Examination of the dossier for the proprietary medicinal product included for a period of 5 years by Order of 21 March 2006 (Official Gazette of 31 March 2006)

**TASMAR 100 mg, film-coated tablet**  
B/100 (CIP code: 345 466-4)

**Applicant:** MEDA PHARMA

tolcapone  
ATC code: N04BX01

List I  
Medicine with prescription restricted to neurologists.  
Medicine requiring special monitoring during treatment.

**Date of Marketing Authorisation:**
- MA of 27 August 1997 in the indication “Adjunct treatment to standard treatments with levodopa/benserazide or levodopa/carbidopa in patients with Parkinson’s disease and end-of-dose motor fluctuations which cannot be stabilised with these combinations”
- Suspension of the European MA in December 1998 following the occurrence of serious cases of hepatotoxicity and neuroleptic malignant syndrome.
- Lifting of the suspension of MA in April 2004, subject to a restriction of therapeutic indications and new prescribing conditions and monitoring procedures (correction of MA of 22 December 2004)

**Reasons for request:**
- Re-assessment of the IAB in the context of Article 163-12 of the Social Security Code.  
- Request for renewal of inclusion on the list of medicines refundable by National Health Insurance.

Medical, Economic and Public Health Assessment Division
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Tolcapone

1.2. 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. 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.

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.”

1.3. Dosage

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

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.

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. 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 treatment, every 4 weeks for the next 6 months and every 8 weeks thereafter. If the dosage 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. TASMAR treatment should also be discontinued if ALT (alanine amino transferase) and/or AST (aspartate amino transferase) exceed the upper limit of normal or if symptoms or signs suggest the onset of hepatic failure.

Levodopa adjustments during TASMAR treatment:

As TASMAR decreases the breakdown of levodopa in the body, adverse 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 treatment, 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 recommendations 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 adverse 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 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.

Patients with renal impairment:
No dose adjustment of TASMAR is recommended for patients with mild or moderate renal impairment (creatinine clearance of ≥ 30 ml/min). 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.

Patients with hepatic impairment:
TASMAR is contraindicated for patients with liver disease or increased liver enzymes. […]

Method of administration:
TASMAR is administered orally three times daily. TASMAR may be taken with or without food.”

1.4. Special warnings and precautions for use

“TASMAR therapy should only be initiated by physicians experienced in the treatment 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. Regular 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 of recovery. Liver injury has most often occurred between 1 month and 6 months after starting treatment with TASMAR. Additionally late onset hepatitis after 18 months of treatment has been reported rarely. It should also be noted that female patients may have a higher risk of liver injury.

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 treatment, every 4 weeks for the next 6 months and every 8 weeks thereafter. If the dosage 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 of liver injury if TASMAR is re-introduced. Accordingly, such patients should not be considered for re-treatment.” […]
2. REMINDER OF THE COMMITTEE’S OPINIONS AND CONDITIONS OF INCLUSION

Opinion on inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital use
2 November 2005

The actual benefit of TASMAR is low.

As regards the results presented and the alternatives available, TASMAR does not provide any improvement in actual benefit (IAB V) in current management.

3. SIMILAR MEDICINAL PRODUCTS

3.1. ATC Classification (2010)

N  Nervous system
N04 Anti-Parkinson drugs
N04B Dopaminergic agents
N04BX Other dopaminergic agents
N04BX01 Tolcapone

3.2. Medicines in the same therapeutic category

Entacapone
- in free combination with levodopa/DDCI\(^1\) (COMTAN):
  Adjunct treatment to standard treatments with levodopa/benserazide or levodopa/carbidopa in patients with Parkinson’s disease and end-of-dose motor fluctuations who cannot be stabilised with these combinations.
  or
- in fixed combination with entacapone/carbidopa/levodopa (STALEVO):
  Treatment of adult patients with Parkinson’s disease and end-of-dose motor fluctuations who cannot be stabilised with the combination levodopa/DDCI.

3.3. Medicines with a similar therapeutic aim

Proprietary medicinal products with the same therapeutic aim are those indicated in combination with levodopa in the treatment of Parkinson’s disease (dopamine agonists and MAOBIs). Subcutaneous apomorphine is indicated in the second-line treatment of severe fluctuations in the activity of dopa therapy during the disease.

4. ANALYSIS OF AVAILABLE DATA

4.1. Efficacy

The company supplied the results of two open replacement studies and one non-comparative study evaluating the efficacy of the product on a quality of life scale; this last-mentioned study\(^2\) will not be described.

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\(^1\) Dopa-decarboxylase inhibitor

The Canesi prospective non-controlled study\(^3\) was performed in 66 patients regarded as non-responders to entacapone who were treated with tolcapone 100 mg three times a day; in 49 of them the antiparkinsonian treatment consisted of a levodopa/dopamine agonist combination. At 6 months, 11 patients had stopped tolcapone during the first month of treatment (2 patients on account of elevated transaminases). The doses of levodopa were reduced on account of dyskinesia in 35 of the 55 patients followed up. A reduction in daily "off" time (\(\geq 25\%\)) was observed in 36 patients in this descriptive study.

The open study by Ries\(^4\) evaluated the efficacy and tolerance of treatment with tolcapone for 10 weeks as replacement for treatment with a dopamine agonist (pergolide, lisuride or bromocriptine) in patients with Parkinson's disease on L-dopa who were randomised to two groups: discontinuation of the dopamine agonist for 6 days (\(n = 72\)) or for 23 days (\(n = 78\)). A reduction in "off" time, which is of questionable clinical relevance (about 15\%) was observed in this study with a low level of evidence.

### 4.2. Adverse effects

The data from periodic tolerance reports analysed for the period from January 2005 to March 2009 showed a reduction in the risk of hepatotoxicity after the introduction of restricted prescribing conditions and special monitoring procedures.

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<tr>
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<tbody>
<tr>
<td>Estimated number of patients treated</td>
<td>100,000</td>
<td>80,000</td>
<td>43,000</td>
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<tr>
<td>Hepatic adverse events*</td>
<td>156</td>
<td>63</td>
<td>43</td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td>26</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>8</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Death</td>
<td>3</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Risk of the onset of serious hepatotoxicity</td>
<td>1 in 2700</td>
<td>1 in 13,300</td>
<td>1 in 8600</td>
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* including abnormalities of the liver enzymes

A retrospective observational study\(^5\) was performed in 1725 patients treated with tolcapone between January 1999 and January 2001. Measurement of transaminases in 11,883 blood samples showed higher transaminases than normal in 3.9\% of patients, more than twice the normal level in 0.9\% of patients.

### 4.3. Cochrane Review 2010

A Cochrane Review in 2010\(^6\) evaluated the efficacy and tolerance of adjuvant treatment to levodopa therapy in Parkinson's disease patients with motor fluctuations.

The literature search covered in particular the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), MEDLINE, EMBASE, PubMed, LILACS and Web of Science.

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This review included 44 randomised, double-blind controlled studies versus placebo (8436 patients) that evaluated three classes of adjuvant treatment to levodopa therapy (dopamine agonist, COMTI, MAOBI) in Parkinson’s disease patients with motor complications. The mean patient follow-up period was 20 weeks. Patients had been suffering from the disease for an average of 9 years. Analysis of the data confirms that these antiparkinsonian drugs administered as add-ons reduce the “off” time, allow the dose to be reduced and improve motor scores. However, dyskinesia and other adverse effects such as constipation, hallucinations and vomiting are increased. Indirect comparisons of the three classes of antiparkinsonian drugs suggest that symptom control is better with dopamine agonists than with COMTIs and MAOBIs. COMTIs and MAOBIs have comparable efficacy. As regards evidence of a difference between the different medicines, tolcapone seems to be more effective than entacapone. However, since tolcapone has been associated with several cases of fatal hepatotoxicity, in Europe its use is reserved for patients in whom entacapone has failed and is accompanied by obligatory hepatic monitoring.

4.4. Conclusion

In view of the indirect comparison data from the Cochrane Review of 2010, tolcapone seems to be more effective than entacapone. The tolerance data obtained in restricted prescribing conditions and with special supervision procedures confirm the need for rigorous monitoring of patients treated with tolcapone so as to better control the incidence of cases of serious hepatotoxicity.

5. DATA ON USE OF THE MEDICINAL PRODUCT

These proprietary medicinal products are not sufficiently used in general practice to appear in the available prescription panels.

6. TRANSPARENCY COMMITTEE CONCLUSIONS

6.1. Actual benefit

Parkinson’s disease combines resting tremor, rigidity, akinesia or bradykinesia and loss of postural reflexes. These motor disorders are joined, as the disease progresses, by neurovegetative disorders, pain and sensory complaints and mental disorders. Parkinson’s disease usually starts insidiously, develops slowly and progressively and is characterised by progression towards disability and a marked deterioration in quality of life. It is a life-threatening disease.

TASMAR an antiparkinsonian medicine that is intended as symptomatic therapy.

In view of the hepatotoxic risk, the efficacy/adverse effects ratio of TASMAR remains modest.

TASMAR is indicated in patients who have not responded to or have been intolerant of other COMT inhibitors (entacapone).

Public health benefit:

The public health burden of Parkinson’s disease is significant. In the limited subpopulation of Parkinson’s disease patients for whom tolcapone may be indicated, i.e. in whom entacapone has failed, the public health burden is small.

delaying the onset of severe functional limitations in the persons affected is a public health objective (Law of 9 August 2004 on public health policy).

to date, in view of the available data showing the modest efficacy of the medicinal product TASMAR and a rare risk of acute hepatitis, there is no impact of the medicinal product TASMAR at population level in therapeutic use.

Consequently, no public health benefit is contributed by TASMAR.

The actual benefit of TASMAR remains low.
6.2. Therapeutic use\textsuperscript{7-10}

After a phase of good symptom control on levodopa ("honeymoon"), the health of Parkinson’s disease patients will deteriorate through the onset of dopa-induced motor disorders (motor fluctuations and dyskinesia) and signs peculiar to the disease (dysautonomic, cognitive and psychobehavioural disorders) which are in most cases dopa-resistant.

Given the motor complications linked to dopamine treatment, it is necessary to look for medicines that are likely to aggravate the “off” periods and dyskinesia, then to optimise the dopa therapy (splitting of the daily dose, adjustment of administration schedules, prescription of different pharmaceutical forms).

Therapeutic management of these complications may also prompt the combination of other medicines with levodopa:
- dopamine agonist (oral, subcutaneous),
- COMT inhibitor (entacapone, tolcapone indicated in patients who have not responded to or are intolerant of entacapone because of its hepatic toxicity),
- MAOBI (selegiline, rasagiline).

Rehabilitation occupies an important place in the management of Parkinson’s disease patients. Rehabilitation methods, even short-term ones, must be adjusted to the uncertainties and fluctuations of the disease.
Stereotactic surgery is an effective option in the treatment of severe motor disorders in progressive Parkinson’s disease and refractory tremor.

6.3. Target population

The number of patients likely to benefit from TASMAR in the event of intolerance or failure of entacapone cannot be specified. The number of patients at risk annually is estimated at 6000 in Europe (about 400 patients in France).

6.4. Transparency Committee recommendations

The transparency Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance in the indications and at the dosages in the Marketing Authorisation.

4.4.1 Packaging

The product packaging is 100 tablets per bottle. The packaging for 30 days’ treatment in a dosage of 100 mg three times a day (the recommended dose) contains 90 tablets. The dose can be increased to 200 mg three times a day (i.e. 180 tablets a month).

4.4.2 Reimbursement rate: 15%

4.4.3 Exception drug status

The Committee recommends giving TASMAR exception drug status.

\textsuperscript{7} Parkinson’s Disease: diagnostic and therapeutic criteria. Consensus conference - 3 March 2000