SHARED CARE GUIDELINES FOR THE PRESCRIBING OF LEFLUNOMIDE FOR RHEUMATOID ARTHRITIS OR PSORIATIC ARTHRITIS

INDICATION

This shared care guideline has been prepared to support healthcare professionals in the implementation of shared care management of patients who have been prescribed leflunomide for the treatment of rheumatoid arthritis or psoriatic arthritis in accordance with its marketing authorisation.

Leflunomide is commonly used as sole therapy but is sometimes used in combination with other disease modifying drugs (DMARDS) and biologic therapies.

AREAS OF RESPONSIBILITY FOR SHARED CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of leflunomide can be shared between the rheumatology 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 GP is required to inform the rheumatology specialist, in writing, that they do not wish to participate in shared care and, in this instance, total clinical responsibility for the patient for the diagnosed condition will remain with the specialist.

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

Shared care is only appropriate if it provides the optimum solution for the patient.

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

Specialist Responsibilities	
1	To assess the patient and establish/confirm the diagnosis
2	To determine a management strategy and ensure appropriate follow-up in conjunction with the GP
3	To initiate leflunomide treatment including: • Ensuring the suitability of the patient for leflunomide treatment including performing all relevant pre-treatment assessments (blood tests to include: FBC, LFTs, U&Es , blood pressure and pregnancy screen if appropriate) • Providing at least the initial 28 days' supply of medication • Discussing and agreeing the management strategy with the patient including: o informing them of possible side-effects to the treatment and ensuring they are aware of who to contact in this instance o the need for a washout procedure of the drug before any planned pregnancy • Ensuring the patient understands the proposed plan for follow-up Writing to the patient's GP advising them of the treatment commenced, including appropriate prescribing information, the intention to 'share care' unless the specialist team are informed otherwise, ongoing blood monitoring requirements (including who is responsible for checking the results) and arrangements for follow-up.
4	To be available for advice if the patient's condition changes and to arrange for the patient to be followed up in the rheumatology out-patient clinic as necessary.

General Practitioner Responsibilities	
1	To confirm in writing, without delay, if they do not wish to participate in shared care.
2	After initial 28 day supply, to continue to supply leflunomide at the dose specified by specialist team

3	To ensure practice system is in place to recall patient for monitoring blood tests where relevant unless the GP is assured that secondary care have a recall system in place.
4	To prevent ongoing prescription of leflunomide if patient is not compliant with blood testing
5	To monitor side effects/complications of treatment and seek advice from the specialist team as necessary
6	To deal with general health issues of the patient
7	To check for possible drug interactions when newly prescribing concurrent medications, noting there is a risk of toxicity with other haemotoxic and hepatotoxic drugs

Patient's role	
1	To report to the specialist or GP if he/she does not have a clear understanding of the treatment and to report any concerns
2	To attend appropriate hospital and GP appointments
3	To have required monitoring/tests carried out at regular intervals
4	To report any adverse events to the doctor who is prescribing their treatment
5	To read the drug information given to them
6	To take responsibility for appropriate contraceptive precautions
7	To restrict alcohol intake as advised in the patient information literature

SUPPORTING INFORMATION

Dosage and Administration
The recommended dose is 10-20mg orally, once daily. Its therapeutic effect usually starts after 4-6 weeks and improvement may continue for a further 4-6 months.

Contraindications
Leflunomide is contraindicated in:

- patients with a known hypersensitivity to the drug (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) or to any of the listed excipients
- patients with severe impairment of liver function
- patients with severe immunodeficiency states, e.g. AIDS
- patients with significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid or psoriatic arthritis
- patients with serious infections (note: leflunomide increases susceptibility to infections which should be treated promptly)
- patients with moderate to severe renal insufficiency
- patients with severe hypoproteinaemia, e.g. in nephrotic syndrome
- pregnant and breast feeding women, or women of childbearing potential who are not using reliable contraception during treatment with leflunomide and thereafter as long as the plasma levels of the active metabolite are above 0.02 mg/l (see also section 4.6).
- men with partners of child bearing potential, who are not using reliable contraception during treatment with leflunomide

Pregnancy must be excluded before the start of treatment with leflunomide.

Live vaccines are contraindicated for patients taking leflunomide. However, the annual flu and pneumonia vaccine **should** be given.

Special Warnings
Rare cases of severe liver injury, including cases with fatal outcome, have been reported during treatment with leflunomide. Most of the cases occurred within the first 6 months of treatment. Co-medication with other hepatotoxic medicinal products was frequently present. It is considered essential that monitoring recommendations are strictly adhered to.

The patient should be advised that excess alcohol should be avoided.

For ALT (SGPT) elevations between 2 – and 3 – fold the upper limit of normal, dose reduction from 20 mg to 10 mg may be considered.
If ALT (SGPT) elevations of more than 2 – fold the upper limit of normal persist or if ALT elevations of more than 3 – fold the upper limit of normal are present, leflunomide must be discontinued and wash-out procedures considered. It is recommended that monitoring of liver enzymes be maintained after discontinuation of leflunomide treatment until liver enzyme levels have normalised.

A washout procedure (using cholestyramine or activated charcoal) should be performed before desired pregnancy.

Caution is advised when leflunomide is given together with drugs, other than NSAIDs, metabolised by CYP2C9 such as phenytoin, warfarin, phenprocoumon and tolbutamide.

Very rare but serious side effects include: Leflunomide induced lung disease. This may occur acutely at any time during therapy. It is not always fully reversible. Pulmonary symptoms (especially a dry, non productive cough and unexplained shortness of breath) may require interruption of treatment and careful investigation including chest x-ray in the first instance.

Side Effects
Common:
Diarrhoea, nausea, weight loss, rash.
Increase in blood pressure (usually mild and in patients with pre existing hypertension)
Side effects can often be managed by dose reduction but may require cessation of treatment if severe.

Less common:
Rare cases of severe liver injury, headache, dizziness, asthenia and paraesthesia. Bone marrow toxicity. Tenosynovitis. Alopecia, eczema and dry skin. Very rarely cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme reported. Leukopenia is common but total leukocyte count < 2g/litre is rare.

This list is not exhaustive – the manufacturer's summary of product characteristics (SPC) and the most current edition of the British National Formulary (BNF) should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

Monitoring
Blood monitoring incorporating FBC, LFTs and ESR/CRP should be performed fortnightly for the first 8 weeks of treatment. Thereafter, blood monitoring can be performed monthly.

Where patients are stable on treatment and monitoring results have been satisfactory for 12 months, FBC, LFTs and ESR/CRP can be performed every 2-3 months. U&Es should be monitored every 3/6 months.

Blood pressure should be checked after one month and thereafter blood pressure and weight should be checked at periodic intervals.

If Leflunomide is prescribed in combination with other hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) monthly blood monitoring should continue.

N.B.
Awareness of the NICE guidance on medicines adherence, available at: http://guidance.nice.org.uk/CG76/NICEGuidance/pdf/English, and the availability of patient

support plans should support patients to adhere to their medications and is the responsibility of all healthcare professionals.

References

1. Arava (leflunomide, Sanofi-Aventis) Summary of Product Characteristics. May 2011.
2. BSR National Guidelines For the Monitoring of Second Line Drugs, 2008
3. DARE safety and disease activity monitoring guidelines for Dorset 2009

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Approved By	Bournemouth, Dorset and Poole Health Technologies Forum	December 2011
Review Date	December 2013 or before in the light of new evidence and/or recommendations	