

Shared care guideline for Leflunomide for active rheumatoid arthritis and psoriatic arthritis in adults

General principles

This agreement outlines suggested ways in which the responsibilities for managing the prescribing of the drug treatment and clinical indication listed in the table below can be shared between the Specialist and General Practitioner (GP). The Specialist(s) is responsible for initiating treatment, prescribing the drug and monitoring of therapy until such a time as when the patient is deemed to be stable. If GPs are not confident to undertake these roles, then they are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the Specialist.

If a Specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication between the specialist, the GP and the patient. The intention to undertake shared care should be explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it. Patients on leflunomide are under regular follow-up, which provides an opportunity to discuss drug therapy.

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

Indications

Leflunomide is an immunomodulatory agent unrelated to other disease modifying anti-rheumatic drugs (DMARDs). It is indicated for the treatment of moderate to severe active rheumatoid arthritis and psoriatic arthritis. Therapeutic effects usually take 4 to 6 weeks with maximum benefits reached in 4 to 6 months.

Leflunomide decreases the autoimmune response and arrests activated autoimmune lymphocytes thought to be involved in the pathogenesis of rheumatoid arthritis.

Presentation/Dose/Administration

Oral:

Leflunomide is administered orally and is available as 10mg and 20mg tablets. The recommended dose is 20mg daily, but 10mg daily may be used in case of intolerance or in combination with methotrexate.

Responsibility for monitoring Leflunomide			
MONITORING	RESPONSIBILITY	CONDITIONS	TESTS
Pre-treatment	Hospital team	All	FBC, creatinine and U&Es, LFTs. Check BP. If > 140/90, treat hypertension before starting leflunomide. Record body weight. Results to be known before drug is commenced
Initiation to stabilisation	Hospital team	All	FBC, LFTs, BP and weight every month for six months.
Ongoing	GP	All	After six months: FBC, LFTs, BP and weight every two months . If co-prescribed with another immunosuppressant or potentially hepatotoxic drug, continue monitoring at least once a month .

Criteria for managing events & symptoms occurring during Leflunomide therapy in primary care		
LABORATORY EVENTS	VALUES	ACTION
WBC	Decrease to < 3.5 x 10 ⁹ /L	Withhold until discussed with specialist team. Neutrophil between 1-2 repeat.
Neutrophils	Decrease to < 2.0 x 10 ⁹ /L	
Platelets	< 150 x 10 ⁹ /L	
AST and ALT	2 - 3x upper limit of reference range	If current dose >10mg daily, reduce to 10mg daily and re-check weekly until normalised. If AST and ALT returning to normal leave on 10mg daily. If LFTs remain elevated, withdraw and discuss with specialist team.
	> 3x upper limit of reference range	Re-check LFTs within 72h , if remain more than three times the reference range, stop drug and discuss with specialist team.
Fall in albumin	< 150 x 10 ⁹ /L	Repeat LFTs as early sign of liver toxicity. Stop and discuss with specialist team if continue to deteriorate.
BP >140/90		Treat in line with National Institute For Clinical Excellence (NICE) guidance. If patient develops severe hypertension which remains uncontrolled despite optimal antihypertensive treatment, stop leflunomide and consider washout.

SYMPTOMS	MANAGEMENT
Rash/Itch, hair Loss, headache	Consider dose reduction; if severe, stop, consider washout*.
Gastrointestinal disturbances (diarrhoea, nausea)	Symptomatic treatment and consider dose reduction; if severe or persistent, stop and consider washout*.
Hypertension	If blood pressure >140/90 treat in line with NICE guidance. If remains uncontrolled stop and consider washout*.
Abnormal bruising or severe sore throat	Check FBC immediately and withhold until results available. Follow relevant course of action from table above. Discuss with specialist team if necessary.
Weight loss	Monitor carefully. If >10% weight loss with no other cause identified, reduce dosage or stop and consider washout*.
Dry cough, breathlessness	Stop if increasing shortness of breath occurs. Seek urgent advice from specialist team.

Washout Procedure

Leflunomide has a **long half-life of up to 6 weeks**. Adverse effects may be seen for a long time after the drug is stopped. A washout procedure can be considered in patients having severe side effects or in men or women considering conception. (If a waiting period of up to approximately 2 years under reliable contraception is considered impractical, prophylactic institution of a washout procedure is advisable).

It is usually recommended to give colestyramine 8g TDS or activated powdered charcoal 50g QDS for 11 days then measure metabolite A771 726 twice at intervals of at least 14 days. This should fall to less than 0.02 mg/l. It is recommended to wait at least 3 months before considering conception.

Key adverse drug reactions (ADRs)

- Gastrointestinal disturbances (diarrhoea, nausea, vomiting, anorexia, weight loss, oral mucosal disorders, abdominal pain).
- CNS disturbances (headache, paraesthesia, dizziness, asthenia, anxiety). If dizziness impairs ability to concentrate and react patients should be advised from driving and using machines.
- Hypertension.
- Hepatobiliary disorders including elevation of liver parameters and rarely hepatitis, jaundice/cholestasis.
- Biochemical changes (hypokalaemia, hypophosphatemia, hyperlipidaemia).
- Blood disorders (leucopenia, eosinophilia, thrombocytopenia, anaemia): uncommon.
- Skin reactions (rash, dry skin, alopecia, pruritus, Stevens-Johnson syndrome): uncommon.
- Musculoskeletal and connective tissue disorders such as tenosynovitis.

NB. Patients should be advised to report any mouth ulcers, sore throat, fever, epistaxis, unexpected bruising or bleeding and any unexpected illness or infection and should be seen URGENTLY for a full blood count, liver function tests, urea and electrolytes.

This document only lists the key important ADRs. For comprehensive information on adverse drug reactions, cautions, contra-indications and interactions, please refer to the current British National Formulary and Summary of Product Characteristics.

Contraindications & precautions

Contraindications

- Patients under 18 years.
- Pregnancy and lactation. According to recent BSR guidelines, based on limited evidence, leflunomide may not be a human teratogen but it is still not recommended in women planning pregnancy. Women on leflunomide considering pregnancy should stop and undergo colestyramine washout before switching to alternative medication compatible with pregnancy. There is no human evidence of increased congenital abnormalities on leflunomide if washout is given. Therefore, if accidental conception occurs on leflunomide, the drug should be stopped immediately and colestyramine washouts given until plasma levels are undetectable. No data exist on excretion into breast milk, therefore breastfeeding is not recommended. Based on very limited evidence, leflunomide may be compatible with paternal exposure. **Women of child-bearing potential should use reliable contraception.**

Women who wish to become pregnant after receiving leflunomide should have plasma levels of the leflunomide metabolite checked (after wash out period) and **pregnancy should be avoided until levels have reached below 0.02mg/l**

- Moderate or severe renal insufficiency or hepatic impairment.
- Hypersensitivity (especially previous Stevens- Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) to the active substance, the principal active metabolite, peanut or soya or to any of the excipients (see Summary of Product Characteristics).
- Serious infection or severe immunodeficiency states eg AIDS.
- Patients with significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid arthritis.
- Severe hypoproteinaemia, e.g. in nephrotic syndrome.

Precautions

- Extreme caution in blood disorders.
- Due to a potential for additive hepatotoxic effects, it is recommended that alcohol consumption be avoided during treatment with leflunomide
- Leflunomide induced lung disease is a very rare but serious side effect. 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.
- **Vaccinations:** live vaccines should be AVOIDED (i.e. oral polio, MMR, BCG and yellow fever and oral typhoid). Passive immunization should be carried out using Varicella zoster immunoglobulin (VZIG) in non-immune patients exposed to active chickenpox or shingles. **Annual flu and pneumococcal vaccination is recommended.**

Drug interactions

- The long half-life of leflunomide means that serious adverse effects and interactions can occur after treatment has been stopped. Additional monitoring is required after treatment is continued
- Caution is advised when leflunomide is given together with drugs (other than NSAIDs) metabolised by cytochrome P450 such as **phenytoin** (enhances the effects), **tolbutamide** (enhances the effects) and **warfarin** (increases the INR).
- Concomitant use with other DMARDs is usually not advised. The combinations may be recommended by **SPECIALISTS ONLY**.

See [BNF](#) and manufacturer's SPC [Home - electronic Medicines Compendium \(eMC\)](#) for up-to-date advice

Consultant /Specialist responsibilities

- Identify those patients who will benefit from treatment with leflunomide.
- Undertake pre-treatment monitoring of FBC, U&Es, LFTs, BP and body weight.
- Ensure that the patient/carer is an informed recipient in therapy, provide necessary education on their treatment regimen and any monitoring or follow up that is required and issue local patient information leaflets.
- Provide patients with a patient held record book; undertake pre-treatment monitoring of FBC, LFTs, U&Es, creatinine, in the record book.
- Initiate leflunomide and stabilise patient on a therapeutic dose of leflunomide before referral to the GP.
- Send a letter to the GP requesting a formal agreement to share care and transfer care to GP only after receipt of a completed and signed agreement from the GP.
- Ensure prior dissemination of sufficient information to patient's GP and other carers.
- Inform the GP that leflunomide has been commenced, the dose and future plans for dose changes in keeping with the shared care agreement.
- Clinical and laboratory supervision of the patient by blood monitoring and routine clinic follow-up on a regular basis.
- Send a letter/results notification to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring are stated.
- Where the GP is not performing the phlebotomy, the blood test form **MUST** be annotated to request that blood results are also copied to the GP.
- Evaluation of any reported adverse effects by GP or patient.
- Advise GP on review, duration or discontinuation of treatment where necessary. Where urgent action is required following tests the **hospital team will telephone the patient and inform GP.**
- Inform GP of patients who do not attend clinic appointments.
- Counsel the patient on contraception and what to do if pregnancy occurs. Document in the notes.
- Provide access to backup advice and support facilities at all times.
Ensure, where timing is appropriate, that the patient has received a flu vaccine prior to commencing treatment that is likely to cause immunosuppression. Document this in the patient notes and inform the GP it has been given.

GP responsibilities

- Reinforce the patient's understanding of the nature, effect and potential side effects of the drug before prescribing it as part of the shared care programme and contact the Specialist for clarification where appropriate.
- Prescribe leflunomide at the dose recommended by the hospital Specialist once the patient is stabilised on treatment and side effects have been excluded as far as possible by the hospital. Any decision to alter treatment should usually be taken by the hospital Specialist.
- Monitor blood results (FBC, LFT U&E), BP and body weight in line with recommendations in this document.
- Check for possible drug interactions when newly prescribing or stopping concurrent medication.
- Monitor patient's overall health and well-being.
- Report any adverse events to the Consultant/Specialist, where appropriate.
- Report any adverse events to the CSM, where appropriate.
- Stop Leflunomide if serious adverse drug effect/reaction and contact Specialist team.
- Help in monitoring the progression of disease.

CCG Responsibilities

- To provide feedback to trusts via South West Essex Medicines Management Committee.
- To support GPs to make the decision whether or not to accept clinical responsibility for prescribing.
- To support trusts in resolving issues that may arise as a result of shared care.

Patient/ Carer responsibilities

- Report any adverse effects to their GP and/or Specialist
- Ensure they have a clear understanding of their treatment.
- Report any changes in disease symptoms to GP and/or Specialist
- Alert GP and/or Specialist of any changes of circumstance which could affect management of disease e.g. plans for pregnancy.
- Take/ administer the medication as prescribed.
- Undertake any monitoring as requested by the GP and/or Specialist.

Contact details

Consultant, medical staff and nurse practitioners at the Basildon and Thurrock University Hospitals NHS Foundation Trust (BTUH) are available to give advice and can be contacted either through the main hospital switchboard or direct:

Department / Specialist	Contact Telephone Number
Hospital switchboard – ask for specialist or On-Call Specialist	01268 524900
Rheumatologist out-of-hours	
Rheumatology	

Document Control	
Version:	Draft v0.12
Shared Care Guidelines are also available electronically via: to insert website link after approval	
Approved by:	South West Essex Medicines Management Committee
Date of issue	November 2016
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LEFLUNOMIDE PATIENT INFORMATION LEAFLET

This form will be completed by the Hospital Specialist and given to the patient once stabilised and a fax back has been received from the GP accepting the transfer of responsibility to primary care.

You have been prescribed **Leflunomide** tablets

for.....

This **treatment** will continue until stopped by your doctor

Your GP has been given all the necessary information regarding your condition and treatment.

The date for your next hospital appointment is

The success and safety of your treatment also depends on you.

- You will have been given information, which tells you about your treatment and condition.
- Avoid excessive alcohol consumption.
- Do not take any over-the-counter medicines, herbal, complementary or alternative medicines and treatments without getting advice from your doctor.
- Avoid contact with chicken pox or shingles.
- Avoid driving and hazardous work until you have learned how Leflunomide affects you, as this drug can occasionally cause dizziness.
- Leflunomide can increase the skin’s sensitivity to sunlight and the risk of developing some forms of skin cancer. Use sun block and wear a hat and light clothing when out in strong sunshine.
- Do **not** use sunlamps or sun beds.
- You will need to have blood tests at least every three months.
- Your GP/ Practice Nurse needs to see you every

If you experience any of the following side-effects, urgently see your GP:

- Mouth ulcer, sore throat, sore mouth.
- Feeling generally unwell.
- Feeling sick, upset stomach, diarrhoea.
- Rashes – new rash or severe itching anywhere on the body.

Stop treatment and get immediate medical advice if you develop:

- An infection with fever and or chills or a severe sore throat.
- Sudden shortness of breath (breathlessness).
- The whites of your eyes or skin become yellow
- Severe itching of the skin .
- New unexplained bleeding or bruising.
- Severe and continuing abdominal pain or diarrhoea or vomiting.
- If you think you are pregnant contact the IBD nurse or Specialist
- If you have any concerns about your treatment contact your GP or the hospital.

The direct-dial telephone numbers for the department are.....

GP LEFLUNOMIDE SHARED MONITORING AGREEMENT 1ST LETTER

Name of GP

Address

Drop code of GP.....

Dear Dr

Re: Patient's name.....

Date of birth.....

Hospital number.....

NHS number.....

I have seen this patient and believe that he/she is suitable for treatment with Leflunomide or:

.....

I have initiated the patient on **Leflunomide**mg tablets

Take..... tablets (.....mg) once a day.

I will be prescribing and monitoring this patient at our clinic until such a time that the patient is deemed stable, which is likely to be in the region of months.

I would like to seek your agreement to take over the prescribing and monitoring of this patient's treatment after this stabilisation period as per agreed shared care guideline which is enclosed for your information.

Please complete, sign and fax back the form below to stated safe haven fax.

I thank you in anticipation.

Yours sincerely

Dr
(Consultant)

LEFLUNOMIDE SHARED CARE GP/PRACTICE FAX BACK FORM

Patient name..... Hospital number.....

Dear GP

You will take over monitoring of the patient including responsibility for organising blood tests and other tests required in accordance with the shared care guidance (enclosed). You will be responsible for reviewing underlying disease including complications and efficacy of therapy.

PLEASE COMPLETE, SIGN AND FAX BACK TO CLINIC/HOSPITAL:

I agree to take over the prescribing and monitoring of this medication and disease.

Signed by (GP).....

Name of GP

Address

or

I am not willing to undertake shared care for this patient because.....
.....
.....

Signed by (GP).....

Name of GP

Address

Please return to

Or Faxback to:.....

References:

1. Cambridge University Hospitals NHS Foundation Trust. Leflunomide- guidelines for its use in rheumatic diseases Approved September 2013, review date February 2015.
2. City & Hackney NHS and Homerton University Hospital: Leflunomide shared care guideline. Approved January 2010.
3. BNF 70.
4. Leflunomide (Arava®; Sanofi) Summary of Product Characteristics accessed on Electronic Medicines Compendium (eMC). Last Updated on eMC 10 October 2014. Last accessed November 17, 2016.
5. NICE Clinical Knowledge Summaries: DMARDs (<https://cks.nice.org.uk/dmards>). Last accessed November 17, 2016.