Cardiff & Vale (C&V) UHB Corporate Medicines Management Group (c MMG)
SHARED CARE AND NEAR PATIENT TESTING

Drug: LEFLUNOMIDE **Protocol number CV 11**

Indication: RHEUMATOID ARTHRITIS and PSORIATIC ARTHRITIS

General Guidance

This protocol sets out details for the shared care of patients taking **leflunomide** and should be read in conjunction with the General Guidelines for Shared Care. Sharing of care requires communication between the specialist, GP and patient. The intention to share care should be explained to the patient by the doctor initiating treatment. **The doctor who prescribes the medication legally assumes responsibility for the drug and the consequences of its use.** The prescriber has a duty to keep themselves informed about the medicines they prescribe, their appropriateness, effectiveness and cost. They should also keep up to date with the relevant guidance on the use of the medicines and on the management of the patient's condition.

Background

Leflunomide is indicated for the treatment of adult patients with:
• active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD),
• active psoriatic arthritis.

Recent or concurrent treatment with hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) may result in an increased risk of serious adverse reactions; therefore, the initiation of leflunomide treatment has to be carefully considered regarding these benefit/risk aspects.

Responsibilities

A. Consultant responsibilities

1. When treatment is **initiated** send Shared Care/ Near Patient Testing request form with Shared Care Protocol to GP.
2. Baseline and monitoring until patient is stabilised of biochemical parameters (see page 2). (If Near Patient Testing not agreed then monitoring will be continued after patient is stabilised)
3. Initiate therapy following full discussion with the patient of benefits and risks
4. Titrate leflunomide dose according to schedule below, adjusting dose as appropriate and undertake monitoring of clinical response and side effects.
5. When a GP positive response to SC / NPT has been received and patient has been stabilized send a letter to GP "handing over" the Shared Care / Near Patient Testing of the patient to the GP.
6. To counsel patients (male and female) to take contraceptive precautions during treatment and for 2 years after treatment has ceased (refer to special precautions). Record in GP referral letter that contraceptive advice has been given.
7. Respond to any request from GP to review the patient due to adverse effects of therapy.

8. Advise the GP on continuing or stopping leflunomide therapy following medical review of patient and associated drug therapy.
9. If Near Patient Testing not agreed notify GP if patient is failing to attend for appropriate monitoring and advise GP on appropriate action.

B. General practitioner responsibilities

1. Within one week of receipt return the completed Shared Care/Near Patient Testing request form to indicate whether or not willing to undertake Shared Care/Near Patient Testing.
2. Prescribe **leflunomide** as part of the shared care agreement.
3. Monitor the general health of the patient.
3. Where Near Patient Testing is agreed monitor the parameters indicated (see below), document results in the patient's monitoring booklet and report to and seek advice from the consultant on any aspect of patient care which is of concern.
4. Report adverse effects of therapy to the consultant and the Medicines and Health Care products Regulatory Agency (MHRA).
5. Recommend that patient receives pneumococcal vaccination and yearly influenza vaccination.
6. If Near Patient Testing not agreed, to act on advice provided by the Consultant if patient does not attend for appropriate monitoring.

C. Patient responsibilities

1. Consent to treatment with leflunomide.
2. Attend regular appointments with specialist centre and GP.
3. Report any side effects to the specialist or GP whilst taking leflunomide
4. Provide monitoring booklet to be updated.

Dosage Regimen

10 - 20mg once daily when monotherapy is used. In cases of combination therapy with another potentially hepatotoxic DMARD like methotrexate, 10mg once daily is recommended (therapeutic efficacy may be reduced with reduced dosage).
Loading dose of 100mg daily for 3 days may be used to speed up onset of effect but unacceptable gastrointestinal side effects such as diarrhoea may occur so often omitted in routine practice.
A loading dose is not recommended when used as part of combination therapy.

Monitoring

<u>Before treatment</u>

FBC, Creatinine and Electrolytes, LFT

Blood pressure – if > 140/90 on 2 consecutive readings 2 weeks apart treat hypertension before starting leflunomide.

Weight – to allow assessment of weight loss which may attributable to leflunomide

<u>During treatment</u>

FBC & LFT - every 4 weeks for 6 months and if stable 2 monthly thereafter.
Blood pressure – at every monitoring visit.
Weight – at every monitoring visit.

Withold leflunomide and discuss with specialist if any of the following occurs:

WBC	$< 4.0 \times 10^9$/L
Neutrophils	$< 1.5 \times 10^9$/L
Platelets	$< 150 \times 10^9$/L
AST/ALT	> 3-fold rise from upper limit of reference range

Abnormal bruising or severe sore throat (check FBC immediately)
Increased shortness of breath

If **AST/ALT** between 2- 3 times upper limit of reference range and if the current dose is more than 10mg day, reduce to 10mg/day and recheck weekly until normalised. If the AST/ALT is returning to normal , leave on 10mg/day. If LFTs remain elevated withdraw the drug and discuss with the specialist.

If **AST/ALT** more than 3 times upper limit of reference range, repeat LFTs within 72 hours and if still more than 3 times the reference range, stop leflunomide and consider washout.

Rash or itch – consider dosage reduction with or without anti-histamines. If severe, stop and and consider washout.

Hair loss – consider dosage reduction; if severe, stop and consider washout.

If **BP > 140/90mmHg** on 2 consecutive readings 2 weeks apart, treat with antihypertensive agents before stopping the leflunomide. If BP remains uncontrolled, stop l and and consider washout.

Headache – if severe consider dosage reduction. If headaches persist, stop leflunomide and consider washout.

GI upset (nausea & diarrhoea) – if loading dose has been used, give symptomatic treatment. If steady state has been reached, give symptomatic treatment and consider dosage reduction. If symptoms severe or persistent stop and consider washout.

Weight loss – monitor carefully. If > 10% weight loss with no other cause identified. Reduce dosage or stop and consider washout.

Breathlessness – if increasing shortness of breath occurs, stop leflunomide and consider washout.

Washout procedure – To aid drug elimination in cases of serious adverse effect or before conception stop treatment and give cholestyramine 8g tid or activated charcoal 50g qid, each for 11 days; the concentration of active metabolite after washout should be less than 20 microgram/l (measured on 2 occasions 14 days apart) in men and women before conception (consult product literature)

Please note that in addition to absolute values for haematological indices a rapid fall or a consistent downward trend in any value should prompt caution and extra vigilance

Patient monitoring record booklets will be provided by the hospital.

Adverse effects

Mucocutaneous: Mouth ulcers, allergic skin reactions (eczema and dry skin), pruritis, increased hair loss, skin rash (including Stevens Johnson syndrome and toxic epidermal necrolysis)

Haematological: Reduced white cell or platelet count (see above).

Gastrointestinal: Diarrhoea, nausea, vomiting, anorexia.

Hepatic: Elevated liver enzymes (see above).

Cardiovascular: Possible small rises in blood pressure (mean of 3mm systolic. 2mm diastolic) in pre-existing hypertension.

Pulmonary: Pulmonary infiltration/pneumonitis is an acute allergic reaction which has been reported with leflunomide. Patients should be made aware of this rare complication and if they become short of breath, they should stop tablets and seek urgent medical advice. If combination therapy is used with methotrexate, the patient should be made aware of the possible added risk even though this may not be clinically significant.

Notable drug interactions (refer to BNF & SPC)

Leflunomide can interact with many drugs, particularly with phenytoin, tolbutamide and warfarin and may enhance the effects of these drugs

As leflunomide has an extremely long elimination half- life (2 weeks) interactions with these drugs may occur even after leflunomide has been discontinued and their seriousness may necessitate use of the washout procedure (detailed above).

For drug information please contact one of the rheumatology pharmacists or your local Medicines Information Dept.

Special Recommendations

Leflunomide is contraindicated in severe immunodeficiency, serious infections, impaired liver function due to any cause, severe unexplained hypoproteinaemia,. moderate to severe renal impairment and impairment of bone marrow function as indictated by anaemia and cytopenias due to causes other than rheumatoid arthritis and psoriatic arthritis.

Live vaccines should be avoided in patients taking leflunomide.

In patients receiving leflunomide exposed to chickenpox or shingles, passive immunization should be carried out using varicella zoster immunoglobulin (VZIG).

Patients should be asked to limit alcohol intake to well within national limits 4 – 8 units a week.

Leflunomide is teratogenic and must not be given to pregnant women or women of child bearing potential unless reliable contraception is used. Women planning a pregnancy should either discontinue the drug 2 years prior to conception or have a rapid removal of its active metabolite by following the washout procedure. Men should use effective contraception during treatment and for 3 months after stopping leflunomide.

Blood concentrations should be checked prior to planned pregnancy especially if within 2 years of stopping leflunomide or following washout. Any pregnancy within 2 years of discontinuing leflunomide should be discussed with the rheumatologist if drug washout has not been performed, and the pharmaceutical company informed

Leflunomide must be avoided in breast-feeding as animal studies indicate that metobolites are secreted into the breast milk.

Contact information

If you suspect an adverse reaction has occurred please stop the drug and contact the rheumatology department at the University Hospital of Wales – 029 20 742346, 742627, 743184, 743575, 742626 or after 5pm by rheumatology radiopage through the switchboard on 02920 747747.

For drug information queries, please contact one of the rheumatology pharmacists on 02920 746665.

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