Before starting treatment with TASMAR, the physician should determine whether the patient is a candidate for an oral drug treatment for Parkinson’s disease. A careful patient history should be obtained to determine whether the patient is a candidate for an oral drug treatment for Parkinson’s disease.

Because of the risks of potentially fatal acute liver injury, TASMAR should not be used in patients with severe hepatic impairment (Child-Pugh class B or C).

Clinical studies in patients with hepatic impairment have not been carried out.

Because of the risk of liver injury, it is essential that periodic monitoring of liver enzymes should be undertaken during treatment with TASMAR. If signs or symptoms of liver injury occur, treatment with TASMAR should be discontinued immediately.

The liver is a major organ of metabolism and is responsible for detoxification of many drugs and their metabolites. Therefore, it is important to monitor liver function periodically during treatment with TASMAR. If liver function tests are abnormal, treatment with TASMAR should be discontinued immediately.

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Advise patients that they may develop postural (orthostatic) hypotension:

- \( 0.001 \text{ g/kg/day} \) 12 mg tolcapone, 3.6 mg tolcapone tid
- \( 0.001 \text{ g/kg/day} \) 12 mg tolcapone, 10.8 mg tolcapone tid

Any risk observed was due to Parkinson’s disease or other factors, such as the use of tolcapone. The increased risk was observed in both tolcapone and placebo groups. The risk of developing melanoma was higher in patients with Parkinson’s disease than the general population. Whether the increased risk was due to tolcapone or other factors is not clear.

Three cases of pleural effusion, one with pulmonary fibrosis, occurred in patients receiving tolcapone. The pleural effusions were asymptomatic and did not require medical intervention. The development of pleural effusion in these patients was not associated with changes in their tolcapone dosage.

TASMAR therapy should not be initiated if the patient:
- \( \text{SGOT/ALT} \) values greater than 2 times the upper limit of normal
- has a history of liver disease
- is suspected to have a metabolic disorder of liver function
- is taking medications that are substrates for CYP2D6
- has documented renal impairment
- has a history of renal impairment
- has a history of urinary tract diseases or disorders

TASMAR should not be initiated in patients who have two SGPT/ALT or bilirubin values greater than the upper limit of normal. (See BOXED WARNING, and CLINICAL PHARMACOLOGY).

Dyskinesia 20 42 51
Nausea 18 30 35
Dystonia 17 19 22
Diarrhea 8 16 18
Constipation 5 6 8
Xerostomia 2 5 6
Cough 19 29 28
Respiratory System — frequent:
- Dyspnea 2 3 3
- Stiffness 1 2 2
- Arthritis 1 2 1
- Hypokinesia 1 1 3
- Micturition Disorder 1 2 1
- Pain Neck 1 2 2
- Agitation 0 1 1
- Euphoria 0 1 0
- Fever 0 0 1

The threshold for the lethal plasma concentration for tolcapone based on human exposure or greater; no renal tumors were observed at exposures of 1, 6.3 and 13 times the human exposure in male rats and 6.3 and 13 times the human exposure in male mice.

There is no experience from clinical studies regarding the use of TASMAR in patients with hepatic disease.

Consequently, the mean age of patients in tolcapone clinical trials was about 45 years. Whether this estimate is an appropriate basis for extrapolation to a older population is not clear.

PATIENTS UNDERGOING OR UNDER CONSIDERATION FOR LIVER TRANSPLANTATION:

Hospitalization is advised. General supportive measures should be instituted, particularly those aimed at reducing cardiovascular parameters.

Valeant Pharmaceuticals North America LLC

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC in the United States at 1-800-FDA-1088 or www.fda.gov/medwatch.

Clinical studies showed that patients with Parkinson’s disease who exhibited dyskinesia tended to show a decrease in dyskinesia during treatment with tolcapone. However, the frequency of dyskinesia was not reduced to the same extent as the frequency of dystonia. In some patients, dyskinesia increased during tolcapone therapy.

Intake of food or water did not influence the absorption of tolcapone. However, it is recommended that tolcapone be administered at least 1 hour before or 2 hours after meals.

A second subject who received the 500 mg single dose of tolcapone in the ICH S7B study died following the tolcapone administration. Autopsy did not reveal any evidence of drug-related events or events that could have contributed to the death. Post-mortem drug levels were not performed.

During the postmarketing development of tolcapone, three patient deaths have been reported in association with tolcapone therapy. All three patients were receiving tolcapone in combination with levodopa/carbidopa. Two of these cases were reported in the United States. In one case, the patient was a 68 year old female with end stage liver disease and was hospitalized while receiving tolcapone and levodopa/carbidopa. In the second case, the patient was a 75 year old male with a history of advanced Parkinson’s disease and was treated with levodopa/carbidopa, tolcapone and tetrabenazine. The third case was reported in Australia and involved a 57 year old male with a history of advanced Parkinson’s disease. The patient was treated with levodopa/carbidopa and tolcapone. The patient was found dead 6 days after initiation of tolcapone therapy.

Tolcapone is always given concomitantly with levodopa/carbidopa, and should not be used to treat patients who are not known to respond to levodopa or carbidopa (80/20 mg/kg/day). However, patients have been treated with tolcapone alone at doses of 150 mg, 300 mg, and 600 mg/day for periods up to 28 days.

Disulfiram was reported to increase the blood levels and the tissue levels of tolcapone. This effect may be due to inhibition of tolcapone metabolism by disulfiram. However, the effect of disulfiram on the pharmacokinetics of tolcapone was not studied in a formal drug interaction study.

After treatment with tolcapone, tolcapone plasma concentrations decreased more slowly than tolcapone plasma concentrations in patients with normal renal function. However, these differences were not statistically significant.

Four patients who were treated with tolcapone had an episode of acute hepatic failure following the discontinuation of tolcapone therapy. The survival rate of these patients was not known. All four patients were taking tolcapone in combination with levodopa/carbidopa. Two of the four patients were hospitalised at the time of the hepatic failure. One of the patients was treated with levodopa/carbidopa and tolcapone for a period of 4 months. The second patient was treated with levodopa/carbidopa and tolcapone for a period of 12 months. The third patient was treated with levodopa/carbidopa and tolcapone for a period of 3 months. The fourth patient was treated with levodopa/carbidopa and tolcapone for a period of 6 months.

The following is a list of the UK of potentially serious drug interactions:

- The combination of tolcapone and tolbutamide has been shown to result in significant increases in tolbutamide levels.
- Patients should be monitored for adverse events and the dosage of levodopa/carbidopa and tolcapone should be adjusted as necessary.
- Patients who have a history of hepatic impairment should be monitored closely during treatment with tolcapone. The tolcapone dosage should be decreased if the patient develops signs or symptoms of liver dysfunction.
- Patients who have a history of renal impairment should be monitored closely during treatment with tolcapone. The tolcapone dosage should be decreased if the patient develops signs or symptoms of renal dysfunction.
- Patients who have a history of urinary tract disease or disorder should be treated with calcium (see box).

Examination of the relative incidences of adverse events in those patients treated with tolcapone is confounded by the different doses used in the tolcapone clinical trials. However, it is evident from these clinical trials that the frequency and severity of adverse events reported in those patients treated with tolcapone are similar to those reported in those patients treated with levodopa alone.

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A second subject who received the 500 mg single dose of tolcapone in the ICH S7B study died following the tolcapone administration. Autopsy did not reveal any evidence of drug-related events or events that could have contributed to the death. Post-mortem drug levels were not performed.

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- Patients who have a history of urinary tract disease or disorder should be treated with calcium (see box).

Adverse Events:

- Patients who also receive tolcapone should be monitored closely during treatment with tolcapone. The tolcapone dosage should be decreased if the patient develops signs or symptoms of liver dysfunction.
- Patients who also receive tolcapone should be monitored closely during treatment with tolcapone. The tolcapone dosage should be decreased if the patient develops signs or symptoms of renal dysfunction.
- Patients who also receive tolcapone should be monitored closely during treatment with tolcapone. The tolcapone dosage should be decreased if the patient develops signs or symptoms of urinary tract disease or disorder.