

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. Check patient's immune status to *Herpes Zoster* and notify GP to enable coding to occur. For patients eligible for the national programme clinically assess the patient and advise the GP on individual suitability for the vaccine.
6. 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.
7. 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.

8. Respond to any request from GP to review the patient due to adverse effects of therapy.
9. Advise the GP on continuing or stopping leflunomide therapy following medical review of patient and associated drug therapy.
10. 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.
4. Where Near Patient Testing is agreed monitor the parameter agreed monitor and seek advice from the consultant on any aspect of patient care which is of concern.
5. Report adverse effects of therapy to the consultant and the Medicines and Health Care products Regulatory Agency (MHRA).
6. Recommend that patients that receives pneumococcal vaccination and yearly influenza vaccination. (Patients may also be eligible for Zostavax as part of the national shingles vaccination programme but this will depend on consultant advice on the individual's suitability)
7. 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

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

Before treatment

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

During treatment

FBC & LFTs - every 4 weeks for 6 months and if stable 2 monthly thereafter.

BP should be checked every 4 weeks until stable (secondary care), then every 2 months (GP) at the same time as having the 2 monthly blood tests

Weight –every two months.

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

WBC	< 4.0 x 10 ⁹ /L
Neutrophils	< 1.5 x 10 ⁹ /L
Platelets	< 150 x 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	

* patients may continue treatment if WBC is 3.0 - 4.0 x 10⁹/L if the neutrophil count is above 1.5 x 10⁹/L

If **AST/ALT** is between 2- 3 times the upper limit of reference range and if the current leflunomide dose is 20mg, reduce to 10mg/day and recheck LFTs weekly until they return to normal. If the AST/ALT returns to normal within 3 weeks leave on 10mg/day. If LFTs do not return to normal within 3 weeks then discontinue leflunomide 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.

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

Rash or itch – consider dosage reduction with or without anti-histamines. If severe, stop 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 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 (secondary care responsibility) – 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)

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 indicated by anaemia and cytopenias due to causes other than rheumatoid arthritis and psoriatic arthritis.
- Live vaccines should generally be avoided in patients taking leflunomide although local specialist advice is that Zostavax may be given for patients, eligible for the national programme, taking leflunomide $\leq 20\text{mg/day}$ either alone or in combination with prednisolone $\leq 20\text{mg}$ daily. Specialist advice should be sought for other treatment regimes.

- In patients receiving leflunomide exposed to chickenpox or shingles whose immune status to *Herpes Zoster* is unknown or negative, prophylactic aciclovir (po) (unlicensed use) should be prescribed 40mg/kg daily in four divided doses for 7 days starting one week after exposure.
- If a patient on leflunomide develops chickenpox then aciclovir should be started urgently. If the rash is severe and extensive and the patient is systemically unwell then he/she will need to be admitted urgently via the medical assessment unit as intravenous acyclovir and possibly other support will be required. If the patient is well however and the rash is no worse than would usually be seen then there is no indication for urgent admission or referral. The patient can be treated at home with oral aciclovir and advised to seek medical advice if there is any worsening of their condition.
- 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 metabolites 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.

The contact numbers for the rheumatology department are 02920 742627, 02920 742626 and 02920 743184. The fax number is 02920 745017. The rheumatology nurses help line number is 02920 748191.

Date of review December 2021