SHARED CARE GUIDELINES

Homerton University Hospital NHS
NHS Foundation Trust

NHS City and Hackney

LEFLUNOMIDE

In Rheumatological Conditions for Adults ≥ 18 years of age

INTRODUCTION

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.

DOSE AND ADMINISTRATION

A starting dose of **10 mg** once daily, increasing to **20 mg** as tolerated. No dose reduction is required in the elderly or in those with mild renal impairment.

CAUTIONS.

- Extreme caution in blood disorders.
- Renal impairment.
- Hepatic imparment.
- Alcohol intake should be kept well within national limits).
- Recent/concomitant treatment with other hepatotoxic or myelotoxic DMARDs
- **Vaccinations**: live vaccines should be AVOIDED (ie 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.

CONTRA-INDICATIONS

- Patients under 18 years.
- Pregnancy and lactation.
- **Teratogenesis** - Female patients should stop drug at **least 2 years before** possible conception and males at **least 3 months before**. A washout procedure (using colestyramine or activated charcoal) may reduce this period to 2 to 3 months – see below for guidance.

- Moderate or severe renal (eg creatinine clearance ≤ 20ml/min) or hepatic impairment.
- Active infection or immunodeficiency.
- Severe anaemia, leucopenia or thrombocytopenia.
- Severe hypoproteinaemia.
- Uncontrolled hypertension.

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COMMON/SIGNIFICANT 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 2C9 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**.

Refer to the BNF for comprehensive list.

SIDE- EFFECTS

- Gastrointestinal disturbances (diarrhoea, nausea, vomiting, anorexia, 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.
- Biochemical changes (hypokalaemia, hypophosphataemia, hyperlipidaemia).
- Blood disorders (leucopenia, eosinophilia, thrombocytopenia, anaemia).
- Skin reactions (rash, dry skin, alopecia, pruritis, Stevens-Johnson syndrome).

See BNF for comprehensive list.

Important: discontinue treatment and institute washout procedure in case of severe side-effects.

** **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.**

MONITORING STANDARDS FOR LEFLUNOMIDE IN RHEUMATOLOGY

The following standards have been agreed for the monitoring of leflunomide in rheumatology patients.

Pre-treatment	FBC, LFTs, U&Es, ESR, BP (treat hypertension before initiating drug), weight.
Monitoring	FBC and LFTs every 2 weeks for first 6 months, then every 8 weeks thereafter **Note**: severe, potentially life-threatening hepatotoxicity reported usually in first 6 months BP every four weeks until dose stable for first 6 months, then every 8 weeks thereafter. Blood checks should be continued long-term, at least once monthly, if co-prescribed with another immunosuppressant or potentially hepatotoxic agent.

** **Monitoring should continue for 3 months AFTER treatment has STOPPED.**

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EVENTS AND ACTION

Laboratory Events	Values	Action
WBC	Decrease to < 3.5 x 10^9/L	**Withhold until discussed with specialist team.**
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		Repeat LFTs as early sign of liver toxicity. Stop and discuss with specialist team if continue to deteriorate.

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.
Weight loss	Monitor carefully. If >10% weight loss with no other cause identified, reduce dosage or stop and consider washout.
Breathlessness	Stop if increasing shortness of breath occurs. Discuss with specialist team.

WASHOUT PROCEDURE

Contact Rheumatology Department – only to be performed on advice of specialist team.

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 Cholestryramine 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.

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REMEMBER if unsure at any point: Contact the Consultant Rheumatologist on 020 8510 7612 or Specialist Nurse on 020 8510 7200 or Rheumatology Specialist Registrar on bleep 120, through the Homerton Hospital switchboard.

Share care guideline: is a document which provides information allowing patients to be managed safely by primary care, secondary care and across the interface. It assumes a partnership and an agreement between a hospital specialist, GP and the patient and also sets out responsibility for each party. The intention to shared care should be explained to the patient and accepted by them. Intrinsic in the shared care agreement is that the prescribing doctor should be appropriately supported by a system of communication and cooperation in the management of patients. The doctor who prescribes the medicine has the clinical responsibility for the drug and the consequence of its use.

Responsibility of Consultant prescribing leflunomide in shared care agreement

1. Ensure that the patient/carer is an informed recipient in therapy
2. Ensure that patients understand their treatment regimen and any monitoring or follow up that is required (using advocacy if appropriate)
3. Ensure baseline investigations are appropriate before commencing treatment
4. Initiate leflunomide and stabilise patient on a therapeutic dose of leflunomide before referral to the GP
5. Send a letter to the GP requesting shared care for this patient
6. Clinical and laboratory supervision of the patient by blood monitoring and routine clinic follow-up on a regular basis
7. Send a letter/results notification to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring
8. Evaluation of any reported adverse effects reported by GP or patient
9. Advise GP on review, duration or discontinuation of treatment where necessary
10. Inform GP of patients who do not attend clinic appointments
11. Ensure that back up advice is available at all times

Responsibility of General Practitioner prescribing in shared care agreement

1. Check and reinforce patient 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
2. Monitor patient's overall health and well-being
3. Prescribe leflunomide after communication with specialist regarding the need for treatment
4. Monitor treatment as outlines by shared care guideline
5. Promptly refer to the specialist if there is a change in the patient's condition
6. Report any adverse events to the consultant where appropriate
7. Report ant adverse events to the CHM where appropriate
8. Help in monitoring the progression of disease

Responsibility of PCT

1. To provide feedback to trusts via Trust Medicines Committee
2. To support GPs to make the decision whether or not to accept clinical responsibility for prescribing
3. To develop and revise shared care guidelines
4. To support trusts in resolving issues that may arise as a result of shared care

Patient responsibility

1. Report any adverse effects to their GP and/or specialist
2. Ensure they have a clear understanding of their treatment
3. Report any changes in disease symptoms to GP and/ or specialist
4. Alert GP and/or specialist of any changes of circumstances which could affect management of disease e.g. becoming pregnant of plans for starting a family.

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References:
Monitoring and events/action data based on BSR guidelines (also available at http://cks.library.nhs.uk) and BNF 57 (March 2009):

Chakravarty, K., McDonald, H., Pullar, T. et al. (2008) BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. Rheumatology 47(6), 924-925. [Last accessed 28 April 2009]

Disease Modifying Antirheumatic Drugs (DMARDS) Leflunomide (Arava). North and East Devon Health Comminity Shared Care Prescribing Guideline. July 2006.