# LEFLUNOMIDE

## Referral Criteria

- These guidelines are for patients over 16 years of age.
- Shared Care is only appropriate if it provides the optimum solution for the patient.
- Prescribing responsibility will only be transferred when it is agreed by the consultant and the patients' GP
- Safe prescribing must be accompanied by effective monitoring
- When transfer is agreed, the patient will be given a supply of leflunomide sufficient for 4 week maintenance therapy
- **The doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.**

## SHARED CARE RESPONSIBILITIES

### Consultant

1. Undertake the necessary testing to confirm a diagnosis for which leflunomide treatment is recommended.
2. Ensure the patient's concurrent drug therapy is stabilised and there are no contra-indications to treatment with leflunomide
3. Ensure that patient is aware of risks and benefits of medication and has read appropriate information leaflet.
4. Ensure the patient understands the shared care agreement and has signed the Patient Agreement Letter (page 7-8)
5. Perform baseline tests (see Monitoring section) and provide results to GP
6. Initiate treatment and prescribe until the patient has been on a stable dose for minimum of SIX weeks.
7. Send a letter to the GP requesting shared care for this patient.
8. Review the patient in outpatients as clinically appropriate and advise the GP promptly after these reviews on when to adjust the dose, stop treatment or consult with the specialist.
9. Inform GP, by letter, of each clinic attendance and action taken for the management of the patient ensuring current dose, most recent blood results and frequency of monitoring are stated.
10. Evaluate any reported adverse effects by GP or patient.
11. Inform GP of patients who do not attend clinic appointments, admin to contact patient to rearrange
12. Ensure that backup advice is available at all times. (see Contacts section) and respond to any GP queries as soon as practicable
13. Report any adverse effects to the GP and CHM
    http://www.mhra.gov.uk/Safetyinformation/Howwemonitorthesafetyofproducts/Medicines/TheYellowCardScheme/Informationforhealthcareprofessionals/index.htm

### General Practitioner

1. Monitor patient's overall health and well-being.
2. Consider request to prescribe under shared care arrangements and reply only if you do not agree to share care, in a timely manner within 14 days as outlined on page 6 with clinical reasons and return to Consultant and Pharmacy department.
3. Ensure compatibility with other concomitant medication.
4. Prescribe at the dose recommended
5. Monitor U&E, creatinine, FBC and LFTs at recommended frequencies (see Monitoring section) and refer if abnormal.
6. Adjust the dose as advised by the specialist.
7. Stop treatment on advice of specialist or immediately if any urgent need to stop treatment arises (see monitoring section).
8. Report any adverse events to the specialist and CHM.
   http://www.mhra.gov.uk/Safetyinformation/Howwemonitorthesafetyofproducts/Medicines/TheYellowCardScheme/Informationforhealthcareprofessionals/index.htm
9. Inform specialist of any change in the medical condition of patient which may have effect on disease / medications.
10. Ensure patient is offered an annual flu vaccination and a one off pneumococcal vaccination

### Patient

1. Report to specialist or GP if there is not a clear understanding of their treatment and discuss any concerns in relation to treatment

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2. Report any adverse effects to their GP and/or specialist whilst taking Leflunomide, especially unexplained bruising/bleeding, fever, infections or mouth ulcers which should be reported immediately.
3. Report any changes in disease symptoms to specialist whilst taking Leflunomide.
4. Alert GP and/or specialist of any changes of circumstance which could affect management of disease e.g. plans for pregnancy whilst taking Leflunomide.
5. Inform GP or specialist of any other medicines being taken including over-the-counter products.
6. Attend for regular reviews and blood monitoring tests.

## CONTACT NUMBERS FOR ADVICE AND SUPPORT

| **Princess Alexandra Hospital NHS Trust - Rheumatology** | |
|---|---|
| Consultant via switchboard: | 01279 444455 ext 7434 / 7420 |
| Rheumatology specialist nurse | 01279 444455 ext 7434 |
| Nicola McCutcheon Specialist Rheumatology Pharmacist | Ext 7819 Direct dial 01279 827819 (voicemail) |
| **Princess Alexandra Hospital NHS Trust - Pharmacy** | |
| Medicines Information (for medicines related queries) | 01279 827054 |

## CLINICAL INFORMATION

### Prescribed Indications

| | |
|---|---|
| Licensed indications | Rheumatoid arthritis<br>Psoriatic arthritis |

### Therapeutic Summary

Leflunomide is a disease-modifying anti-rheumatic drug (DMARD) for the treatment of adult patients with active rheumatoid arthritis. Leflunomide is similar in efficacy to sulfasalazine and methotrexate but these remain the agents of choice in the majority of patients.

Leflunomide has a long half-life of 1-4 weeks. This means that occasionally a washout procedure using cholestyramine or activated charcoal will be necessary to enhance the elimination of leflunomide if the patient is experiencing a serious adverse reaction.

### Dose and Route of Administration

**Rheumatoid Arthritis**
Starting dose of 10mg and can be increased to 20mg daily depending on treatment response. The recommended dose for rheumatoid arthritis is leflunomide 10 mg to 20 mg once daily for monotherapy. In cases of combination therapy with another potentially hepatotoxic DMARD (eg methotrexate) 10mg once daily is recommended.
**Psoriatic Arthritis**
Recommended daily dose is 20mg once daily.

The therapeutic effect usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months.
There is no dose adjustment recommended in patients with mild renal insufficiency but it is contraindicated in moderate /severe renal failure.
No dosage adjustment is required in patients above 65 years of age.

Leflunomide tablets should be swallowed whole with sufficient amounts of liquid. The extent of leflunomide absorption is not affected if it is taken with food.

See SPC for more details http://www.medicines.org.uk/emc/medicine/26343

### Adverse Effects and Management

Main side effects are rash, hair loss, GI upset, headache, weight loss and breathlessness

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**IMMUNOSUPRESSION -** Patients who have not had chicken pox and are in contact with anyone with the virus are advised to contact either their own GP or the specialist department to have VZ antibody status checked. If antibodies are negative, it is recommended for these patients to have VZ immunoglobulin. Please see Human Varicella-Zoster Immunoglobulin (VZIG) Doc for further information and contact details

## Cautions

- Localised or systemic infection including Hepatitis B or C or history of TB
- Concomitant administration of hepatotoxic or haematotoxic drugs (e.g. methotrexate) is not advisable according to manufacturer, although combination therapy has been used (BSR guidelines).
- The active metabolite of leflunomide, A771726, has a long half-life, usually 1 to 4 weeks. Serious undesirable effects might occur even if the treatment with leflunomide has been stopped. (See washout procedure)
- Due to a potential for additive hepatotoxic effects, it is recommended that alcohol consumption be avoided during treatment with leflunomide, if possible. BSR guidelines recommend alcohol intake to be well within national limits of 4-8 units per week.

## Contraindications

- Hypersensitivity to leflunomide, or to any of the excipients.
- Severe immunodeficiency
- Serious infections
- Impaired liver function due to any cause
- Severe unexplained hypoproteinaemia
- Renal impairment
- Patients with significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid or psoriatic arthritis.
- Patients should avoid 'live' vaccines such as oral polio, MMR, BCG and yellow fever. An inactivated form of polio is readily available.

## Pregnancy and Lactation

Leflunomide is teratogenic and must not be given to pregnant women or women of child bearing potential unless reliable contraception is used. Women planning to have children should either discontinue the drug 2 yrs prior to conception or have a rapid removal of its active metabolite by following the washout procedure.

Men should use effective contraception 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 wash out. Any pregnancy within 2 yrs of discontinuation of leflunomide should be discussed with rheumatologist if drug washout has not been performed. Notify pharmaceutical company in the event of pregnancy while on leflunomide.

Breast feeding is contra-indicated.

## Washout procedure

To aid drug elimination in cases of serious adverse effect or before conception, stop treatment and give either:

- Cholestyramine 8g three times day for 11 days **OR**
- Activated charcoal 50g four times a day for 11 days

However, also following either of the washout procedures, verification by 2 separate tests at an interval of at least 14 days and a waiting period of one-and-a-half months between the first occurrence of a plasma concentration below 0.02 mg/L and fertilisation is required. (See SPC for full information).

## Interactions with other medications

- Tolbutamide
- Phenytoin

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- Warfarin

Please note that as leflunomide has an extremely long half life, interactions can potentially be serious and more actions may be required beside just discontinuation of the drug e.g. washout. This may also be of practical importance when switching from leflunomide to another DMARD.

## MONITORING STANDARDS FOR LEFLUNOMIDE AT PRINCESS ALEXANDRA HOSPITAL NHS TRUST

The following standards have been agreed for the monitoring of leflunomide in all patients at Princess Alexandra Hospital NHS Trust.

| | | |
|---|---|---|
| **Pre-treatment by Specialist** | Height, weight, blood pressure, FBC, U&Es, LFTs, TPMT phenotype, creatinine, varicella status, hepatitis B&C status<br>Blood pressure: if > 140/90 on two consecutive readings 2 weeks apart, treat hypertension prior to commencing therapy. | |
| **Initial monitoring by Specialist** | FBC<br>Creatinine / calculated GFR<br>ALT +/- AST<br>Albumin | Every 2 weeks until on stable dose for 6 weeks. |
| **Ongoing monitoring by GP** | FBC<br>Creatinine / calculated GFR<br>ALT +/- AST<br>Albumin | Then once on stable dose monitor monthly for 3 months. |
| | FBC<br>Creatinine / calculated GFR<br>ALT +/- AST<br>Albumin | At least every 12 weeks |
| **BP and weight at each monitoring visit** | | |
| **Dose increase** | FBC<br>Creatinine / calculated GFR<br>ALT +/- AST<br>Albumin | Every 2 weeks until on stable dose for 6 weeks, then revert to previous schedule |

## Action and Advice

If a GP has taken blood tests for the general medical management of a patient and blood test results fall into the categories below or the patient reports one of the adverse events below, these are recommendations for considering the withdrawal of Leflunomide therapy:

| **Blood Test Results** | |
|---|---|
| WBC < 3.5 x $10^9$/l | Withhold until discussed with specialist team |
| Neutrophils < 2.0 x $10^9$/l | Withhold until discussed with specialist team |
| Platelets < 150 x $10^9$/l | Withhold until discussed with specialist team |
| > 2-fold rise in AST, ALT (from upper limit of reference range) | Withhold until discussed with specialist team |
| **Symptoms** | |
| Rash or itch | Withhold until discussed with specialist team |
| Abnormal bruising or bleeding | Withhold until FBC results available & discuss with specialist team |
| Severe sore throat | Withhold until FBC results available & discuss with specialist team |
| Hypertension | If BP >140/90 treat as per NICE guidance. If remains uncontrolled, withhold until discussed with rheumatologist. |
| Hair loss | Seek advice from rheumatologist |
| Weight loss | If >10% with no cause identified, withhold until discussed with rheumatology team. |
| Breathlessness | If increasing shortness of breath, withhold until discussed with rheumatology team. |
| GI Upset | Give symptomatic treatment and discuss with rheumatology team. |

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## Further Information

This document does not replace the SPC and BNF and should be read in conjunction with it.

BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs
https://academic.oup.com/rheumatology/article/56/6/865/3053478

## Useful information

West Essex CCG webpage for Shared Cared Guidelines –
Shared Care Letter - West Essex CCG

Arthritis Research UK Patient Information Leaflet
http://www.arthritisresearchuk.org/arthritis-information/drugs/methotrexate.aspx

CKS DMARD
http://cks.nice.org.uk/dmards#!scenario:7

Arthritis Research UK Patient Information Letter
http://www.arthritisresearchuk.org/arthritis-information/drugs/leflunomide.aspx

GMC Prescribing Guidance: Shared Care
https://www.gmc-uk.org/guidance/ethical_guidance/14321.asp

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## GP response to Shared Care Agreement

(only complete & send if NOT participating in shared care)

**This shared care agreement has been approved by the Medicines Management Optimisation Programme Board**

| | |
|---|---|
| Patient Name: | NHS No: |
| Consultant: | Medicine requested for shared care: **leflunomide** |

I will **NOT** be undertaking the GP responsibilities as described in the agreed shared care agreement. My clinical reasons for declining shared care for this patient are listed in the box below:

| |
|---|
| |

Yours sincerely

{GP name}

{Surgery}

**Please send a copy of this response to:**
1. The Specialist/consultant requesting shared care
2. **ANONYMISED COPY OF THIS FORM ONLY** to the E-MAIL: **tpa-tr.ClinicalPharmacy@nhs.net**

(sending a copy of this form to the PAH pharmacy will help to identify any inappropriate requests for shared care e.g. indication not covered, hospital monitoring requirements not fulfilled. It will also help to inform the CCG Medicines Optimisation Team of the reasons shared care is not being undertaken by GPs allowing for changes to be made in future updates to improve patient safety)

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The Princess Alexandra Hospital NHS
NHS Trust

Hamstel Road
Harlow, Essex
CM20 1QX

Tel: 01279 444455

Information for patients:

## SHARED CARE:
## Agreement information and confirmation

**Patient name:**

.....

**Medicine:**

.....

**We would be grateful if you would take time to read this information as it will help us work with you to manage your condition and ensure safe prescribing of the specific medicine listed above.**

### What is a Shared Care Agreement (SCA)?

A Shared Care Agreement (SCA) enables the care you have for a specific condition to be shared between the hospital and your GP.

The agreement means that the medicine the hospital has started, can be continued by your GP, so you won't have to visit the hospital to collect your medicine.

The SCA gives information on your medicine, guidance on the prescribing and monitoring responsibilities for your consultant (in the hospital), your GP and you. For an SCA, to work everyone involved must understand it and communicate effectively.

Your consultant and your GP will need to sign the agreement and if you agree to this approach, we would ask you to sign this letter, to indicate your agreement to have your care managed in this way.

### How does shared care work?

**Your consultant and GP share responsibility for your care.**

The consultant is a specialist in your condition and will start prescribing your medicine, making sure it is suitable for you. There will come a point in your treatment when you may not need to be monitored by the consultant as often and this monitoring can be done by your GP.

Once your GP has agreed to the SCA, they will be able to prescribe the same medicine for you at the dose recommended by the consultant.

The organisation which regulates GPs, the General Medical Council, says that 'when a GP prescribes a medicine, the GP needs to satisfy themselves that the prescription is needed, appropriate for the patient and within the limits of their competence'.

So, your GP can only issue a prescription if the consultant and you keep to the responsibilities you have agreed (see below). If responsibilities are not kept or if the GP no longer feels it is safe to prescribe the medicine, he/she will explain the reasons to you and your consultant, then prescribing responsibilities will be transferred back to the hospital.

### What do I need to do to ensure the SCA can continue?

- **Attend hospital outpatients**
  You must still attend the hospital for regular reviews as directed by your consultant (these may be less frequent than before). If you do not attend your hospital appointments, your GP will not be able to continue issuing prescriptions for this medication.
- **Attend GP appointments**
  You must attend any appointments you have with your GP in relation to this medicine, so they can look after you effectively.
- **Have blood tests as you have been advised to**
  Your consultant should have informed you

*continued overleaf*

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if and how often you need to have blood monitoring tests. You can usually have your blood taken at an appropriate clinic and not need to go to the hospital.

- If you do not have the blood monitoring tests as advised by your consultant, your GP will no longer be able to issue you with prescriptions as it would not be safe to do so.

## What do I do if I am having side-effects to the medicine?

Your consultant should have informed you of the common side-effects to expect and what to do if you experience them. If you think you may be having side-effects from a medicine report these directly to your consultant. Your GP may need to seek advice from your consultant before issuing you with another prescription; this is to ensure it is safe for you to continue on the medication.

## What if my disease symptoms change or get worse?

Report any changes in disease symptoms or circumstances that could affect management of your disease to your consultant.

## What about the other medicines I take?

Inform your GP and the consultant of all other medicines you are taking, including those you may have bought yourself. Do not take new medicines (including those you could buy) until you have discussed this with your pharmacist, GP or consultant.

If you would like to go ahead with a shared care agreement for the specific medication identified on page 1, please sign below to confirm that you:

- Understand the shared care agreement.
- Are happy to have your care for this aspect of your health managed by a shared care agreement.
- You agree to attend regular review appointments as requested.
- You agree to have blood tests as required.

Patient's signature .....

Date .....

Print name .....

If at any point in time you would like this shared care agreement to stop, please talk to your GP.