Epsom and St. Helier University Hospitals NHS Trust

WORKING IN PARTNERSHIP WITH

NHS

Surrey (East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG & Surrey Heath) North East Hampshire & Farnham CCG and Crawley, Horsham & Mid-Sussex CCG

SHARED CARE PRESCRIBING GUIDELINE

Tolcapone for the Treatment of Idiopathic Parkinson's disease

Prescribing Clinical Network classification: Amber

N.B. The eligibility criteria included here apply to new patients commencing treatment under this guideline & not to existing patients whose treatment was initiated under the previous version. However, monitoring and discontinuation criteria apply to all patients.

NOTES to the GP

Amber drugs: Prescribing to be initiated by a hospital specialist (or if appropriate by a GP with specialist interest) but with the potential to transfer to primary care. The expectation is that these guidelines should provide sufficient information to enable GPs to be confident to take clinical and legal responsibility for prescribing these drugs**.**

The questions below will help you confirm this:

- Is the patient's condition predictable?
- Do you have the relevant knowledge, skills and access to equipment to allow you to monitor treatment as indicated in this shared care prescribing guideline?
- Have you been provided with relevant clinical details including monitoring data?

If you can answer YES to all these questions (after reading this shared care guideline), then it is appropriate for you to accept prescribing responsibility. Sign and return a copy of page 4 to the requesting consultant at the Acute Trust. Until the requesting consultant at the Acute Trust has received a signed copy of page 4 indicating that shared care has been agreed all care (including prescribing) remains with the consultant at the Acute Trust.

If the answer is NO to any of these questions, you should not accept prescribing responsibility. You should write to the consultant outlining your reasons for NOT prescribing. If you do not have the confidence to prescribe, we suggest you discuss this with your local Trust/specialist service, who will be willing to provide training and support. If you still lack the confidence to accept clinical responsibility, you still have the right to decline. Your PCT pharmacist will assist you in making decisions about shared care.

Prescribing unlicensed medicines or medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescriber's professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines.

The patient's best interests are always paramount

The GP has the right to refuse to agree to shared care, in such an event the total clinical responsibility will remain with the consultant

Information
This information sheet does not replace the SPC, which should be read in conjunction with this guidance. Prescribers should also refer to the appropriate paragraph in the current edition of the BNF. Link to the relevant SPC website: www.medicines.org.uk

Indications:
Tolcapone is a catechol-O-methyltransferase (COMT) inhibitor and indicated for use with Levodopa responsive idiopathic Parkinson's disease and motor fluctuations who have failed to respond to the COMT inhibitor, Entacapone.

Tolcapone is indicated for use in combination with levodopa/benserazide or levodopa/carbidopa.

Tolcapone is included in the NICE guidelines for Parkinson's Disease (www.nice.org.uk/CG35) which state, that Tolcapone should only be used after Entacapone has failed in people with later Parkinson's Disease due to lack of efficacy or side effects.

Pharmacology:
Tolcapone has a superior efficacy to Entacapone. It is an orally active selective and reversible catechol-O-methyltransferease inhibitor (COMT). It improves the pharmacokinetic profile of Levodopa and therefore increases the duration of each Levodopa dose by increasing the duration of 'on' and decreasing of 'off' phase. It increases the bioavailability of Levodopa by approximately two fold when given concomitantly with Levodopa and decarboxylase inhibitor.

Dose:
100mg three times a day – always as an adjunct to Levodopa/benserazide or Levodopa/carbidopa.
In exceptional circumstances when the anticipated incremental clinical benefit justifies the increased risk of hepatic reactions, the dose may be increased to 200mg three times a day.
The first dose of the day of tolcapone 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. Tolcapone may be taken with or without food

Cautions;
Avoid abrupt withdrawal.

Special populations: Patients with severe renal impairment (creatinine clearance <30 ml/min) should be treated with caution.

Levodopa adjustments during tolcapone treatment:
As tolcapone decreases the breakdown of levodopa in the body, side effects due to increased levodopa concentrations may occur when beginning tolcapone 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 dyskinesia before beginning treatment.
The average reduction in daily levodopa dose was about 30 % in those patients requiring a levodopa dose reduction.
When beginning tolcapone, all patients should be informed of the symptoms of excessive levodopa dosage and what to do if it occurs.

***Hepatotoxity**:*
Potentially life threatening hepatotoxicity including fulminant hepatitis **twice** as likely in females and during the first 6 months. Late onset liver injury reported.

Contraindications;
Pregnancy and Lactation.

Side effects;
Commonly reported are dopaminergic- dyskinesia, nausea, vomiting, sleep disorder, dystonia, hallucinations and confusion.

Neuroleptic Malignant Syndrome is associated with some isolated cases on treatment with Tolcapone. Symptoms are usually onset during treatment of shortly after discontinuation.

Diarrhoea in 16-18% patients and most common reason for withdrawal.

Increases of 3 x upper limit of normal in alanine aminotransferase (ALT) have occurred in 1% of patients taking Tolcapone 100mg TDS and 3% of patients receiving 200mg TDS. Increases have not been associated with any clinical signs and symptoms. In about half the cases, transaminase levels have returned spontaneously to baseline values whilst patients continued Tolcapone treatment. For the remainder, when treatment has been discontinued, transaminase levels have returned to pre- treatment levels. Late onset hepatitis

Rare cases of severe hepatocellular injury in death have been reported during marketed use.

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 tolcapone in association with levodopa

SIDE EFFECT	**ACTION**
ALT and/or AST exceed the upper limit of normal	Treatment should be immediately withdrawn
Symptoms or signs suggesting the onset of hepatic failure (persistent nausea, fatigue, lethargy, anorexia, jaundice, dark urine, pruritus, and right upper quadrant tenderness) develop.	Treatment should be immediately withdrawn If treatment is discontinued: Patients who show evidence of acute liver injury while on tolcapone and are withdrawn from the medicinal product may be at increased risk for liver injury if tolcapone is re-introduced. Accordingly, such patients should not be considered for retreatment.
Marked rigidity (out of keeping with patient's Parkinson's Disease), altered conscious level, elevated temperature, labile blood pressure, tachycardia	Consider Neuroleptic Malignant Syndrome. Discontinue tolcapone. Check CPK & discuss with specialist

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

Interactions:
Tolcapone, is a COMT inhibitor, known to increase the bioavailability of co-administered levodopa. The consequent increase in dopaminergic stimulation can lead to the dopaminergic side effects. The most common of these are increased dyskinesia, nausea, vomiting, abdominal pain, syncope, orthostatic complaints, constipation, sleep disorders, somnolence, hallucination.

Tolcapone may influence the pharmacokinetics of drugs metabolised by COMT: A dose dependent interaction has been observed with benserazide and its active metabolite when Tolcapone+benserazide-50mg/levodopa are used in combination.

Tolcapone interferes with metabolism of catecholamines.

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.

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

MAO inhibitors: Tolcapone 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 tolcapone and levodopa preparations. Selective MAO-B inhibitors should not be used at higher than recommended doses (e.g. selegiline 10 mg/day) when co-administered with tolcapone

Contraindications

Hypersensitivity to tolcapone or any of its other ingredients

- 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 monoamino oxidase (MAO) inhibitors

Criteria for Use

RESPONSIBILITIES and ROLES

Specialist responsibilities
1. Diagnosis of Parkinson's Disease and assessment of suitability of patient for Tolcapone treatment 2. Discuss the aims, benefits and side effects of treatment with the patient as well as their role 3. Explain to the patient their treatment plan including the dosing schedule. 4. Prior to initiation, test and monitor the patient's liver function tests every 2 weeks during the first 3 months of treatment. 5. To initiate therapy by prescribing for a minimum of 3 months 6. Response is seen in first 2 to 3 weeks thus patients not responding will have tolcapone stopped by consultant 7. Monitor and evaluate response to tolcapone therapy, including adverse drug reactions, with the patient and continue/discontinue treatment in line with agreed treatment plan 8. Discuss the possibility of shared care with the patient and ensure they understand the plan for their subsequent treatment 9. Supply GP with summary of patient review (including anticipated length of treatment) and a copy of the shared care guidelines recommending that a shared care arrangement is initiated. 10. Advise GP if treatment is to discontinue at any point. 11. Inform GP if patient does not attend planned follow-up appointment. **12. If the dose is increased to 200 mg three times daily, liver enzyme monitoring should take place before increasing the dose and then be reinitiated following the sequence of frequencies as above.**
General Practitioner responsibilities
1 Subsequent prescribing of Tolcapone at the dose recommended once the patient is stable and after the initial 3 months of treatment. 2 Ensure shared care protocol is accepted, signed and reply to the specialist as soon as practically possible 3 Ensure patient/guardian is fully informed of treatment and side effects. 4 Seek specialist advice if signs/symptoms change/appear. 5 To carry out the following monitoring and take the appropriate action, in the side effects table on page 3 ➢ Liver enzyme monitoring should be checked every 2 weeks of therapy for the first year of therapy, then every 4 weeks for the next 6 months, then every 8 weeks thereafter ➢ **If the dose is increased to 200 mg three times daily, liver enzyme monitoring should take place before increasing the dose and then be reinitiated following the sequence of frequencies as above, when treatment was first initiated.** ➢ Treatment should be discontinued if ALT and/or AST exceed the upper limit of normal or if symptoms of signs suggest the onset of hepatic failure. 6 Stop treatment if diarrhoea is experienced. 7 Stop the treatment immediately if the Parkinson's disease specialist nurse has checked the results and informs the GP to discontinue treatment. 8 Inform specialist of adverse effects and discontinuation of treatment. 9 Report adverse results to MHRA
Patient's / Carer's role
1 Ask the specialist or GP for information, if he or she does not have a clear understanding of the treatment. 2 Share any concerns in relation to treatment with Tolcapone 3 Tell the specialist or GP of any other medication being taken, including over-the-counter products. 4 Read the patient information leaflet included with your medication and report any side effects or concerns you have to the specialist or GP or any member of the health care team.

BACK-UP ADVICE AND SUPPORT

Contact details	**Specialist**	**Telephone No.**	**Email address:**
Specialist:	Dr P Hart Dr D Paviour Dr S Wilson Dr M Htut	020 8296 8066 or 01372 735 735 x6750	paul.hart@esth.nhs.uk dominic.paviour@esth.nhs.uk stephen.wilson@esth.nhs.uk min.htut@esth.nhs.uk

Hospital Pharmacy:	Epsom Hospital St Helier Hospital	01372 735735 ext 6073 020 8296 2466	

AUDIT / SURVEY (to be carried out by specialist clinic
Agreement for transfer of prescribing to GP

Patient details / address:

Name……..

Address……..
……..
……..

DOB…….

Hospital No…….

Drug name and dose:

The following tests, investigations have been carried out:

List any relevant tests:

Date initiated: …….

At the last patient review the drug appeared to be effectively controlling symptoms/ providing benefit:
Yes / No

The patients has now been stabilised on a dose of: ……...

I will arrange to review this patient regularly. Date of next clinic appointment: …….

Consultant: Address: Contact Number	**Agreement to shared care, to be signed by GP and Consultant.** **Consultant Signature:** **……..** **Date:**
GP: Address: Contact Number	**GP Signature:** **……** **Date:**
Main Carer: Contact Number:	**If shared care is agreed and GP has signed above please return a copy of this page to the requesting consultant or alternatively fax to:** **Acute Trust please insert appropriate Fax Number**:
Key worker if appropriate:	

Contact Number:		