Leflunomide

Clinical indication: For the treatment of rheumatological inflammatory diseases

Version 5.1: February 2012 Due for review: July 2015

November 2014:
This Shared Care Protocol has been reviewed and updated with minor amendments to ensure that it reflects current guidance and practice. It will be reviewed thoroughly following publication of updated British Society of Rheumatologists guidance in 2015. At this stage it will be reformatted as a Shared Care Agreement. Please refer to the Summary of Product Characteristics (SPC) available at www.medicines.org.uk for full detail of prescribing information including adverse effects, drug interactions precautions and contra-indications.

Introduction

With the exception of sulfasalazine, DMARDs are usually started after assessment by a rheumatologist. ‘Rheumatological Management and Shared Care Guidelines’ available on website: www.refhelp.scot.nhs.uk

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. Contingency plans must be in place to enable the patient to receive the recommended treatment, should the GP decline to prescribe.

Indication for Therapy

Indications – active joint inflammation usually supported by indices of inflammation.
Duration – most medications require up to 3 to 4 months trial to assess efficacy. Therapy is continued providing the medication is working and there are no side effects. Relapse is common after withdrawal of therapy.

Preparations Available

10mg and 20mg tablets.

Recommended Dosage and Administration

Maintenance dose is 10mg or 20mg once daily. The loading dose is no longer used.

Adverse Effects & Drug Interactions (Please refer to SPC at www.medicines.org.uk for full detail)

Common: mild increases in BP, GI disturbance, rash, reversible alopecia, headache, haematological abnormalities (leucopenia), raised LFTs, paraesthesia, dizziness, eczema, tenosynovitis and asthenia.
Rare: pulmonary infiltration/pneumonitis increased LDH, severe increase in BP and pancytopenia.
Very rare: Stevens-Johnson Syndrome or toxic epidermal necrolysis.

Action if rapid response required: washout for intolerance or prior to starting another DMARD (active metabolite has long half-life) - use cholestyramine 8g three times daily for 11 days or if not tolerated, activated charcoal 50g four times daily for 11 days and re-refer to rheumatologist.

Drug interactions include: other hepatotoxic or haematotoxic medication, phenytoin, warfarin, tolbutamide and live vaccines. Patients on warfarin must have their INR monitored closely for several weeks after stopping leflunomide due to its long half-life. It is recommended that patients receiving leflunomide are not treated with colestyramine because this leads to a rapid and significant decrease in plasma A771726 (the active metabolite of leflunomide).

Precautions and Contra-Indications (Please refer to SPC at www.medicines.org.uk for full detail)

Due to a potential for additive hepatotoxic effects, it is recommended that alcohol consumption be avoided during treatment with leflunomide.

Due to the potential liver and haematological reactions, it is essential that monitoring recommendations are strictly adhered to (see ‘monitoring’ section).

Hypersensitivity to the active substance or to any of the excipients; impairment of liver function, or moderate to severe renal impairment; severe immunodeficiency states or serious infections; significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid or psoriatic arthritis; severe hypoproteinaemia.

Pregnancy and Lactation (Please refer to SPC at www.medicines.org.uk for full detail)

Leflunomide is contraindicated in pregnancy. Women of childbearing potential have to use effective contraception during and up to 2 years after treatment or up to 11 days after washout procedure. The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, they must notify the physician immediately for pregnancy testing, and if positive, the physician and patient must discuss the risk to the pregnancy.

Breast feeding should be avoided.
Shared Care Responsibilities

**Aspects of care for which the consultant is responsible**

- Assessing the need for DMARD.
- Arranging for the patient to receive counselling in verbal and written form.
- Providing relevant baseline investigations.
- Following the patient’s response to treatment at the out-patient clinic.
- Communicating advice to the patient’s GP regarding monitoring requirements.
- At any stage of treatment, advising GP of concerns regarding monitoring or potential adverse effects of treatment.

**Aspects of care for which the general practitioner is responsible**

- Prescribing DMARD under the guidance of the consultant.
- Reporting any suspected adverse reactions to the patient’s consultant and complete a Yellow Card if appropriate.
- Discuss any significant abnormalities with consultant.
- Liaising with the consultant regarding any complications of treatment.
- Monitoring the general health of the patient.
- Monitoring for specific side effects as detailed in “Monitoring” section.
- Provision of pneumococcal and annual influenza vaccination.

**Monitoring**

<table>
<thead>
<tr>
<th>Test</th>
<th>Frequency</th>
<th>Abnormal result</th>
<th>Action if abnormal result</th>
</tr>
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<tbody>
<tr>
<td>FBC</td>
<td>Fortnightly for first 6 months. If stable and not co-prescribed with another immunosuppressant or hepatotoxic drug, two monthly thereafter. Otherwise, continue monthly.</td>
<td>WBC &lt;3.5 x 10^9/l. neutrophils &lt;2.0 x 10^9/l. platelets &lt;150 x 10^9/l.</td>
<td>Withhold and discuss with specialist team.</td>
</tr>
<tr>
<td>LFTs</td>
<td></td>
<td>AST and/or ALT 2-3 times upper limit of normal reference range.</td>
<td>If dose &gt;10mg daily reduce to 10mg daily and recheck weekly. If AST/ALT normalise, leave on 10mg daily. If AST/ALT remain elevated, withhold leflunomide and discuss with specialist team.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AST and/or ALT &gt; three times upper limit of normal reference range.</td>
<td>Recheck LFTs within 72hrs; if still &gt;three times upper limit of normal withhold leflunomide and consider washout with cholestyramine or charcoal; discuss with specialist team.</td>
</tr>
<tr>
<td>BP</td>
<td>At each visit</td>
<td>&gt;140/85mmHg. &gt;130/80mmHg in patients with diabetes or renal disease.</td>
<td>Give antihypertensives as per Lothian Hypertension Guidelines. If BP remains uncontrolled stop leflunomide and consider washout.</td>
</tr>
<tr>
<td>weight</td>
<td></td>
<td>&gt;10% weight loss with no other cause.</td>
<td>Reduce dose or stop and consider washout.</td>
</tr>
</tbody>
</table>

- Abnormal trends should prompt extra vigilance.
- Temporarily withdraw if the patient reports sore throat, unexplained bleeding or bruising, mouth ulcers or other signs of blood dyscrasia or evidence of infection. Perform repeat blood monitoring.
- In the event of an unexplained acute widespread rash, headache, GI upset, or hair loss reduce dose of leflunomide, or stop if severe, and consider washout. For rashes: seek urgent specialist (preferably dermatological) advice; for all: inform rheumatologist. If increasing shortness of breath occurs, stop leflunomide and consider washout.
- Trends in ESR are useful in decision-making and can be undertaken during periods of increased disease activity. Routine ESR monitoring is not required.

**Contact Points**

Rheumatology SpR (via switchboard): 0131 537 1000
Rheumatic Diseases Unit (WGH): 0131 537 1798

GP can access advice from the rheumatology specialist service using the rheumatology on call e-mail which aims to give advice with a 24 hour response time: rheumatology.oncall@nhslothian.scot.nhs.uk

Advice will be communicated back to the GP by e-mail. The GP should copy in the practice’s clinical e-mail address and ask that the reply is sent to all, so that the reply is picked up even if the sender is not available.

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This information was prepared by the Rheumatic Diseases Unit and Pharmacy Department, Western General Hospital, NHS Lothian through liaison with the General Practice Prescribing Committee and LUHD Drug and Therapeutics Committee.