phosphate
Microcrystalline cellulose Povidone
K30
Sodium starch glycolate
Lactose monohydrate
Talc
Magnesium stearate

Film-coat
Hydroxypropyl methylcellulose
Talc
Yellow iron oxide
Ethyl cellulose
Titanium dioxide (E171)
Triacetin
Sodium lauril sulfate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PE/PVDC blisters (pack sizes of 30 or 60 film-coated tablets).
Amber glass bottles without desiccant (pack sizes of 30, 60, 100 or 200 film-coated tablets).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15 DUBLIN
Ireland

8. MARKETING AUTHORISATION NUMBERS

EU/1/97/044/001-3, 7, 8, 10

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 August 1997
Renewal of the authorisation: 31 August 2004
Date of latest renewal: 21 July 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Tasmar 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg tolcapone.

Excipients with known effect
Each film-coated tablet contains 15 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Orange yellow to brown yellow, hexagonal, biconvex, film-coated tablet. “TASMAR” and “200” are engraved on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tasmar is indicated in combination with levodopa/benserazide or levodopa/carbidopa for use in patients with levodopa-responsive idiopathic Parkinson’s disease and motor fluctuations, who failed to respond to or are intolerant of other catechol-*O*-methyltransferase (COMT) inhibitors (see section 5.1). Because of the risk of potentially fatal, acute liver injury, Tasmar should not be considered as a firstline adjunct therapy to levodopa/benserazide or levodopa/carbidopa (see sections 4.4 and 4.8).

Since Tasmar should be used only in combination with levodopa/benserazide and levodopa/carbidopa, the prescribing information for these levodopa preparations is also applicable to their concomitant use with Tasmar.

4.2 Posology and method of administration

Posology

Paediatric population
Tasmar is not recommended for use in children below the age of 18 due to insufficient data on safety or efficacy. There is no relevant indication for use in children and adolescents.

Elderly
No dose adjustment of Tasmar is recommended for elderly patients.

Hepatic impairment (see section 4.3)
Tasmar is contraindicated for patients with liver disease or increased liver enzymes.

Renal impairment (see section 5.2)
No dose adjustment of Tasmar is recommended for patients with mild or moderate renal impairment

(creatinine clearance of 30 ml/min or greater). Patients with severe renal impairment (creatinine clearance <30 ml/min) should be treated with caution. No information on the tolerability of tolcapone in these populations is available (see section 5.2)

Method of administration

The administration of Tasmar is restricted to prescription and supervision by physicians experienced in the management of advanced Parkinson's disease.

Tasmar is administered orally three times daily.
Tasmar may be taken with or without food (see section 5.2).
Tasmar tablets are film-coated and should be swallowed whole because tolcapone has a bitter taste.

Tasmar can be combined with all pharmaceutical formulations of levodopa/benserazide and levodopa/carbidopa (see also section 4.5).

The first dose of the day of Tasmar should be taken together the first dose of the day of a levodopa preparation, and the subsequent doses should be given approximately 6 and 12 hours later. Tasmar may be taken with or without food (see section 5.2).
The recommended dose of Tasmar is 100 mg three times daily, always as an adjunct to levodopa/benserazide or levodopa/carbidopa therapy. Only in exceptional circumstances, when the anticipated incremental clinical benefit justifies the increased risk of hepatic reactions, should the dose be increased to 200 mg three times daily (see sections 4.4 and 4.8). If substantial clinical benefits are not seen within 3 weeks of the initiation of the treatment (regardless of dose) Tasmar should be discontinued.
The maximum therapeutic dose of 200 mg three times daily should not be exceeded, as there is no evidence of additional efficacy at higher doses.

Liver function should be checked before starting treatment with Tasmar and then monitored every 2 weeks for the first year of therapy, every 4 weeks for the next 6 months and every 8 weeks thereafter. If the dose is increased to 200 mg tid, liver enzyme monitoring should take place before increasing the dose and then be reinitiated following the same sequence of frequencies as above (see sections 4.4 and 4.8).

Tasmar treatment should also be discontinued if ALT (alanine amino transferase) and/or AST (aspartate amino transferase) exceed the upper limit of normal or symptoms or signs suggest the onset of hepatic failure (see section 4.4).

Levodopa adjustments during Tasmar treatment

As Tasmar decreases the breakdown of levodopa in the body, side effects due to increased levodopa concentrations may occur when beginning Tasmar treatment. In clinical trials, more than 70 % of patients required a decrease in their daily levodopa dose if their daily dose of levodopa was >600 mg or if patients had moderate or severe dyskinesias before beginning treatment.

The average reduction in daily levodopa dose was about 30 % in those patients requiring a levodopa dose reduction. When beginning Tasmar, all patients should be informed of the symptoms of excessive levodopa dose and what to do if it occurs.

Levodopa adjustments when Tasmar is discontinued

The following suggestions are based on pharmacological considerations and have not been evaluated in clinical trials. Levodopa dose should not be decreased when Tasmar therapy is being discontinued due to side effects related to too much levodopa. However, when Tasmar therapy is being discontinued for reasons other than too much levodopa, levodopa dose may have to be increased to levels equal to or greater than before initiation of Tasmar therapy, especially if the patient had large decreases in levodopa when starting Tasmar. In all cases, patients should be educated on the symptoms of levodopa under-dose

and what to do if it occurs. Adjustments in levodopa are most likely to be required within 1-2 days of Tasmar discontinuation.

4.3 Contraindications

- Hypersensitivity to tolcapone or any of its other ingredients listed in section 6.1.
- Evidence of liver disease or increased liver enzymes.
- Severe dyskinesia.
- A previous history of Neuroleptic Malignant Syndrome (NMS) Symptom Complex and/or nontraumatic rhabdomyolysis or hyperthermia.
- Phaeochromocytoma.
- Treatment with non-selective mono amino oxidase (MAO) inhibitors.

4.4 Special warnings and precautions for use

Tasmar therapy should only be initiated by physicians experienced in the management of advanced Parkinson's disease, to ensure an appropriate risk-benefit assessment. Tasmar should not be prescribed until there has been a complete informative discussion of the risks with the patient.

Tasmar should be discontinued if substantial clinical benefits are not seen within 3 weeks of the initiation of the treatment regardless of dose.

Liver injury

Because of the risk of rare but potentially fatal acute liver injury, Tasmar is only indicated for use in patients with levodopa-responsive idiopathic Parkinson's disease and motor fluctuations, who failed to respond to or are intolerant of other COMT inhibitors. Periodic monitoring of liver enzymes cannot reliably predict the occurrence of fulminant hepatitis. However, it is generally believed that early detection of medicine-induced hepatic injury along with immediate withdrawal of the suspect medication enhances the likelihood for recovery. Liver injury has most often occurred between 1 month and 6 months after starting treatment with Tasmar. Additionally late onset hepatitis after approximately 18 months of treatment has been reported rarely.
It should also be noted that female patients may have a higher risk of liver injury (see section 4.8).

Before starting treatment: If liver function tests are abnormal or there are signs of impaired liver function, Tasmar should not be prescribed. If Tasmar is to be prescribed, the patient should be informed about the signs and symptoms which may indicate liver injury, and to contact the physician immediately.

During treatment: Liver function should be monitored every 2 weeks for the first year of therapy, every 4 weeks for the next 6 months and every 8 weeks thereafter. If the dose is increased to 200 mg tid, liver enzyme monitoring should take place before increasing the dose and then be re-initiated following the sequence of frequencies as above. Treatment should be immediately discontinued if ALT and/or AST exceed the upper limit of normal or if symptoms or signs suggesting the onset of hepatic failure (persistent nausea, fatigue, lethargy, anorexia, jaundice, dark urine, pruritus, right upper quadrant tenderness) develop.

If treatment is discontinued: Patients who show evidence of acute liver injury while on Tasmar and are withdrawn from the medicinal product may be at increased risk for liver injury if Tasmar is reintroduced. Accordingly, such patients should not be considered for re-treatment.

Neuroleptic Malignant Syndrome (NMS)
In Parkinson`s patients, NMS tends to occur when discontinuing or stopping dopaminergic-enhancing medications. Therefore, if symptoms occur after discontinuing Tasmar, physicians should consider increasing the patient's levodopa dose (see section 4.2).

Isolated cases consistent with NMS have been associated with Tasmar treatment. Symptoms have usually onset during Tasmar treatment or shortly after Tasmar has been discontinued. NMS is characterised by motor symptoms (rigidity, myoclonus and tremor), mental status changes (agitation, confusion, stupor and coma), elevated temperature, autonomic dysfunction (labile blood pressure, tachycardia) and elevated serum creatine phosphokinase (CPK) which may be a consequence of myolysis. A diagnosis of NMS should be considered even if not all the above findings are present. Under such a diagnosis Tasmar should be immediately discontinued and the patient should be followed up closely.

Before starting treatment: To reduce the risk of NMS, Tasmar should not be prescribed for patients with severe dyskinesia or a previous history of NMS including rhabdomyolysis or hyperthermia (see section 4.3). Patients receiving multiple medications with effects on different central nervous system (CNS) pathways (e.g. antidepressants, neuroleptics, anticholinergics) may be at greater risk of developing NMS.

Impulse control disorders
Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments such as Tasmar in association with levodopa. Review of treatment is recommended if such symptoms develop.

Dyskinesia, nausea and other levodopa-associated adverse reactions
Patients may experience an increase in levodopa-associated adverse reactions. Reducing the dose of levodopa (see section 4.2) may often mitigate these adverse reactions.

Diarrhoea
In clinical trials, diarrhoea developed in 16 % and 18 % of patients receiving Tasmar 100 mg tid and 200 mg tid respectively, compared to 8 % of patients receiving placebo. Diarrhoea associated with Tasmar usually began 2 to 4 months after initiation of therapy. Diarrhoea led to withdrawal of 5% and 6% of patients receiving Tasmar 100 mg tid and 200 mg tid respectively, compared to 1 % of patients receiving placebo.

Benserazide interaction
Due to the interaction between high dose benserazide and tolcapone (resulting in increased levels of benserazide), the prescriber should, until more experience has been gained, be observant of doserelated adverse reactions (see section 4.5).

MAO inhibitors
Tasmar should not be given in conjunction with non-selective monoamine oxidase (MAO) inhibitors (e.g. phenelzine and tranylcypromine). The combination of MAO-A and MAO-B inhibitors is equivalent to non-selective MAO-inhibition, therefore they should not both be given concomitantly with Tasmar and levodopa preparations (see also section 4.5). Selective MAO-B inhibitors should not be used at higher than recommended doses (e.g. selegiline 10 mg/day) when co-administered with Tasmar.

Warfarin
Since clinical information is limited regarding the combination of warfarin and tolcapone, coagulation parameters should be monitored when these drugs are co-administered.

Special populations
Patients with severe renal impairment (creatinine clearance <30 ml/min) should be treated with caution. No information on the tolerability of tolcapone in these populations is available (see section 5.2).

Tasmar contains lactose and sodium
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take this medicine.
This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Tasmar, as a COMT inhibitor, is known to increase the bioavailability of the co-administered levodopa. The consequent increase in dopaminergic stimulation can lead to the dopaminergic adverse reactions observed after treatment with COMT inhibitors. The most common of these are increased dyskinesia, nausea, vomiting, abdominal pain, syncope, orthostatic complains, constipation, sleep disorders, somnolence, hallucination.

Levodopa has been associated with somnolence and episodes of sudden sleep onset. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with levodopa. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines (see section 4.7). Furthermore a reduction of levodopa dose or termination of therapy may be considered.

Catechols and other drugs metabolised by catechol-*O*-methyltransferase (COMT)
Tolcapone may influence the pharmacokinetics of drugs metabolised by COMT. No effects were seen on the pharmacokinetics of the COMT substrate carbidopa. An interaction was observed with benserazide, which may lead to increased levels of benserazide and its active metabolite. The magnitude of the effect was dependent on the dose of benserazide. The plasma concentrations of benserazide observed after co-administration of tolcapone and benserazide-25 mg/levodopa were still within the range of values observed with levodopa/benserazide alone. On the other hand, after coadministration of tolcapone and benserazide-50 mg/levodopa the benserazide plasma concentrations could be increased above the levels usually observed with levodopa/benserazide alone. The effect of tolcapone on the pharmacokinetics of other drugs metabolised by COMT such as □-methyldopa, dobutamine, apomorphine, adrenaline and isoprenaline have not been evaluated. The prescriber should be observant of adverse reactions caused by putative increased plasma levels of these drugs when combined with Tasmar.

Effect of tolcapone on the metabolism of other drugs
Due to its affinity for cytochrome *CYP2C9 in vitro,* tolcapone may interfere with drugs whose clearance is dependent on this metabolic pathway, such as tolbutamide and warfarin. In an interaction study, tolcapone did not change the pharmacokinetics of tolbutamide. Therefore, clinically relevant interactions involving cytochrome *CYP2C9* appear unlikely.

Since clinical information is limited regarding the combination of warfarin and tolcapone, coagulation parameters should be monitored when these drugs are co-administered.

Drugs that increase catecholamines
Since tolcapone interferes with the metabolism of catecholamines, interactions with other drugs affecting catecholamine levels are theoretically possible.

When Tasmar was given together with levodopa/carbidopa and desipramine, there was no significant change in blood pressure, pulse rate and plasma concentrations of desipramine. Overall, the frequency of adverse reactions increased slightly. These adverse reactions were predictable based on the known adverse reactions to each of the three drugs individually. Therefore, caution should be exercised when potent noradrenaline uptake inhibitors such as desipramine, maprotiline, or venlafaxine are administered to Parkinson's disease patients being treated with Tasmar and levodopa preparations.

In clinical trials, patients receiving Tasmar/levodopa preparations reported a similar adverse reaction profile independent of whether or not they were also concomitantly administered selegiline (a MAO-B inhibitor).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of tolcapone in pregnant women. Therefore, Tasmar should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breast-feeding
In animal studies, tolcapone was excreted into maternal milk.

The safety of tolcapone in infants is unknown; therefore, women should not breast-feed during treatment with Tasmar.

Fertility
In rats and rabbits, embryo-foetal toxicity was observed after tolcapone administration (see section 5.3). The potential risk for humans is unknown.

4.7 Effects on ability to drive and use machines

No studies on the effects of Tasmar on the ability to drive and use machines have been performed. There is no evidence from clinical studies that Tasmar adversely influences a patient's ability to drive and use machines. However patients should be advised that their ability to drive and operate machines may be compromised due to their Parkinson's disease symptoms.

Tasmar, as a COMT inhibitor, is known to increase the bioavailability of the co-administered levodopa. The consequent increase in dopaminergic stimulation can lead to the dopaminergic side effects observed after treatment with COMT inhibitors. Patients being treated with Levodopa and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also section 4.4)

4.8 Undesirable effects

The most commonly observed adverse reactions associated with the use of Tasmar, occurring more frequently than in placebo-treated patients are listed in the table below. However, Tasmar, as a COMT inhibitor, is known to increase the bioavailability of the co-administered levodopa. The consequent increase in dopaminergic stimulation can lead to the dopaminergic side effects observed after treatment with COMT inhibitors. The most common of these are increased dyskinesia, nausea, vomiting, abdominal pain, syncope, orthostatic complains, constipation, sleep disorders, somnolence, hallucination.

The only adverse reaction commonly leading to discontinuation of Tasmar in clinical trials was diarrhoea (see section 4.4).

Very common (≥1/10)
Common (≥1/100 to < 1/10)
Uncommon (≥1/1,000 to < 1/100)
Rare (≥1/10,000 to < 1/1,000)
Very rare (<1/10,000)
Not known (frequency cannot be estimated from the available data)

Experience with Tasmar obtained in parallel placebo-controlled randomised studies in patients with Parkinson's disease is shown in the following table, which lists adverse reactions with a potential relationship to Tasmar.

Summary of potentially Tasmar-related adverse reactions, with crude incidence rates for the phase III placebo-controlled studies:

System organ class	**Incidence**	**Adverse Events**
Infections and infestations	Common	Upper respiratory tract infection
Psychiatric disorders	Very common	Sleep disorder
		Dreaming excessive
		Somnolence
		Confusion
		Hallucination
	Rare	Impulse control disorders* (Libido increased, hypersexuality, pathological gambling, compulsive spending or buying, binge eating, compulsive eating (see section 4.4))
Nervous system disorders	Very common	Dyskinesia
		Dystonia
		Headache
		Dizziness
		Somnolence
		Orthostatic complaints
	Rare	Neuroleptic Malignant Syndrome Symptom Complex (see section 4.4)
	Common	Hypokinesia
		Syncope
Gastrointestinal disorders	Very common	Nausea
		Diarrhoea
	Common	Vomiting
		Constipation
		Xerostomia
		Abdominal pain
		Dyspepsia
Metabolism and nutrition disorders	Very common	Anorexia

Skin and subcutaneous tissue disorders	Common	Sweating increased
Renal and urinary disorders	Common	Urine discoloration
General disorders and administration site conditions	Common	Chest pain
		Influenza like illness
Hepatobiliary disorders	Uncommon	Hepatocellular injury, in rare cases with fatal outcome* (see section 4.4)
Investigations	Common	Increase of alanine aminotransferase (ALT)

**** Adverse reactions for which no frequency could be derived from clinical studies (i.e. where a specific adverse reaction was not observed in clinical trials but was reported post-marketing only) are indicated by an asterisk (*), and the frequency category has been calculated according to EU Guideline.***

Increase of alanine aminotransferase

Increases to more than three times the upper limit of normal (ULN) in alanine aminotransferase (ALT) occurred in 1 % of patients receiving Tasmar 100 mg three times daily, and 3 % of patients at 200 mg three times daily. Increases were approximately two times more likely in females. The increases usually appeared within 6 to 12 weeks of starting treatment, and were not associated with any clinical signs or symptoms. In about half the cases, transaminase levels returned spontaneously to baseline values whilst patients continued Tasmar treatment. For the remainder, when treatment was discontinued, transaminase levels returned to pre-treatment levels.

Hepatocellular injury

Rare cases of severe hepatocellular injury resulting in death have been reported during marketed use (see section 4.4).

Neuroleptic Malignant Syndrome Symptom Complex

Isolated cases of patients with symptoms suggestive of Neuroleptic Malignant Syndrome Symptom Complex (see section 4.4) have been reported following reduction or discontinuation of Tasmar and following introduction of Tasmar when this was accompanied by a significant reduction in other concomitant dopaminergic medications. In addition, rhabdomyolysis, secondary to NMS or severe dyskinesia, has been observed.

Urine discolouration

Tolcapone and its metabolites are yellow and can cause a harmless intensification in the colour of the patient's urine.

Impulse control disorders

Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists and/or other dopaminergic treatments such as Tasmar in association with Levodopa (see section 4.4 `special warnings and precautions for use´).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

4.9 Overdose

Isolated cases of either accidental or intentional overdose with tolcapone tablets have been reported. However clinical circumstances of these cases were so diverse, that no general conclusions can be drawn from the cases.

The highest dose of tolcapone administered to humans was 800 mg three times daily, with and without levodopa coadministration, in a one week study in healthy elderly volunteers. The peak plasma concentrations of tolcapone at this dose were on average 30 µg/ml (compared to 3 and 6 µg/ml with 100 mg tid and 200 mg tid of tolcapone respectively). Nausea, vomiting and dizziness were observed, particularly in combination with levodopa.

Management of overdose
Hospitalisation is advised. General supportive care is indicated. Based on the physicochemical properties of the compound, hemodialysis is unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Anti-Parkinson drugs, other dopaminergic agents, ATC code: NO4BX01

Mechanism of action
Tolcapone is an orally active, selective and reversible catechol-*O*-methyltransferase (COMT) inhibitor. Administered concomitantly with levodopa and an aromatic amino acid decarboxylase inhibitor (AADC-I), it leads to more stable plasma levels of levodopa by reducing metabolism of levodopa to 3-methoxy-4-hydroxy-L-phenylalanine (3-OMD).

High levels of plasma 3-OMD have been associated with poor response to levodopa in Parkinson's disease patients. Tolcapone markedly reduces the formation of 3-OMD.

Pharmacodynamic effects
Studies in healthy volunteers have shown that tolcapone reversibly inhibits human erythrocyte COMT activity after oral administration. The inhibition is closely related to plasma tolcapone concentration. With 200 mg tolcapone, maximum inhibition of erythrocyte COMT activity is, on average, greater than 80 %. During dosing with Tasmar 200 mg three times daily, erythrocyte COMT inhibition at trough is 30 % to 45 %, with no development of tolerance.

Transient elevation above pretreatment levels of erythrocyte COMT activity was observed after withdrawal of tolcapone. However, a study in Parkinson's patients confirmed that after treatment discontinuation there was no significant change in levodopa pharmacokinetics or in patient response to levodopa compared to pretreatment levels.

When Tasmar is administered together with levodopa, it increases the relative bioavailability (AUC) of levodopa approximately twofold. This is due to a decrease in clearance in L-dopa resulting in a prolongation of the terminal elimination half-life ($t_{1/2}$) of levodopa. In general, the average peak levodopa plasma concentration (C_{max}) and the time of its occurrence (t_{max}) were unaffected. The onset of effect occurs after the first administration. Studies in healthy volunteers and parkinsonian patients have confirmed that the maximum effect occurs with 100 – 200 mg tolcapone. Plasma levels of 3OMD were markedly and dose-dependently decreased by tolcapone when given with levodopa/AADC-I (aromatic amino acid decarboxylase - inhibitor) (benserazide or carbidopa).

Tolcapone's effect on levodopa pharmacokinetics is similar with all pharmaceutical formulations of levodopa/benserazide and levodopa/carbidopa; it is independent of levodopa dose, levodopa/AADC-I (benserazide or carbidopa) ratio and the use of sustained-release formulations.

Clinical Efficacy and Safety

Double blind placebo controlled clinical studies have shown a significant reduction of approximately 20 % to 30 % in OFF time and a similar increase in ON time, accompanied by reduced severity of symptoms in fluctuating patients receiving Tasmar. Investigator's global assessments of efficacy also showed significant improvement.

A double-blind trial compared Tasmar with entacapone in Parkinson's disease patients who had at least three hours of OFF time per day while receiving optimised levodopa therapy. The primary outcome was the proportion of patients with a 1 or more hour increase in ON time (see Table 1).

Tab. 1 Primary and Secondary Outcome of double-blind Trial

	Entacapone N=75	Tolcapone N=75	p value	95 % CI
Primary Outcome				
Number (proportion) with ≥1 hour ON time response	32 (43 %)	40 (53 %)	p=0.191	-5.2;26.6
Secondary Outcome				
Number (proportion) with moderate or marked improvement	19 (25 %)	29 (39 %)	p=0.080	-1.4;28.1
Number (proportion) improved on both primary and secondary outcome	13 (17 %)	24 (32 %)	NA	NA

5.2 Pharmacokinetic properties

In the therapeutic range, tolcapone pharmacokinetics are linear and independent of levodopa/AADC-I (benserazide or carbidopa) coadministration.

Absorption

Tolcapone is rapidly absorbed with a t_{max} of approximately 2 hours. The absolute bioavailability of an oral administration is around 65 %. Tolcapone does not accumulate with three times daily dosing of 100 or 200 mg. At these doses, C_{max} is approximately 3 and 6 µg/ml, respectively. Food delays and decreases the absorption of tolcapone, but the relative bioavailability of a dose of tolcapone taken with a meal is still 80 % to 90 %.

Distribution

The volume of distribution (V_{ss}) of tolcapone is small (9 l). Tolcapone does not distribute widely into tissues due to its high plasma protein binding (>99.9 %). *In vitro* experiments have shown that tolcapone binds mainly to serum albumin.

Biotransformation/Elimination

Tolcapone is almost completely metabolised prior to excretion, with only a very small amount (0.5 % of dose) found unchanged in urine. The main metabolic pathway of tolcapone is conjugation to its inactive glucuronide. In addition, the compound is methylated by COMT to 3-O-methyl-tolcapone and metabolised by cytochromes *P*450 3A4 and *P*450 2A6 to a primary alcohol (hydroxylation of the methyl group), which is subsequently oxidised to the carboxylic acid. The reduction to a putative amine, as well as the subsequent *N*-acetylation, occurs to a minor extent. After oral administration, 60 % of drug-related material is excreted into urine and 40 % into faeces.

Tolcapone is a low-extraction-ratio drug (extraction ratio = 0.15), with a moderate systemic clearance of about 7 L/h. The $t_{1/2}$ of tolcapone is approximately 2 hours.

Hepatic impairment
Because of the risk of liver injury observed during post-marketing use, Tasmar is contraindicated in patients with liver disease or increased liver enzymes. A study in patients with hepatic impairment has shown that moderate non-cirrhotic liver disease had no impact on the pharmacokinetics of tolcapone. However, in patients with moderate cirrhotic liver disease, clearance of unbound tolcapone was reduced by almost 50 %. This reduction may increase the average concentration of unbound drug twofold.

Renal impairment
The pharmacokinetics of tolcapone have not been investigated in patients with renal impairment. However, the relationship of renal function and tolcapone pharmacokinetics has been investigated using population pharmacokinetics during clinical trials. The data of more than 400 patients have confirmed that over a wide range of creatinine clearance values (30-130 mL/min) the pharmacokinetics of tolcapone are unaffected by renal function. This could be explained by the fact that only a negligible amount of unchanged tolcapone is excreted in the urine, and the main metabolite, tolcapone-glucuronide, is excreted both in urine and in bile (faeces).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

Carcinogenesis, mutagenesis
3 % and 5 % of rats in the mid- and high- dose groups, respectively, of the 24-month carcinogenicity study were shown to have renal epithelial tumours (adenomas or carcinomas). However, no evidence of renal toxicity was observed in the low-dose group. An increased incidence of uterine adenocarcinomas was seen in the high-dose group of the rat carcinogenicity study. There were no similar renal findings in the mouse or dogs carcinogenicity studies.
Mutagenesis
Tolcapone was shown not to be genotoxic in a complete series of mutagenicity studies.

Toxicity to reproduction
Tolcapone, when administered alone, was shown to be neither teratogenic nor to have any relevant effects on fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Calcium hydrogen phosphate
Microcrystalline cellulose Povidone
K30
Sodium starch glycolate
Lactose monohydrate
Talc
Magnesium stearate

Film-coat
Hydroxypropyl methylcellulose
Talc
Yellow iron oxide
Ethyl cellulose
Titanium dioxide (E171)
Triacetin
Sodium lauril sulfate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PE/PVDC blisters (pack sizes of 30 or 60 film-coated tablets).
Amber glass bottles without desiccant (pack sizes of 100 film-coated tablets).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15 DUBLIN
Ireland

8. MARKETING AUTHORISATION NUMBERS

EU/1/97/044/004-6

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 August 1997
Renewal of the authorisation: 31 August 2004
Date of latest renewal: 21 July 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

ICN Polfa Rzeszów S.A.
ul. Przemysłowa 2
35-105 Rzeszów
Poland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The marketing authorisation holder (MAH) shall submit PSURs for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

This medicine has additional risk minimisation measures for the following risks: Serious hepatic events and Neuroleptic malignant-like syndrome (NMS).
The additional risk minimization measures consist of: Patient diary to record liver test values and dates. In addition, it provides information to patients and caregivers on the medical conditions of hepatic injury as well as neuroleptic malignant-like syndrome.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Bottle Carton and Label

1. NAME OF THE MEDICINAL PRODUCT

Tasmar 100 mg film-coated tablets tolcapone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg tolcapone.

3. LIST OF EXCIPIENTS

Also contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets
60 film-coated tablets
100 film-coated tablets
200 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. For oral use.
The tablets should be swallowed whole. Do not break or crush tablet.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/97/044/007 30 tablets
EU/1/97/044/008 60 tablets
EU/1/97/044/003 100 tablets
EU/1/97/044/0010 200 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tasmar 100 mg (only applicable for the outer packaging)

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Blister Carton

1. NAME OF THE MEDICINAL PRODUCT

Tasmar 100 mg film-coated tablets tolcapone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 100 mg tolcapone.

3. LIST OF EXCIPIENTS

Also contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. For oral use.
The tablets should be swallowed whole. Do not break or crush tablet.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/97/044/001 30 tablets
EU/1/97/044/002 60 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tasmar 100 mg (only applicable for the outer packaging)

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Tasmar 100 mg film-coated tablets tolcapone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Bottle Carton and Label

1. NAME OF THE MEDICINAL PRODUCT

Tasmar 200 mg film-coated tablets tolcapone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 mg tolcapone.

3. LIST OF EXCIPIENTS

Also contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. For oral use.
The tablets should be swallowed whole. Do not break or crush tablet.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/97/044/006 100 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tasmar 200 mg (only applicable for the outer packaging)

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Blister Carton

1. NAME OF THE MEDICINAL PRODUCT

Tasmar 200 mg film-coated tablets tolcapone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 mg tolcapone.

3. LIST OF EXCIPIENTS

Also contains lactose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets
60 film-coated tablets

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Read the package leaflet before use. For oral use.
The tablets should be swallowed whole. Do not break or crush tablet.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

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7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited
Damastown Industrial Park
Mulhuddart
Dublin 15
DUBLIN
Ireland

12. MARKETING AUTHORISATION NUMBER

EU/1/97/044/004 30 tablets
EU/1/97/044/005 60 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tasmar 200 mg (only applicable for the outer packaging)

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Tasmar 200 mg film-coated tablets tolcapone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Viatris Healthcare Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Tasmar 100 mg film-coated tablets tolcapone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Tasmar is and what it is used for

For the treatment of Parkinson's disease, Tasmar is used together with the medicinal product levodopa (as levodopa/benserazide or levodopa/carbidopa).

Tasmar is used when all other alternative medicines cannot stabilise your Parkinson's disease.

For the treatment of your Parkinson's disease you already take levodopa.

A natural protein (enzyme) in your body, the (COMT) Catechol-*O*-methyltransferase breaks down the levodopa. Tasmar blocks this enzyme and thus slows the breakdown of levodopa. This means when it is taken together with levodopa (as levodopa/benserazide or levodopa/carbidopa) you should have an improvement in the symptoms of your Parkinson's disease.

2. What you need to know before you take Tasmar

Do not take Tasmar:
- if you have liver disease or increased liver enzymes
- if you have severe involuntary movement (dyskinesia)
- if you have a previous history of severe symptoms of muscle stiffening, fever or mental confusion (Neuroleptic Malignant Syndrome (NMS) Symptom Complex) and/or if you have damage of skeletal muscle tissue (non-traumatic rhabdomyolysis) or fever (hyperthermia)
- if you are hypersensitive (allergic) to the active substance tolcapone or to any of the other ingredients of Tasmar
- if you have a special type of tumour in the adrenal medulla (Phaeochromocytoma)
- if you take a certain medication to treat depression and anxiety, called non-selective mono amino oxidase (MAO) inhibitors

Warnings and precautions

Talk to your doctor or pharmacist before taking Tasmar.

You should not start taking Tasmar until your doctor

- has described the risks of treatment with Tasmar
- has explained the measures necessary to minimise those risks
- has answered any questions you may have
- if you are pregnant or intend to become pregnant. Your doctor will discuss the risks and benefits of taking Tasmar during pregnancy. The effects of Tasmar have not been studied in infants. You should not breast-feed your infant during treatment with Tasmar.

Tell your doctor if you or your family/carer notices you are developing urges or cravings to behave in ways that are unusual for you or you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These behaviours are called impulse control disorders and can include addictive gambling, excessive eating or spending, an abnormally high sex drive or a preoccupation with an increase in sexual thoughts or feelings. Your doctor may need to review your treatments.

You should only receive Tasmar if your Parkinson's disease is not adequately controlled by the use of other therapies.

In addition, your doctor will stop Tasmar treatment if after 3 weeks you do not improve enough to justify the risks of continuing treatment.

Liver Injury
Tasmar may cause rare but potentially fatal liver injury. Liver injury has occurred most often after 1 month and before 6 months. It should also be noted that female patients may have a higher risk of liver injury. Therefore, the following preventive measures have to be considered.

Before beginning treatment:
To reduce the risk of liver injury you should not use Tasmar if
- you have a liver disease
- in case of elevated liver function tests in the blood test done before starting treatment (tests of alanine amino transferase (ALT) and aspartate amino transferase (AST)).

While receiving treatment:
During treatment, blood tests will be done in the following time intervals:
- every 2 weeks during the first 12 months of therapy, - every 4 weeks during the following 6 months of therapy, - every 8 weeks during further treatment.

The treatment will be stopped, if these blood tests become abnormal.

The treatment with Tasmar may sometimes lead to disturbances in the way the liver works. Therefore, you should contact your doctor immediately if you experience symptoms such as nausea, vomiting, pain in your stomach (particularly over the liver in the right upper area), loss of appetite, weakness, fever, darkening of urine, jaundice (yellow skin or eyes) or if you tire more easily.
If you have been already treated with Tasmar and developed acute liver injury during treatment, Tasmar should not be re-introduced again.

NMS (Neuroleptic Malignant Syndrome)
Symptoms of Neuroleptic Malignant Syndrome (NMS) may occur during Tasmar treatment.
The NMS consists of some or all of the following:
- severe muscle stiffness, jerking movements of muscles, arms or legs, and soreness of muscles. Muscle injury can sometimes cause dark urine.
- other important symptoms are high fever and mental confusion.

Rarely, after abruptly reducing or stopping Tasmar or other antiparkinsonian drugs, you may experience severe symptoms of muscle stiffening, fever or mental confusion. If this happens notify your doctor.

The following preventive measures have to be considered.

Before beginning treatment:
To reduce the risk of NMS you should not use Tasmar if your doctor says you have severe involuntary movement (dyskinesia) or a previous illness that may have been NMS.
Inform your doctor about all prescription and non-prescription medications as the risk of NMS may be increased if you are taking some specific medications.

While receiving treatment:
If you develop any symptoms as described above, that you think may be NMS, you should report them to your doctor immediately.
Do not stop Tasmar or any other Parkinson's medications without telling your doctor as this may increase the risk of NMS.

Inform your doctor also:
- if you have any illnesses other than Parkinson's disease
- if you are allergic to other medicines, food and dyes
- if soon after beginning and during treatment with Tasmar you have symptoms which may be caused by levodopa such as involuntary movement (dyskinesia) and nausea.

If you feel unwell, you should contact your doctor because you may need to take less levodopa.

Children and adolescents
Tasmar is not recommended for use in children below the age of 18 due to insufficient data on safety or efficacy. There is no relevant indication for use in children and adolescents.

Other Medicines and Tasmar
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed (non-prescription medicines and herbals).

Please inform your doctor about all other medicines you are taking especially:
- antidepressants
- *alpha*-methyldopa (used to treat increased blood pressure)
- apomorphine (used for Parkinson's disease)
- dobutamine (used for the chronic heart disease)
- adrenaline and isoprenaline (both used for heart attacks)
- anticoagulants of the warfarin type (that prevent blood clotting). In this case your doctor may perform regular blood tests to monitor how easily your blood clots.

If you go to hospital or if you are prescribed a new medicine, you must tell your doctor that you are taking Tasmar.

Tasmar with food and drink and alcohol
Tasmar can be taken with or without food.
Tasmar should be taken with 1 glass of water.

Pregnancy and breast-feeding and fertility
You must tell your doctor if you are pregnant or intend to become pregnant. Your doctor will discuss the risks and benefits of taking Tasmar during pregnancy.

The effects of Tasmar have not been studied in infants. You should not breast-feed your infant during treatment with Tasmar.

Driving and using machines
Since your ability to drive a car or operate machinery may be affected by Parkinson's disease, you should discuss this with your doctor.

Tasmar has an effect on the symptoms of your Parkinson's disease.
Tasmar used with your other Parkinson medicines can cause excessive drowsiness (somnolence) and sudden sleep onset episodes (you may suddenly fall asleep). Therefore you must refrain from driving or operating machines until such recurrent episodes and excessive drowsiness have resolved.

Tasmar contains lactose and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodiumfree'.

3. How to take Tasmar

Always take Tasmar exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure.

Dose and frequency of administration
Your doctor should always begin your treatment with the standard dose of 3 times daily 1 tablet (100 mg (1 tablet)).
If benefits are not seen within 3 weeks of the initiation of the treatment, Tasmar should be discontinued.
To improve efficacy your doctor should only increase the dose to 3 times daily 2 tablets (200 mg three times a day) if the increase in how your Parkinson's disease symptoms are controlled outweighs the expected increase in side effects. The side effects at the higher dose can often be severe and affect your liver. If you do not get better at the higher dose after a total of 3 weeks, your doctor should stop your treatment with Tasmar.

When beginning and during treatment with Tasmar, your dose of levodopa may need to be changed. Your doctor will advise you what to do.

How to take the medication: Swallow
Tasmar with 1 glass of water.
Do not break or crush the tablets.
The first tablet Tasmar is to be taken in the morning together with your other parkinsonian medicine 'levodopa'.
The following doses of Tasmar should be taken 6 and 12 hours later.

Time of day	Dose	Note
Morning	1 film-coated tablet Tasmar	Together with the first daily dose of levodopa
During the day	1 film-coated tablet Tasmar	
Evening	1 film-coated tablet Tasmar	

If you take more Tasmar than you should
Contact your doctor, pharmacist or hospital immediately as you may need urgent medical attention. If another person accidentally takes your medicine, contact a doctor or hospital immediately as he or she may need urgent medical attention.

Symptoms of overdose may include nausea, vomiting, dizziness and breathing difficulties.

If you forget to take Tasmar
Take it as soon as you remember, then continue to take it at the usual times. However, if taking the next dose should be directly ahead, do not make up for the forgotten dose. Do not take a double dose to make up for forgotten individual doses. If you have forgotten several doses, please inform your doctor and follow the advice given to you.

If you stop taking Tasmar
Do not reduce or stop taking your medicine unless your doctor tells you to. Always follow the instructions of your doctor about the duration of the treatment with Tasmar.

4. Possible side effects

Like all medicines, this medicine can have side effects, although not everybody gets them.

The frequency of possible side effects listed below is defined using the following convention:

Very common	may affect more than 1 in 10 people
Common	may affect up to 1 in 10 people
Uncommon	may affect up to 1 in 100 people
Rare	may affect up to 1 in 1,000 people
Very rare	may affect up to 1 in 10,000 people
Not known	frequency cannot be estimated from the available data

Tell your doctor or a pharmacist as soon as possible:
- if you **do not feel well** while you are taking Tasmar
- if you experience symptoms such as **nausea, vomiting, abdominal pain, loss of appetite, weakness, fever, darkening of urine or jaundice** since uncommonly disturbances in the way the liver works, sometimes severe hepatitis was observed,
- if you notice a **darkening of your urine** since this could be a sign of a muscular or liver injury.
  Any other yellow urine discolouring is usually harmless.
- if you develop **persistent or severe diarrhoea**

Soon after beginning and during your treatment with Tasmar, you may have symptoms caused by levodopa such as involuntary movement and nausea. Therefore, if you feel unwell, you should contact your doctor since you may need to have your levodopa dose changed.

Other possible side effects:

Very common:
- involuntary movement (dyskinesia)
- nausea, decreased appetite, diarrhoea
- headache, dizziness - sleep problems, somnolence

- feeling lightheaded while you stand (orthostatic complaints)
- mental confusion and hallucinations
- movement disorder with involuntary muscle spasms or malpositions (dystonia)
- dreaming excessive

Common:
- chest pain
- constipation, dyspepsia, stomach ache, vomiting, dry mouth
- fainting - increased sweating
- influenza-like symptoms
- reduced voluntary and involuntary movement (hypokinesia)
- upper respiratory tract infection
- increase of specific liver enzymes
- urine discoloration

Uncommon:
- liver injury, in rare cases with fatal outcome

Rare:
- severe symptoms of muscle stiffening, fever or mental confusion (Neuroleptic Malignant Syndrome) when antiparkinsonian treatments are abruptly reduced or withdrawn
- impulse control disorders (inability to resist the impulse of an action that could be harmful) This may include:
    - Strong impulse to gamble excessively despite serious personal or family consequences.
    - Altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive.
    - Uncontrolled excessive shopping or spending.
    - Binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than needed to satisfy your hunger).

Tell your doctor if you experience any of these behaviours; they will discuss ways of managing or reducing the symptoms.

Reporting of side effects
If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V*.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tasmar

Keep this medicine out of the sight and reach of children.

Do not use after the expiry date which is stated on the pack.

This medicinal product does not require any special storage conditions.

Do not use Tasmar if you notice that the tablets are damaged.

6. Contents of the pack and other information

What Tasmar contains

- The active substance is tolcapone (100 mg in each film-coated tablet).
- The other ingredients are:
  Tablet core*:* calcium hydrogen phosphate, microcrystalline cellulose, povidone K30, sodium starch glycolate, lactose monohydrate (see Section 2 'Tasmar contains lactose'), talc, magnesium stearate.
  Film-coat*:* hydroxypropyl methylcellulose, talc, yellow iron oxide, ethyl cellulose, titanium dioxide (E171), triacetin, sodium lauril sulfate.

What Tasmar looks like and contents of the pack

Tasmar is a pale to light yellow, oval shaped, film-coated tablet. "TASMAR" and "100" are engraved on one side. Tasmar is supplied as film-coated tablets containing 100 mg tolcapone. It is available in blisters in pack sizes of 30 or 60 tablets and in glass bottles in pack sizes of 30, 60, 100 or 200 filmcoated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Viatris Healthcare Limited Damastown
Industrial Park
Mulhuddart
Dublin 15
DUBLIN
Ireland

Manufacturer

ICN Polfa Rzeszów S.A.
ul. Przemysłowa 2
35-105 Rzeszów
Poland

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in:

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the user
Tasmar 200 mg film-coated tablets tolcapone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Tasmar is and what it is used for
For the treatment of Parkinson's disease, Tasmar is used together with the medicinal product levodopa (as levodopa/benserazide or levodopa/carbidopa).
Tasmar is used when all other alternative medicines cannot stabilise your Parkinson's disease.

For the treatment of your Parkinson's disease you already take levodopa.
A natural protein (enzyme) in your body, the (COMT) Catechol-*O*-methyltransferase breaks down the levodopa. Tasmar blocks this enzyme and thus slows the breakdown of levodopa. This means when it is taken together with levodopa (as levodopa/benserazide or levodopa/carbidopa) you should have an improvement in the symptoms of your Parkinson's disease.

2. What you need to know before you take Tasmar

Do not take Tasmar:
- if you have liver disease or increased liver enzymes
- if you have severe involuntary movement (dyskinesia)
- if you have a previous history of severe symptoms of muscle stiffening, fever or mental confusion (Neuroleptic Malignant Syndrome (NMS) Symptom Complex) and/or if you have damage of skeletal muscle tissue (non-traumatic rhabdomyolysis) or fever (hyperthermia)
- if you are hypersensitive (allergic) to the active substance tolcapone or to any of the other ingredients of Tasmar
- if you have a special type of tumour in the adrenal medulla (Phaeochromocytoma)
- if you take a certain medication to treat depression and anxiety, called non-selective mono amino oxidase (MAO) inhibitors

Warnings and precautions
Talk to your doctor or pharmacist before taking Tasmar.
You should not start taking Tasmar until your doctor

- has described the risks of treatment with Tasmar
- has explained the measures necessary to minimise those risks
- has answered any questions you may have
- if you are pregnant or intend to become pregnant. Your doctor will discuss the risks and benefits of taking Tasmar during pregnancy. The effects of Tasmar have not been studied in infants. You should not breast-feed your infant during treatment with Tasmar.

Tell your doctor if you or your family/carer notices you are developing urges or cravings to behave in ways that are unusual for you or you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These behaviours are called impulse control disorders and can include addictive gambling, excessive eating or spending, an abnormally high sex drive or a preoccupation with an increase in sexual thoughts or feelings. Your doctor may need to review your treatments.

You should only receive Tasmar if your Parkinson's disease is not adequately controlled by the use of other therapies.

In addition, your doctor will stop Tasmar treatment if after 3 weeks you do not improve enough to justify the risks of continuing treatment.

Liver Injury
Tasmar may cause rare but potentially fatal liver injury. Liver injury has occurred most often after 1 month and before 6 months. It should also be noted that female patients may have a higher risk of liver injury. Therefore, the following preventive measures have to be considered.

Before beginning treatment:
To reduce the risk of liver injury you should not use Tasmar if
- you have a liver disease
- in case of elevated liver function tests in the blood test done before starting treatment (tests of alanine amino transferase (ALT) and aspartate amino transferase (AST)).

While receiving treatment:
During treatment, blood tests will be done in the following time intervals:
- every 2 weeks during the first 12 months of therapy,
- every 4 weeks during the following 6 months of therapy,
- every 8 weeks during further treatment.

The treatment will be stopped, if these blood tests become abnormal.

The treatment with Tasmar may sometimes lead to disturbances in the way the liver works. Therefore, you should contact your doctor immediately if you experience symptoms such as nausea, vomiting, pain in your stomach (particularly over the liver in the right upper area), loss of appetite, weakness, fever, darkening of urine, jaundice (yellow skin or eyes) or if you tire more easily.
If you have been already treated with Tasmar and developed acute liver injury during treatment, Tasmar should not be re-introduced again.

NMS (Neuroleptic Malignant Syndrome)
Symptoms of Neuroleptic Malignant Syndrome (NMS) may occur during Tasmar treatment.
The NMS consists of some or all of the following:
- severe muscle stiffness, jerking movements of muscles, arms or legs, and soreness of muscles. Muscle injury can sometimes cause dark urine.
- other important symptoms are high fever and mental confusion.

Rarely, after abruptly reducing or stopping Tasmar or other antiparkinsonian drugs, you may experience severe symptoms of muscle stiffening, fever or mental confusion. If this happens notify your doctor.

The following preventive measures have to be considered.

Before beginning treatment:
To reduce the risk of NMS you should not use Tasmar if your doctor says you have severe involuntary movement (dyskinesia) or a previous illness that may have been NMS.
Inform your doctor about all prescription and non-prescription medications as the risk of NMS may be increased if you are taking some specific medications.

While receiving treatment:
If you develop any symptoms as described above, that you think may be NMS, you should report them to your doctor immediately.
Do not stop Tasmar or any other Parkinson's medications without telling your doctor as this may increase the risk of NMS.

Inform your doctor also:
- if you have any illnesses other than Parkinson's disease
- if you are allergic to other medicines, food and dyes
- if soon after beginning and during treatment with Tasmar you have symptoms which may be caused by levodopa such as involuntary movement (dyskinesia) and nausea.

If you feel unwell, you should contact your doctor because you may need to take less levodopa.

Children and adolescents
Tasmar is not recommended for use in children below the age of 18 due to insufficient data on safety or efficacy. There is no relevant indication for use in children and adolescents.

Other Medicines and Tasmar
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed (non-prescription medicines and herbals).

Please inform your doctor about all other medicines you are taking especially:
- antidepressants
- *alpha*-methyldopa (used to treat increased blood pressure)
- apomorphine (used for Parkinson's disease)
- dobutamine (used for the chronic heart disease)
- adrenaline and isoprenaline (both used for heart attacks)
- anticoagulants of the warfarin type (that prevent blood clotting). In this case your doctor may perform regular blood tests to monitor how easily your blood clots.

If you go to hospital or if you are prescribed a new medicine, you must tell your doctor that you are taking Tasmar.

Tasmar with food and drink and alcohol
Tasmar can be taken with or without food.
Tasmar should be taken with 1 glass of water.

Pregnancy and breast-feeding and fertility
You must tell your doctor if you are pregnant or intend to become pregnant. Your doctor will discuss the risks and benefits of taking Tasmar during pregnancy.

The effects of Tasmar have not been studied in infants. You should not breast-feed your infant during treatment with Tasmar.

Driving and using machines
Since your ability to drive a car or operate machinery may be affected by Parkinson's disease, you should discuss this with your doctor.

Tasmar has an effect on the symptoms of your Parkinson's disease.
Tasmar used with your other Parkinson medicines can cause excessive drowsiness (somnolence) and sudden sleep onset episodes (you may suddenly fall asleep). Therefore you must refrain from driving or operating machines until such recurrent episodes and excessive drowsiness have resolved.

Tasmar contains lactose and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodiumfree'.

3. How to take Tasmar

Always take Tasmar exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure.

Dose and frequency of administration
Your doctor should always begin your treatment with the standard dose of 3 times daily 1 tablet (100 mg (1 tablet)).
If benefits are not seen within 3 weeks of the initiation of the treatment, Tasmar should be discontinued.
To improve efficacy your doctor should only increase the dose to the higher dose (200 mg three times a day) if the increase in how your Parkinson's disease symptoms are controlled outweighs the expected increase in side effects. The side effects at the higher dose can often be severe and affect your liver. If you do not get better at the higher dose after a total of 3 weeks, your doctor should stop your treatment with Tasmar.

When beginning and during treatment with Tasmar, your dose of levodopa may need to be changed. Your doctor will advise you what to do.

How to take the medication: Swallow
Tasmar with 1 glass of water.
Do not break or crush the tablets.
The first tablet Tasmar is to be taken in the morning together with your other parkinsonian medicine 'levodopa'.
The following doses of Tasmar should be taken 6 and 12 hours later.

Time of day	Dose	Note
Morning	1 film-coated tablet Tasmar	Together with the first daily dose of levodopa
During the day	1 film-coated tablet Tasmar	
Evening	1 film-coated tablet Tasmar	

If you take more Tasmar than you should
Contact your doctor, pharmacist or hospital immediately as you may need urgent medical attention. If another person accidentally takes your medicine, contact a doctor or hospital immediately as he or she may need urgent medical attention.

Symptoms of overdose may include nausea, vomiting, dizziness and breathing difficulties.

If you forget to take Tasmar
Take it as soon as you remember, then continue to take it at the usual times. However, if taking the next dose should be directly ahead, do not make up for the forgotten dose. Do not take a double dose to make up for forgotten individual doses. If you have forgotten several doses, please inform your doctor and follow the advice given to you.

If you stop taking Tasmar
Do not reduce or stop taking your medicine unless your doctor tells you to. Always follow the instructions of your doctor about the duration of the treatment with Tasmar.

4. Possible side effects

Like all medicines, this medicine can have side effects, although not everybody gets them.

The frequency of possible side effects listed below is defined using the following convention:

Very common	may affect more than 1 in 10 people
Common	may affect up to 1 in 10 people
Uncommon	may affect up to 1 in 100 people
Rare	may affect up to 1 in 1,000 people
Very rare	may affect up to 1 in 10,000 people
Not known	frequency cannot be estimated from the available data

Tell your doctor or a pharmacist as soon as possible:
- if you **do not feel well** while you are taking Tasmar
- if you experience symptoms such as **nausea, vomiting, abdominal pain, loss of appetite, weakness, fever, darkening of urine or jaundice** since uncommonly disturbances in the way the liver works, sometimes severe hepatitis was observed,
- if you notice a **darkening of your urine** since this could be a sign of a muscular or liver injury.
  Any other yellow urine discolouring is usually harmless.
- if you develop **persistent or severe diarrhoea**

Soon after beginning and during your treatment with Tasmar, you may have symptoms caused by levodopa such as involuntary movement and nausea. Therefore, if you feel unwell, you should contact your doctor since you may need to have your levodopa dose changed.

Other possible side effects:

Very common:
- involuntary movement (dyskinesia)
- nausea, decreased appetite, diarrhoea
- headache, dizziness
- sleep problems, somnolence
- feeling lightheaded while you stand (orthostatic complaints)
- mental confusion and hallucinations
- movement disorder with involuntary muscle spasms or malpositions (dystonia)
- dreaming excessive

Common:
- chest pain
- constipation, dyspepsia, stomach ache, vomiting, dry mouth
- fainting - increased sweating
- influenza-like symptoms
- reduced voluntary and involuntary movement (hypokinesia)
- upper respiratory tract infection
- increase of specific liver enzymes
- urine discoloration
-

Uncommon:
- liver injury, in rare cases with fatal outcome

Rare:
- severe symptoms of muscle stiffening, fever or mental confusion (Neuroleptic Malignant Syndrome) when antiparkinsonian treatments are abruptly reduced or withdrawn
- impulse control disorders (inability to resist the impulse of an action that could be harmful) This may include:
    - o Strong impulse to gamble excessively despite serious personal or family consequences.
    - o Altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive.
    - o Uncontrolled excessive shopping or spending.
    - o Binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than needed to satisfy your hunger).

Tell your doctor if you experience any of these behaviours; they will discuss ways of managing or reducing the symptoms.

Reporting of side effects
If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V*.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tasmar

Keep this medicine out of the sight and reach of children.

Do not use after the expiry date which is stated on the pack.

This medicinal product does not require any special storage conditions.

Do not use Tasmar if you notice that the tablets are damaged.

6. Contents of the pack and other information

What Tasmar contains

- The active substance is tolcapone (200 mg in each film-coated tablet).
- The other ingredients are:
  Tablet core*:* calcium hydrogen phosphate, microcrystalline cellulose, povidone K30, sodium starch glycolate, lactose monohydrate (see Section 2 'Tasmar contains lactose'), talc, magnesium stearate.
  Film-coat*:* hydroxypropyl methylcellulose, talc, yellow iron oxide, ethyl cellulose, titanium dioxide (E171), triacetin, sodium lauril sulfate.

What Tasmar looks like and contents of the pack

Tasmar is an orange yellow to brown yellow, oval shaped, film-coated tablet. "TASMAR" and "200" are engraved on one side. Tasmar is supplied as film-coated tablets containing 200 mg tolcapone. It is available in blisters in pack sizes of 30 or 60 tablets and in glass bottles in pack sizes of 100 filmcoated tablets.

Not all pack sizes may be marketed.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.