

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.
For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tasmar 100 mg is a pale to light yellow, hexagonal, biconvex, film-coated tablet. "TASMAR" and "100" are engraved on one side.

4. CLINICAL PARTICULARS

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.

4.1 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 COMT inhibitors (see 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 4.4 and 4.8). If substantial clinical benefits are not seen within 3 weeks of the initiation of the treatment, Tasmar should be discontinued.

4.2 Posology and method of administration

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

Posology

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

Patients with impaired renal function (see 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 hepatic impairment (see 4.3): Tasmar is contraindicated for patients with liver disease or increased liver enzymes.

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

Children: Tasmar should not be used in children as there are no data available. There is no identified potential use of tolcapone in paediatric patients.

Method of administration

Tasmar is administered orally three times daily. The first dose of the day of Tasmar should be taken together with 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 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 4.5).

4.3 Contraindications

Tasmar is contraindicated in patients with:

- Evidence of liver disease or increased liver enzymes
- Severe dyskinesia
- A previous history of Neuroleptic Malignant Syndrome Symptom Complex (NMS) and /or non-traumatic Rhabdomyolysis or Hyperthermia.
- Hypersensitivity to tolcapone or any of its other ingredients.
- Pheochromocytoma.

4.4 Special warnings and special 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 medication-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 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 drug 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 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 4.3). Patients receiving multiple medications with effects on different CNS pathways (e.g. antidepressants, neuroleptics, anticholinergics) may be at greater risk of developing NMS.

Dyskinesia, nausea and other levodopa-associated adverse reactions: Patients may experience an increase in levodopa-associated adverse reactions. Reducing the dose of levodopa (see 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 events (see 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 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.

Lactose intolerance: Each tablet contains 7.5 mg lactose; this quantity is probably not sufficient to induce symptoms of lactose intolerance.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 5.2).

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 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.

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 dosage or termination of therapy may be considered.

Protein binding: Although tolcapone is highly protein bound, *in vitro* studies have shown that tolcapone did not displace warfarin, tolbutamide, digitoxin and phenytoin from their binding sites at therapeutic concentrations.

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 effects 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.

Tolcapone did not change the pharmacokinetics of desipramine, even though both drugs share glucuronidation as their main metabolic pathway.

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

Tolcapone did not influence the effect of ephedrine, an indirect sympathomimetic, on hemodynamic parameters or plasma catecholamine levels, either at rest or during exercise. Since tolcapone did not alter the tolerability of ephedrine, these drugs can be co-administered.

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 events increased slightly. These adverse events 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 event profile independent of whether or not they were also concomitantly administered selegiline (a MAO-B inhibitor).

4.6 Pregnancy and lactation

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

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.

Lactation: 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.

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 events 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 event commonly leading to discontinuation of Tasmar in clinical trials was diarrhoea (see 4.4).

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.

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

Isolated cases of patients with symptoms suggestive of Neuroleptic Malignant Syndrome Symptom Complex (see 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.

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	Placebo N=298 (%)	100 mg tid Tolcapone N=296 (%)	200 mg tid Tolcapone N=298 (%)
Gastrointestinal disorders	Very common	Nausea	17.8	30.4	34.9
		Anorexia	12.8	18.9	22.8

System organ class	Incidence*	Adverse Events	Placebo N=298 (%)	100 mg tid Tolcapone N=296 (%)	200 mg tid Tolcapone N=298 (%)
		Diarrhoea	7.7	15.5	18.1
	Common	Vomiting	3.7	8.4	9.7
		Constipation	5.0	6.4	8.4
		Xerostomia	2.3	4.7	6.4
		Abdominal pain	2.7	4.7	5.7
		Dyspepsia	1.7	4.1	3.0
General disorders and administration site conditions	Common	Chest pain	1.3	3.4	1.0
Infections and infestations	Common	Upper respiratory tract infection	3.4	4.7	7.4
Nervous system disorders	Very common	Dyskinesia	19.8	41.9	51.3
		Dystonia	17.1	18.6	22.1
		Headache	7.4	9.8	11.4
		Dizziness	9.7	13.2	6.4
	Common	Hypokinesia	0.7	0.7	2.7
Psychiatric disorders	Very common	Sleep disorder	18.1	23.6	24.8
		Excessive dreaming	17.1	21.3	16.4
		Somnolence	13.4	17.9	14.4
		Confusion	8.7	10.5	10.4
		Hallucination	5.4	8.4	10.4
Renal and urinary disorders	Common	Urine discoloration	0.7	2.4	7.4
Respiratory, thoracic and mediastinal disorders	Common	Influenza	1.7	3.0	4.0
Skin and subcutaneous tissue disorders	Common	Sweating increased	2.3	4.4	7.4
Vascular disorders	Very common	Orthostatic complaints	13.8	16.6	16.8
	Common	Syncope	2.7	4.1	5.0

* Very common (>1/10); common (>1/100 <1/10), uncommon (>1/1,000 < 1/100); rare (1/10,000 <1/1,000); very rare (< 1/10,000)

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

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.

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Anti-Parkinson drug, ATC code: NO4BX01

Clinical pharmacology

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 studies

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.

Metabolism/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 (anhydrous)
Microcrystalline cellulose
Polyvidone K30
Sodium starch glycollate
Lactose monohydrate
Talc
Magnesium stearate.

Film-coat:

Methylhydroxypropylcellulose,
Talc
Yellow iron oxide (E 172)
Ethylcellulose
Titanium dioxide (E 171)
Triacetin
Sodium lauryl 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 glass bottles (pack sizes of 30, 60 and 100 film-coated tablets).
Not all pack sizes may be marketed

6.6 Instructions for use and handling and disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Valeant Pharmaceuticals Ltd.
Cedarwood, Chineham Business Park
Crockford Lane
Basingstoke
Hampshire, RG24 8WD

United Kingdom

8. MARKETING AUTHORISATION NUMBERS

Tasmar 100 mg tablets: EU/1/97/044/001-3, 7-8

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 August 1997 / 31 october2004

10. DATE OF REVISION OF THE TEXT