

THE SHEFFIELD AREA PRESCRIBING GROUP

Shared Care Protocol

For

Leflunomide in Adults

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Shared Care Protocol for Leflunomide

Statement of Purpose

This Shared Care Protocol has been written to enable the continuation of care by primary care clinicians of patients initiated and stabilised on leflunomide by the rheumatology department at Sheffield Teaching Hospitals. The patient will continue to remain under the care of the consultant and primary care will only be requested to take over prescribing of leflunomide within its licensed indication.

Responsibilities of consultant clinician

- To discuss benefits and side effects of treatment with the patient/carer and obtain informed consent.
- To undertake pre-treatment tests
- To initiate leflunomide in appropriate patients and issue patient with patient information leaflet and counsel on contraceptive advice, if applicable
- To prescribe leflunomide until the patient is stable, for a minimum of 6 months
- To contact patient's GP to request prescribing under shared care using Shared Care Transfer Form. Send a link to or copy of the shared care protocol to the patients GP.
- To advise the GP regarding continuation of treatment, including the length of treatment
- To advise GP regarding frequency of any weight monitoring that may be needed in primary care
- To discuss any concerns with the GP regarding the patient's therapy
- To monitor disease appropriately whilst the patient is under shared care

Responsibilities of the primary care clinician

- To refer appropriate patients to secondary care for assessment
- To agree to prescribe for patients in line with the shared care protocol and return completed Shared Care Transfer form to the rheumatology department.
- To report any adverse reaction to the [MHRA](#) and the referring consultant
- To continue to prescribe for the patient as advised by the consultant
- To undertake monitoring as per shared care protocol, see below and transcribe results clearly into the patients individual management plan (a 'blue book' which the patient will have been given from STH)
- To inform the consultant if the patient discontinues treatment for any reason
- To seek the advice of the consultant if any concerns with the patient's therapy
- To conduct an annual face to face medication review or more frequent if required
- In the event that the GP is not able to prescribe, or where the shared care protocol is agreed but the consultant is still prescribing certain items e.g. hospital only product; the GP will provide the consultant with full details of existing therapy promptly by secure method on request.
- For medication supplied from another provider GPs are advised to follow recommendations for [Recording specialist issued Drugs on Clinical Practice Systems](#) Check for possible drug interactions when newly prescribing or stopping concurrent medication

Responsibilities of patients/carers

- To attend hospital and GP clinic appointments and to bring monitoring booklet (if required). Failure to attend will potentially result in the medication being stopped.
- Present rapidly to the GP or specialist should their clinical condition significantly worsen.
- Report any suspected adverse effects to their specialist or GP whilst taking leflunomide, including mouth ulceration, sore throat with ulceration, unexplained bruising/bleeding, peripheral neuropathy, dyspnoea, cough, unexplained fever, unexpected weight loss

- To read the drug information given to them
- To take leflunomide as prescribed
- Inform the specialist, GP or community pharmacist dispensing their prescriptions of any other medication being taken – including over-the-counter medication.
- To take responsibility for appropriate contraceptive precautions, where applicable
- To restrict alcohol intake as advised in the patient information literature

Indication

Leflunomide is indicated for the treatment of adult patients with:

- active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD)
- active psoriatic arthritis (not all brands are licensed for this indication)

Selection of patients

All adult patients will be treated and stabilised on leflunomide by a secondary care specialist. Once stabilised patients are suitable for referral to a primary care service – this will usually take 6 months. However the practice and the hospital may agree to transfer patients sooner where they judge this clinically appropriate or specified through patient choice

The following patients are excluded from this Shared Care Protocol:

- Moderate or severe renal impairment;
- Significant hepatic impairment;
- Severe pleural effusion or ascites;
- Children under 16 years;
- Pregnancy and breast feeding

Dosage

Oral

Maintenance dose of leflunomide: 10mg – 20mg daily

Continue NSAIDs or analgesics at least until treatment response

Contra-indications

- Hypersensitivity to the active substance (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) or to any of the excipients
- Severe hypoproteinaemia
- Impairment of liver function
- Moderate or severe renal impairment (eGFR <50mL/minute/1.73 m²)
- Pregnancy, breast-feeding and women of child bearing potential not using reliable contraception (see below under Pregnancy and breast feeding section)
- Severe immunodeficiency states/serious infections.
- Patients with significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid or psoriatic arthritis.
- Live vaccines, e.g. rubella, BCG, , yellow fever, etc, should not be given to patients taking leflunomide, see also [additional information](#) section below.
- Patients with serious infections

Pregnancy and breast feeding

If a stable patient on leflunomide is considering conception (or becomes pregnant) refer them immediately to secondary care. Note: Both men and women receiving leflunomide must use contraception throughout the treatment period, and for at least two years in women (3 months in men) after discontinuation of treatment. Alternatively a washout period can be undertaken; either colestyramine - 8g TDS for 11 days or activated charcoal - 50g QDS for 11 days. The plasma concentration of the active metabolite after washout should be less than 20 micrograms/litre (measured on 2 occasions 14 days apart) in men or women before conception. A waiting period of one and a half months between the first occurrence of a plasma concentration below 20 micrograms/litre and fertilisation is required. For more information consult product information. Please note that washout will inhibit action of oral contraceptives and therefore alternative contraception is required.

Animal studies indicate that leflunomide or its metabolites pass into breast milk. Breast-feeding women must, therefore, not receive leflunomide.

Side –effects

The details below are not a complete list and the [BNF](#) and the [SPC](#) remain authoritative.

- Common - nausea, vomiting, oral ulceration, minor hair thinning, abdominal discomfort, diarrhoea, headaches, leucopenia, hypertension*, rash, elevation of liver parameters.
- Uncommon – thrombocytopenia and anaemia. Patients should be warned to report a sore throat and abnormal bleeding/bruising, peripheral neuropathy

*Hypertension: consider dose reduction, introduction of anti-hypertensive agent in line with [NICE NG 136](#) - discontinuation of treatment if no response. NB Hypertension should be controlled prior to commencing treatment.

Monitoring

Secondary care – At baseline: pregnancy test (if clinically indicated); extended LFTs (including GGT); U&Es; creatinine; FBC; CRP; CXR; PFTs; body weight and BP (if BP raised above 140/90 mm Hg a further three readings need to be taken before commencing leflunomide); and the patient will undergo further monitoring in line with the local procedure at STH which includes checking weight and BP. The patient will then be transferred to shared care with primary care when stable.

Primary Care - FBC, extended LFTs, U&Es, creatinine and CRP, three monthly, in line with BSR DMARD monitoring guidance. BP should be checked at each monitoring visit and frequency of weight monitoring will be advised by specialist. Also remind patient to report any side effects at each monitoring visit.

Specialist will advise GPs regarding any changes in monitoring if doses are increased or leflunomide is prescribed in combination with methotrexate.

Caution needed:

If CRP is significantly and persistently raised above what is normal for that patient, the first step is to consider infection, and ask the patient about a flare in symptoms of their disease. If infection is present, this should be treated and blood tests then repeated. If there is no apparent explanation for the elevated CRP, this should be repeated a few weeks later, and if remains unchanged or higher, the secondary care team should be contacted.

Falling trend in WBC or platelets over 3 counts

Stop leflunomide and contact helpline (see below) if:

WBC $<3.5 \times 10^9/L$

Neutrophils $<1.6 \times 10^9/L$

ALT and /or AST >100U/L

Platelet count <100 x 10⁹/L

eGFR <40 ml/min/1.73m²

Patient becomes pregnant – leflunomide washout will be needed, see [pregnancy and breastfeeding](#) section above

Overdose - contact secondary care as leflunomide washout may be needed

New onset significant shortness of breath, and dry cough associated with new abnormality on CXR (leflunomide may rarely cause a pneumonitis, usually within first 6 months of treatment for RA)

In the event of the following abnormalities, leflunomide can be continued, but tests repeated within 2-3 weeks and then seek advice from department initiating leflunomide if the abnormality is persistent.

eGFR < 50 (but above 40) ml/min/1.73m²

Unexplained eosinophilia >0.5x10⁹/L

Lymphocytes < 0.5 10⁹/L

MCV>105fL: check B12, folate and thyroid function - if abnormal prescribe as appropriate

Platelet count <130 (but >100) x 10⁹/L

Unexplained reduction in albumin <30g/L

ALT and or AST 70-100 U/L (consider recent flu vaccination i.e. within the last 2-3 weeks, as possible cause)

Patient develops pleural effusion or ascites, as increased risk of toxicity

Unexplained bruising / bleeding, fever, sore throat with oral or pharyngeal ulceration

Unexplained > 10% weight loss

Uncontrolled hypertension >140/90 mmHg despite standard anti-hypertensives

Increasing shortness of breath or cough in the absence of obvious infection

New onset peripheral neuropathy

Infections

Leflunomide may cause patients to be more susceptible to infections, including opportunistic infections. In the event of a patient developing an infection requiring antibiotic treatment, check FBC and CRP and withhold leflunomide for the duration of antibiotic treatment. Infections may be more severe in nature and may, therefore, require early and vigorous treatment. In the event that severe, uncontrolled infections occur, it may be necessary to interrupt leflunomide treatment and administer a washout procedure as described under [pregnancy](#) section.

Interactions

The details below are not a complete list and the [current BNF](#) and the [SPC](#) remain authoritative.

Other hepatotoxic drugs, other myelotoxic drugs, colestyramine, phenytoin, tolbutamide, warfarin, live vaccines

Concomitant methotrexate is not advisable except on advice of rheumatologist

Leflunomide has a very long half-life (2 weeks) and therefore potential interactions may take time to become clinically apparent. Extra monitoring is needed if starting or stopping leflunomide in a patient also

taking warfarin, phenytoin or tolbutamide.

Additional Information

Live vaccines, e.g. rubella, BCG, small pox, yellow fever, should not be given to patients taking leflunomide (refer to [Green book](#) for further advice on vaccines).

Patients on leflunomide for the management of inflammatory conditions may not be sufficiently immunosuppressed to contraindicate administration of Zostavax® (shingles vaccine). The degree of immunosuppression should be assessed on a case by case basis. Practitioners should refer to the latest edition of the [Green-book-chapter-28a](#) for advice. If clinicians administering the vaccine have concerns about the degree of immunosuppression they should first contact the relevant specialist.

NB pneumococcal polysaccharide vaccine & annual inactivated flu vaccine should be given.

Alcohol

The SPC states to avoid alcohol consumption whilst taking leflunomide, due to additive hepatotoxic effects. If patients do consume alcohol the [Versus Arthritis patient information leaflet](#) states patients should discuss with their doctor or rheumatology nurse specialist and only drink in small amounts. If concerned with alcohol consumption, watch LFTs and discuss with secondary care.

Re-Referral guidelines

See under [monitoring section](#) above

Pregnancy and / or preconception advice / management

Deterioration of disease

Financial implications

If leflunomide is issued under the shared care arrangements then drug costs will move from secondary to primary care. In primary care leflunomide will be issued on FP10 prescriptions. Outpatient appointments at STH will be reduced, but there will be an increase in payments to GPs under the DMARD Local Commissioned Service.

Support, education and information

A drug information sheet and shared care booklet has been issued to your patient.

If any problems occur or you have any concerns please contact relevant specialist:

Rheumatology help line (Mon-Fri 0900-1600)

(0114) 2713086
(option 3)

On call specialist via STH NHS Foundation Trust switchboard:

(0114) 2711900

Alternatively messages can be sent to this advice line: Sth.ropd@nhs.net

Secondary care assumes responsibility for the monitoring and re-prescription of leflunomide until stable dosage has been successfully achieved.

Patient information leaflets

These are provided to patients by secondary care, but can also be downloaded here <https://www.versusarthritis.org/about-arthritis/treatments/drugs/leflunomide/>

References

British Society of Rheumatology DMARD guidelines - 2017

<https://academic.oup.com/rheumatology/article/56/6/865/3053478#97289271>

Full list of side-effects is given in the leflunomide summary of product characteristics (SPC), available from www.emc.medicines.org.uk .

BNF <https://www.medicinescomplete.com/mc/bnf/current/>

Suggestions for Drug Monitoring in Adults in Primary Care – UKMI document -2017

<https://www.sps.nhs.uk/wp-content/uploads/2017/12/Drug-monitoring-2017.pdf>

Amendments October 2022:

Amended Primary care Monitoring, changed from “weight to be checked at each monitoring visit” to “frequency of weight monitoring will be advised by specialist”

Added to Responsibilities of consultant clinician “To advise GP regarding frequency of any weight monitoring that may be needed in primary care”

Added to responsibilities of patients/carers to report “unexpected weight loss”

Added to monitoring in Secondary care “which includes checking weight and BP”