Shared Care Guidelines for Tolcapone (Tasmar®) in Parkinson's Disease

For use in (clinical areas):	Neurology and primary care
For use by (staff groups):	Consultant Neurologists and General Practitioners
For use for (patients):	Patients with levodopa-responsive idiopathic Parkinson's disease and motor fluctuations, who have failed to respond to or are intolerant of Entacapone
Document owner:	Pharmacy
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Introduction
Tolcapone is a catechol-*O*-methyltransferase (COMT) inhibitor. It is licensed for use in combination with levodopa/benserazide or levodopa/carbidopa for use in patients with levodopa-responsive idiopathic Parkinson's disease and motor fluctuations, who have failed to respond to or are intolerant of other COMT inhibitors.

Shared Care
A shared care protocol is used to facilitate the sharing of care and transfer of prescribing. This would usually take place once the patient's condition is stable; the patient is demonstrably benefiting from the treatment and is free from any significant side effects. GPs should only take on the prescribing when they are confident in the use of the drug, in the context of the protocol. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

Indication for Therapy
Within Milton Keynes, Tolcapone will be the second-line COMT inhibitor adjunct therapy to co-beneldopa or co-careldopa for use in patients with levodopa-responsive idiopathic Parkinson's disease and motor fluctuations, who failed to respond to or are intolerant of the first-line COMT inhibitor Entacapone.

Preparations Available
Tolcapone is available as 100mg film coated tablets

Shared care responsibilities and roles

Aspects of Care for which the Consultant is responsible

1. Confirm diagnosis. Perform LFT baseline tests and assess suitability for tolcapone treatment.
2. Obtain patient's agreement to proposed shared care arrangement.
3. Counsel patient;
   a. Discuss benefits and side effects of tolcapone treatment with the patient, particularly liver toxicity.
   b. Ensure patient understands the dosing regime and which warning symptoms to report.
   c. Advise patient of signs of excessive levodopa dosage and what action to take.
   d. Provide written information and a dose and monitoring record for the patient/carer;
   e. Liaise with Parkinson's Disease Nurse Specialist (PDNS).
4. Initiate and stabilise treatment with tolcapone. Arrange and monitor LFTs 2-weekly for the first two months.
5. Advise the GP by standard letter of the diagnosis and proposed treatment, and invite the GP to share care.
6. Recommend dose of tolcapone and any concomitant medication to the GP.
7. Advise GP of monitoring tests needed, test intervals and date of review appointment.
8. Ensure compliance with NICE Clinical Guideline 35. Parkinson's disease: diagnosis and management in primary and secondary care, NICE CG35.
9. Periodically review patient's condition and medication need at agreed intervals.
10. Communicate promptly with the GP in writing when to adjust the dose, stop or change treatment. Supervise discontinuation of tolcapone therapy if lack of substantial clinical benefit, signs of hepatotoxicity or neuroleptic malignant syndrome.
11. Have a mechanism in place to receive rapid referral of a patient in the event of deteriorating clinical condition.
12. Ensure that clear backup arrangements exist for GPs to obtain advice and support.
13. Report adverse events to the GP. The MHRA asks that all suspected reactions (including those considered not to be serious) are reported through the Yellow Card Scheme even if it is not certain that the drug has caused it.

Aspects of Care for which the General Practitioner is responsible

1. Reply to the request for shared care as soon as practicable.
2. Prescribe tolcapone at the dose recommended, and any concomitant medication as directed.
3. Comply with terms of Local Enhanced Service Contract and NICE Clinical Guideline 35. Parkinson's disease: diagnosis and management in primary and secondary care, NICE CG35.
4. Arrange testing and monitoring of LFTs every two weeks for the first year from the third month of treatment, every 4 weeks for the next six months, and thereafter every 8 weeks.
5. Monitor the patient's overall health and well-being when patient presents and at intervals agreed with specialist.
6. Consult promptly with the specialist when: test results are abnormal, or patient defaults from blood test appointments or patient reports side-effects;
7. Adjust the dose/stop/change treatment as advised by the specialist.
8. Stop treatment immediately if an urgent need arises and consult with specialist.
9. Check compatibility with other or new concomitant medication (eg computer-generated warnings).
10. Periodically remind patient of which warning symptoms to report.
11. Report adverse events to the consultant specialist. The MHRA asks that all suspected reactions (including those considered not to be serious) are reported through the Yellow Card Scheme even if it is not certain that the drug has caused it.

Patient's Role

1. Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
2. Share any concerns about treatment with tolcapone with the specialist, GP or PDNS.
3. Inform specialist or GP of any other medication being taken, including over-the-counter products or herbal remedies.
4. Do not miss any blood tests or other appointments without first consulting the GP or specialist.
5. Report any suspected pregnancy of the patient to the GP or specialist.
6. Consume alcohol only in moderate amounts unless the specialist has advised that alcohol should be avoided.
7. Report any adverse effects or warning symptoms particularly those suggestive of liver failure, to the specialist or GP. The MHRA asks that all suspected reactions (including those considered not to be serious) are reported through the Yellow Card Scheme even if it is not certain that the drug has caused it.

Clinical monitoring

Parameters to monitor	Baseline	Every 2 weeks		Every 4 weeks		Every 8 weeks
		Weeks 0 to 8	Weeks 9 to 52	Weeks 53 to 78	Weeks 79 to 104	Week 105 & thereafter
LFTs*	CONS	CONS	GP	GP	GP	GP

CONS – Consultant; GP – General Practitioner;

* **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 TDS, liver enzyme monitoring should take place before increasing the dose and then be reinitiated following the sequence of frequencies as above..

The Hospital Consultant will:	• arrange testing and monitoring of LFTs every two weeks for the first two months or until stabilised; • resume care and re-initiate monitoring protocol if the dose of tolcapone is increased to 200mg tds, conduct regular patient review. • inform patients to report somnolescence, signs of liver failure, or any persistent side-effects to the GP without delay. When beginning tolcapone, all patients should be informed of the symptoms of excessive levodopa dosage and what to do if it occurs.
The GP will:	• arrange testing and monitoring of LFTs every two weeks for the first year from the third month of treatment, every 4 weeks for the next six months, and thereafter every 8 weeks. • counsel patient, when s/he presents, for potentially serious or persistent side-effects; these should always be discussed with the PDNS and dose reduction or rarely cessation considered;
The GP will continue treatment but seek advice	• If blood monitoring results are more than two weeks old for the first year, more than 1 month for the next 6 months or more than 2 months old thereafter. • If patient presents with somnolescence.
Urgently contact the neurologist or PDNS and admit the patient:	• In the event of a hypersensitivity reaction. • if patient presents with symptoms resembling of Neuroleptic Malignant Syndrome (NMS) - stupor, muscle rigidity, hyperthermia • If ALT and/or AST exceed the upper limit of normal or • Symptoms or signs suggesting the onset of hepatic failure (persistent nausea, fatigue, lethargy, anorexia, jaundice, dark urine, pruritus, right upper quadrant tenderness) develop

Recommended Dosage and Administration

The dosage is usually 100mg tds in combination with co-beneldopa or co-carbidopa. A maximum dose of 200mg tds in combination with co-beneldopa or co-carbidopa may be appropriate in exceptional circumstances only and should only be initiated by, or following consultation with, the hospital specialist.

If substantial clinical benefits are not seen within 3 weeks of the initiation of the treatment (regardless of dose), tolcapone should be discontinued.

Adverse Effects and Drug Interactions

Potentially life-threatening hepatotoxicity including fulminant hepatitis reported rarely, usually in women and during the first 6 months, but late-onset liver injury also reported
Most side effects observed with tolcapone are attributable to the enhanced levodopa bioavailability that results from COMT inhibition; the most common of these (occurring in more than 5% of patients in placebo-

controlled clinical studies) are dyskinesias, nausea, vomiting, constipation, abdominal pain, sleep disorder, somnolence, syncope, orthostatic complaints, hallucination and anorexia. The most common non-dopaminergic side effect is diarrhoea.

NB. Patients must be advised to exercise caution while driving or operating machines during treatment with tolcapone. Patients who have experienced somnolence must refrain from driving or operating machines.

Tolcapone may influence the pharmacokinetics of drugs metabolised by COMT, although no interaction was seen with carbidopa. Tolcapone interacts with benserazide, the magnitude of effect being dependent on the dose of benserazide, which may lead to increased levels of benserazide and its active metabolite. During the initial stages of tolcapone therapy the patient should be monitored for unusual side-effects or signs of potentiation of effect. Avoid concomitant use of MAOI antidepressants. Antiparkinsonian effects of dopaminergics antagonised by methyldopa. Effects of dopaminergics possibly enhanced by memantine. Tolcapone may interfere with drugs metabolised by cyt CYP2C9 eg warfarin (tolbutamide in unaffected).

Precautions and Contra-Indications

Tolcapone should be used with caution: in patients with severe renal impairment, dyskinesia, taking medicines that cause orthostatic hypotension, or dependent on alcohol; in pregnant women and women of child-bearing age. Female patients should not breast feed.
Tolcapone should only be withdrawn under the supervision of the patient's Hospital Consultant. Avoid abrupt withdrawal, unless there are reasonable grounds to do so as per advice in Table on page 3.
Patients receiving multiple medications with effects on different CNS pathways (e.g. antidepressants, antipsychotics, anticholinergics) may be at greater risk of developing Neuroleptic Malignant Syndrome (NMS). If NMS is suspected, the patient should be admitted to hospital immediately. The GP should not abruptly discontinue the drug.

Tolcapone is contra-indicated in patients with:

- known hypersensitivity to tolcapone or any other ingredient in the tablet
- liver impairment or increased liver enzymes
- concomitant treatment with non-selective MAOIs eg phenelzine, tranylcypromine
- severe dyskinesia
- previous tolcapone-induced hepatic injury
- phaeochromocytoma
- a known history of neuroleptic malignant syndrome, rhabdomyolysis, hyperpyrexia or confusion
- with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

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Supply

At current prices, 28 days' treatment at 100mg TDS costs £95.20 (+VAT)

Contact numbers

Consultant Neurologist: *John Jacob* **01908 826816**

Parkinson's Disease Nurse Specialist (PDNS): *Pete Smith* **01908 650425**

Pharmacy Medicines Information: **01908 243949**

References

1. Summary of Product Characteristics: Tasmar 100 mg Tablets. Last updated on the eMC: 22/03/2013.
2. British National Formulary (BNF) Nov 2014. Via http://evidence.nhs.uk/formulary/bnf/current/4-central-nervous-system/49-drugs-used-in-parkinsonism-and-related-disorders
3. Northamptonshire Prescribing Advisory Group, NGH Shared Care Monitoring Arrangements for Tolcapone in Parkinson's Disease. (May 2008).
4. NICE Clinical Guideline 35 , June 2006. Parkinson's disease: diagnosis and management in primary and secondary care. *Following the recent review recommendation (July 2011), an update of this guideline is currently in the process of being scheduled into the work programme. Details of any update will be available on the NICE guidelines in development webpage.*