SHARED CARE GUIDELINES FOR PRESCRIBING ENTACAPONE OR STALEVO® IN PARKINSON'S DISEASE

INDICATION

By inhibiting metabolism of levodopa, entacapone allows a reduction in dose of levodopa and reduces end-of-dose deterioration. COMT inhibitors can be used as an adjunct to levodopa therapy in patients who cannot be stabilised, particularly those with "end-of-dose" fluctuations

Stalevo® is a combination preparation containing levodopa, carbidopa and entacapone. It reduces the number of tablets that patients need to take and ensures levodopa and entacapone are taken together. May be considered for patients:

- receiving levodopa and entacapone for whom compliance is a problem;
- receiving treatment with levodopa at the point at which entacapone would have been introduced;
- who have difficulty swallowing larger tablets.

AREAS OF RESPONSIBILITY FOR SHARED CARE

This shared care agreement outlines ways in which the responsibilities for managing the prescribing of entacapone/Stalevo® can be shared between the specialist and general practitioner (GP). GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it.

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

REFERRAL AND INITIATION

Diagnosis should be undertaken by a consultant specialising in Parkinson's disease. Pharmacological measures should not be initiated prior to specialist referral.
At the time of diagnosis or review it may not be applicable to initiate new medication from secondary care. Where this is the case a pharmacological regimen will be recommended by the specialist team and the GP asked to initiate treatment at an appropriate time, supported by the specialist nurses.

Specialist Responsibilities	
1	To assess the patient and establish the need for entacapone or Stalevo® therapy within the agreed local prescribing guideline.
2	Where appropriate: o to initiate and stabilise treatment; o obtain consent from the patient's GP to continue prescribing once treatment has been stabilised (usually after 4 weeks) or if a delay in initiation is required to obtain their consent to start treatment when indicated, o monitor the patient and their therapy at six monthly intervals.
3	To provide the GP with appropriate prescribing information and any additional information requested.

4	To be available for advice if the patient's condition changes.
5	To ensure that procedures are in place for the rapid re-referral of the patient by the GP.
6	To ensure the patient has given informed consent to their treatment.
7	To liase with the GP on any suggested changes in prescribed therapy.

General Practitioner Responsibilities	
1	Initially, to refer the patient for specialist advice.
2	Where appropriate to initiate or continue (usually after 4 weeks) to prescribe entacapone or Stalevo® as part of a shared care arrangement.
3	To re-refer the patient back to the specialist team when necessary. .
4	To deal with general health issues of the patient.
5	To report any adverse effects or other concerns relating to these treatments to the specialist team.
6	Monitor concordance with therapy

Patient's role (or that of carer)	
1	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
2	Attend appropriate GP and other follow up appointments
3	Share any concerns in relation to treatment with the dopamine agonist
4	Use written and other information on the medication.
5	Seek help urgently if suspect side effects, or otherwise unwell.

SUPPORTING INFORMATION

DOSE

Entacapone: Initial doses will be determined by the consultant. One 200 mg tablet is taken with each levodopa/dopa decarboxylase inhibitor dose. The maximum recommended dose is 200 mg ten times daily, i.e. 2,000 mg of entacapone.
Entacapone enhances the effects of levodopa. Hence, to reduce levodopa-related dopaminergic adverse reactions, e.g. dyskinesias, nausea, vomiting and hallucinations, it is often necessary to adjust levodopa dosage within the first days to first weeks after initiating entacapone treatment. The daily dose of levodopa should be reduced by about 10-30% by extending the dosing intervals and/or by reducing the amount of levodopa per dose, according to the clinical condition of the patient

Stalevo®

Stalevo® is available in tablet strengths containing levodopa/carbidopa/entacapone as follows:

- 50mg/12.5mg/200mg
- 75mg/12.5mg/200mg
- 100mg/25mg/200mg
- 125mg/25mg/200mg
- 150mg/37.5mg/200mg
- 200mg/37.5mg/200mg

The optimum daily dose will be determined by the consultant. Patients should be instructed to take only one Stalevo® tablet per dose administration. Patients receiving less than 70-100 mg carbidopa a day are more likely to experience nausea and vomiting.
The **maximum** Stalevo® dose is 10 tablets daily for all strengths, except the maximum recommended daily Stalevo® 200 mg/50 mg/200 mg dose is 7 tablets per day (due to dose of carbidopa).
Patients already taking adjunctive entacapone with standard levodopa/carbidopa at doses equal to available tablet strengths of Stalevo® can be directly transferred to the combination preparation without any alteration of dose. Where an equivalent preparation of Stalevo® is not available, Stalevo® dosing should be carefully titrated.

Where entacapone is **not** currently being used, Stalevo® may be considered at corresponding doses for patients not stabilised on their standard levodopa/dopadecarboxylase inhibitor treatment. Most patients will require a 10-30% reduction in levodopa dose after treatment is first initiated which is usually achieved by reducing the frequency of dosing. For patients with dyskinesia or whose daily levodopa dose is **above** 800mg, entacapone should be introduced as a separate medication before transferring to Stalevo® if necessary.

SAFETY ISSUES

Note: The following section is based on entacapone. In addition for Stalevo®, the BNF should be referred to for cautions and side effects associated with levodopa.

Contra-indications

The summaries of product characteristics state the following:

- hypersensitivity to active substances or excipients;
- pregnancy and breast feeding;
- liver impairment;
- narrow-angle glaucoma (Stalevo);
- phaeochromocytoma;
- concomitant use of non-selective MAOIs or selective MAO-A plus selective MAO-B inhibitor;
- previous history of neuroleptic malignant syndrome (NMS) and/or non-traumatic rhabdomyolysis

Special warnings/precautions

Neither NMS nor rhabdomyolysis have been reported in association with entacapone treatment from controlled trials in which entacapone was discontinued abruptly. A rare number of cases have since been reported.

Nevertheless, as NMS has been reported rarely in Parkinson's disease patients when other dopaminergic medications were withdrawn abruptly, prescribers should exercise **caution** when discontinuing entacapone.

Entacapone may aggravate levodopa-induced orthostatic hypotension and should be given cautiously to patients who are taking other medicinal products that may cause orthostatic hypotension.

Entacapone in association with levodopa has been associated with **somnolence and episodes of sudden sleep onset**. Patients should be warned of the possibility of these effects and of the need to exercise caution when driving or operating machinery. Patients who have been affected should refrain from driving or operating machines until these effects have stopped recurring.

Drug interactions

Entacapone may interfere with the metabolism of some drugs e.g. adrenaline, dopamine, dobutamine, apomorphine and paroxetine. **Caution** also with concomitant use of selective MAO-A inhibitors, tricyclic antidepressants and noradrenaline re-uptake inhibitors e.g. venlafaxine. Refer also to contra-indications.

Entacapone and iron preparations should be taken at least 2-3 hours apart.

Side-effects

The most frequent adverse effects caused by entacapone relate to the increased dopaminergic activity and occur most commonly at the beginning of treatment.

Dyskinesias may be provoked or worsened necessitating a further decrease in levodopa dose.

The most frequent non-dopaminergic adverse events are gastrointestinal symptoms including nausea, vomiting, abdominal pain, constipation, diarrhoea and dry mouth.

Urine may be discoloured reddish-brown. Refer to special warnings regarding somnolence and episodes of sudden sleep onset.

Rare reports of clinically significant increases in liver enzymes have been reported but there is no requirement to routinely monitor liver function.
Slight decreases in haemoglobin, erythrocyte count and haematocrit have been reported during entacapone treatment that may lead to iron-deficiency anaemia with long-term treatment.

The manufacturers of each drug's summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

References

1. Pharmacological Management of Parkinson's Disease. Updated by the Bournemouth, Dorset and Poole Prescribing Forum. June 2010
2. British National Formulary 57. March 2010.

Written By	**Parkinson's Disease Working Group**	**May 2010**
Approved By	**Bournemouth, Dorset and Poole Prescribing Forum**	**June 2010**

Review Date	**June 2012 or before in the light of new evidence and/or recommendations**