

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 tablet contains 7.5 mg lactose
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 first-line 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 patients

No dose adjustment of Tasmar is recommended for elderly patients.

Patients with hepatic impairment (see section 4.3)

Tasmar is contraindicated for patients with liver disease or increased liver enzymes.

Patients with 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 non-traumatic 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 re-introduced. 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 dose-related 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).

Lactose intolerance: Tasmar contains lactose. Patients with hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

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 complaints, 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 co-administration 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 α -methyl dopa, 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 complaints, constipation, sleep disorders, somnolence, hallucination.

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

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$), not known (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

System organ class	Incidence	Adverse Events
		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 Levedopa (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 3-OMD 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 $\mu\text{g/ml}$, 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 *P450 3A4* and *P450 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 two-fold.

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 glycollate

Lactose

Talc

Magnesium stearate.

Film-coat:

Hydroxypropylmethylcellulose

Talc

Yellow iron oxide

Ethylcellulose

Titanium dioxide

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

Tasmar is available in PVC/PE/PVDC blisters (pack sizes of 30 and 60 film-coated tablets) and in amber glass bottles without desiccant (pack sizes of 30, 60,100 and 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

Meda AB

Pipers väg 2A

S-170 09 Solna

Sweden

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 July2014

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 tablet contains 15 mg lactose
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 first-line 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 patients

No dose adjustment of Tasmar is recommended for elderly patients.

Patients with hepatic impairment (see section 4.3)

Tasmar is contraindicated for patients with liver disease or increased liver enzymes.

Patients with 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 non-traumatic 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 re-introduced. 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 dose-related 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).

Lactose intolerance: Tasmar contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose malabsorption should not take this medicine.

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 complaints, 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. Furthermore a reduction of levodopa dose or termination of therapy may be considered (see section 4.7).

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 co-administration 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 α -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 reaction 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 complaints, 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 ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$), not known (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

System organ class	Incidence	Adverse Events
	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 discoloration: 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 Levedopa (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

Mecahnism 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 3-OMD 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 $\mu\text{g/ml}$, 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 *P450 3A4* and *P450 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 two-fold.

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 glycollate
Lactose
Talc
Magnesium stearate.

Film-coat:

Hydroxypropylmethylcellulose,
Talc
Yellow iron oxide
Ethylcellulose
Titanium dioxide

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

Tasmar is available in PVC/PE/PVDC blisters (pack sizes of 30 and 60 film-coated tablets) and in 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

Meda AB
Pipers väg 2A
S-170 09 Solna
Sweden

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
35-959 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**

The marketing authorisation holder shall submit periodic safety update reports 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 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.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Outer Carton and bottle label, 30, 60, 100, 200 film-coated tablets

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

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

Meda AB
Pipers väg 2A
S-170 09 Solna
Sweden

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

Batch

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 carton)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Outer carton for blister packs [30 and 60 film-coated tablets]

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

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

Meda AB
Pipers väg 2A
S-170 09 Solna
Sweden

12. MARKETING AUTHORISATION NUMBER

EU/1/97/044/001 30 tablets

EU/1/97/044/002 60 tablets

13. BATCH NUMBER

Batch

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)

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Tasmar 100 mg film-coated tablets
Tolcapone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Meda AB.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
Outer carton and bottle label, 100 film-coated tablets

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
tolcapone 200 mg

3. LIST OF EXCIPIENTS

Also contains lactose.
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

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

Meda AB
Pipers väg 2A
S-170 09 Solna
Sweden

12. MARKETING AUTHORISATION NUMBER

EU/1/97/044/006 100 tablets

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tasmar 200 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Outer Carton and blister packs, 30 and 60 film-coated tablets

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
tolcapone 200 mg

3. LIST OF EXCIPIENTS

Also contains lactose
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

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

Meda AB
Pipers väg 2A
S-170 09 Solna
Sweden

12. MARKETING AUTHORISATION NUMBER

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

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tasmar 200 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Tasmar 200 mg film-coated tablets
Tolcapone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Meda AB

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
2. What do you need to know before you take Tasmar
3. How to take Tasmar
4. Possible side effects
5. How to store Tasmar
6. Contents of the pack and other information

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 tumor in the adrenal medulla (Pheochromocytoma)
- 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

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

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 '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 missed 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. 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; these 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 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 glycollate, Lactose, Talc, Magnesium stearate.
 - Film-coat: Hydroxypropylmethylcellulose, Talc, Yellow iron oxide, Ethylcellulose, Titanium dioxide, 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 and 60 tablets and in glass bottles in pack sizes of 30, 60, 100 and 200 film-coated tablets.

Not all pack-sizes may be marketed.

Marketing Authorisation Holder and Manufacturer**Marketing Authorisation Holder:**

Meda AB
Pipers väg 2A
S-170 09 Solna
Sweden

Manufacturer:

ICN Polfa Rzeszów S.A.
ul. Przemysłowa 2
35-959 Rzeszów
Poland

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

België/Belgique/Belgien

MEDA Pharma S.A./N.V.
Chaussée de la Hulpe 166/
Terhulpesteenweg 166
B-1170 Brussels
Tél/Tel: +32 2 5 04 08 11

Luxembourg/Luxemburg

MEDA Pharma S.A./N.V.
Chaussée de la Hulpe 166/
Terhulpesteenweg 166
B-1170 Brussels
Belgique/Belgien
Tél/Tel: +32 2 5 04 08 11

България

MEDA Pharmaceuticals Switzerland GmbH
представителство за България
Одрин 71-75
1303 София
Тел: +359 2 4177977

Magyarország

MEDA PHARMA Hungary Kereskedelmi Kft.
H-1139 Budapest
Váci ut 91
Tel.: +36 1 236 3410

Česká republika

MEDA Pharma s.r.o.
Kodaňská 1441/46
CZ 100 00 Praha 10
Tel: +420 234 064 203

Malta

Alfred Gera & Sons Ltd.
10, Triq il-Masġar
Qormi QRM 3217
Tel:+356 21 446 205

Danmark

Meda A/S
Solvang 8
DK-3450 Allerød
Tlf: +45 44 52 88 88

Nederland

MEDA Pharma B.V.
Krijgsman 20
NL-1186 DM Amstelveen
Tel: +31 20 751 65 00

Deutschland

MEDA Pharma GmbH & Co. KG
Benzstraße 1
D-61352 Bad Homburg v.d.H.
Tel: + 49 6172 888 01

Norge

Meda A/S
Askerveien 61
N-1384 Asker
Tlf: +47 66 75 33 00

Eesti

Meda Pharma SIA
Parda tn 4
10151 Tallinn
Tel: +372 62 61 025

Österreich

MEDA Pharma GmbH
Guglgasse 15
A-1110 Wien
Tel: + 43 1 86 390 0

Ελλάδα

MEDA Pharmaceuticals A.E.
Ευρυτανίας 3
Χαλάνδρι, 15231
Τηλ: +30 210 6775690
Fax: +30 210 6775695

España

MEDA Pharma S.L.
Avenida de Castilla, 2
Parque Empresarial San Fernando
Edificio Berlin
E-28830 San Fernando de Henares (Madrid)
Tel: +34 91 669 93 00

France

MEDA Pharma
42 rue Washington
75008 Paris
Tél: +33 1 56 64 10 70

Hrvatska

Medical Intertrade d.o.o.
Dr. Franje Tuđmana 3
10431 Sveta Nedelja
Tel: +385 1 3374 010

Ireland

Meda Health Sales Ireland Ltd.
Unit 34/35, Block A Dunboyne Business Park
Dunboyne
IRL - Co Meath
Tel: +353 1 802 66 24

Ísland

Meda AB
Box 906
S-170 09 Solna
Svíþjóð.
Sími: +46 8 630 1900

Italia

Meda Pharma S.p.A.
Via Felice Casati, 20
20124 Milano
Tel: +39 039 73901

Κύπρος

Χρ.Γ. Παπαλοΐζου Λτδ
Λεωφ. Κιλκίς 35
2234 Λατσιά
Τηλ. +357 22 49 03 05

Polska

Meda Pharmaceuticals Sp.z.o.o.
ul. Domaniewska 39A
02-672 Warszawa
Tel: +48 22 697 7100

Portugal

MEDA Pharma Produtos Farmacêuticos, SA
Rua do Centro Cultural 13
P-1749-066 Lisboa
Tel: +351 21 842 0300

România

MEDA Pharmaceuticals Switzerland GmbH
Reprezentanta Romania
Calea Floreasca 141-143, et4
014467 Bucuresti
Tel.: +40 21 230 90 30

Slovenija

MEDA Pharmaceuticals Switzerland GmbH
Podružnica Ljubljana
Cesta 24. junija 23
SI-1231 Ljubljana
Tel: +386 (0)59 096 951

Slovenská republika

MEDA Pharmaceuticals Switzerland GmbH,
Podružnica Ljubljana
Cesta 24. junija 23
1231 Ljubljana
Tel: +386 (0)59 096 951

Suomi/Finland

Meda Oy
Vaisalantie 4/ Vaisalavägen 4
FI-02130 Espoo/ Esbo
Puh/Tel: +358 20 720 9550

Sverige

Meda AB
Box 906
S-170 09 Solna
Tel: +46 8 630 1900

Latvija

SIA Meda Pharma
Vienibas gatve 109
LV-1058 Riga, Latvia
Tel.: +371 67616137

United Kingdom

Meda Pharmaceuticals Ltd.
Skyway House
Parsonage Road
Takeley
Bishop's Stortford
CM22 6PU - UK
Tel: +44 845 460 0000

Lietuva

SIA Meda Pharma
Veiverių g. 134,
LT-46352 Kaunas, Lithuania
Tel. + 370 37330509

This leaflet was last revised in:

Package leaflet: Information for the user

Tasmar 200 mg film-coated tablets
Tolcapone

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2. What do you need to know before you take Tasmar
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- 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)
- 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 tumor in the adrenal medulla (Pheochromocytoma)
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Warnings and precautions

Talk to your doctor or pharmacist before taking Tasmar.

You should not start taking Tasmar until your doctor

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- has explained the measures necessary to minimise those risks,
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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.

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

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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)).

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During treatment, blood tests will be done in the following time intervals:

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- 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

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

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 ,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 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; these 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 out of the sight and reach of children.

Do not use after the expiry date 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 glycollate, Lactose monohydrate, Talc, Magnesium stearate.
 - Film-coat: Hydroxypropylmethylcellulose, Talc, Yellow iron oxide, Ethylcellulose, Titanium dioxide, 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 and 60 tablets and in glass bottles in pack sizes of 100 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder:

Meda AB
Pipers väg 2A
S-170 09 Solna
Sweden

Manufacturer:

ICN Polfa Rzeszów S.A.
ul. Przemysłowa 2
35-959 Rzeszów
Poland

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

België/Belgique/Belgien

MEDA Pharma S.A./N.V.
Chaussée de la Hulpe 166/
Terhulpesteenweg 166
B-1170 Brussels
Tél/Tel: +32 2 5 04 08 11

Luxembourg/Luxemburg

MEDA Pharma S.A./N.V.
Chaussée de la Hulpe 166/
Terhulpesteenweg 166
B-1170 Brussels
Belgique/Belgien
Tél/Tel: +32 2 5 04 08 11

България

MEDA Pharmaceuticals Switzerland GmbH
представителство за България
Одрин 71-75
1303 София
Тел: +359 2 4177977

Magyarország

MEDA PHARMA Hungary Kereskedelmi Kft.
H-1139 Budapest
Váci ut 91
Tel.: +36 1 236 3410

Česká republika

MEDA Pharma s.r.o.
Kodaňská 1441/46
CZ 100 00 Praha 10
Tel: +420 234 064 203

Malta

Alfred Gera & Sons Ltd.
10, Triq il-Masġar
Qormi QRM 3217
Tel:+356 21 446 205

Danmark

Meda A/S
Solvang 8
DK-3450 Allerød
Tlf: +45 44 52 88 88

Nederland

MEDA Pharma B.V.
Krijgsman 20
NL-1186 DM Amstelveen
Tel: +31 20 751 65 00

Deutschland

MEDA Pharma GmbH & Co. KG
Benzstraße 1
D-61352 Bad Homburg v.d.H.
Tel: + 49 6172 888 01

Norge

Meda A/S
Askerveien 61
N-1384 Asker
Tlf: +47 66 75 33 00

Eesti

Meda Pharma SIA
Parda tn 4
10151 Tallinn
Tel: +372 62 61 025

Österreich

MEDA Pharma GmbH
Guglgasse 15
A-1110 Wien
Tel: + 43 1 86 390 0

Ελλάδα

MEDA Pharmaceuticals A.E.
Ευρυτανίας 3
Χαλάνδρι, 15231
Τηλ: +30 210 6775690
Fax: +30 210 6775695

Polska

Meda Pharmaceuticals Sp.z.o.o.
ul. Domaniewska 39A
02-672 Warszawa
Tel: +48 22 697 7100

España

MEDA Pharma S.L.
Avenida de Castilla, 2
Parque Empresarial San Fernando
Edificio Berlin
E-28830 San Fernando de Henares (Madrid)
Tel: +34 91 669 93 00

France

MEDA Pharma
42 rue Washington
75008 Paris
Tél: +33 (0)1 56 64 10 70

Hrvatska

Medical Intertrade d.o.o.
Dr. Franje Tuđmana 3
10431 Sveta Nedelja
Tel: +385 1 3374 010

Ireland

Meda Health Sales Ireland Ltd.
Unit 34/35, Block A Dunboyne Business Park
Dunboyne
IRL - Co Meath
Tel: +353 1 802 66 24

Ísland

Meda AB
Box 906
S-170 09 Solna
Svíþjóð.
Sími: +46 8 630 1900

Italia

Meda Pharma S.p.A.
Via Felice Casati, 20
20124 Milano
Tel: +39 039 73901

Κύπρος

Χρ.Γ. Παπαλοΐζου Λτδ
Λεωφ. Κιλκίς 35
2234 Λατσιά
Τηλ. +357 22 49 03 05

Latvija

SIA Meda Pharma
Vienibas gatve 109
LV-1058 Riga, Latvia
Tel.: +371 67616137

Portugal

MEDA Pharma Produtos Farmacêuticos, SA
Rua do Centro Cultural 13
P-1749-066 Lisboa
Tel: +351 21 842 0300

România

MEDA Pharmaceuticals Switzerland GmbH
Reprezentanta Romania
Calea Floreasca 141-143, et4
014467 Bucuresti
Tel.: +40 21 230 90 30

Slovenija

MEDA Pharmaceuticals Switzerland GmbH
Podružnica Ljubljana
Cesta 24. junija 23
SI-1231 Ljubljana
Tel: +386 (0)59 096 951

Slovenská republika

MEDA Pharmaceuticals Switzerland GmbH,
Podružnica Ljubljana
Cesta 24. junija 23
1231 Ljubljana
Tel: +386 (0)59 096 951

Suomi/Finland

Meda Oy
Vaisalantie 4/ Vaisalavägen 4
FI-02130 Espoo/ Esbo
Puh/Tel: +358 20 720 9550

Sverige

Meda AB
Box 906
S-170 09 Solna
Tel: +46 8 630 1900

United Kingdom

Meda Pharmaceuticals Ltd.
Skyway House
Parsonage Road
Takeley
Bishop's Stortford
CM22 6PU - UK
Tel: +44 845 460 0000

Lietuva

SIA Meda Pharma

Veiverių g. 134,

LT-46352 Kaunas, Lithuania

Tel. + 370 37330509

This leaflet was last revised in: