790FM.2.1 LEFLUNOMIDE FOR USE IN RHEUMATOLOGY
Shared Care Protocol

This protocol provides prescribing and monitoring guidance for leflunomide therapy. It should be read in conjunction with the Buckinghamshire responsibilities for amber protocol medicines (appendix 3 of Buckinghamshire Joint Formulary Policy), the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF.

BACKGROUND FOR USE

Leflunomide is a disease modifying antirheumatic drug (DMARD). It should only be initiated by a Rheumatologist. It's uses in this shared care protocol include:

- **Rheumatoid arthritis (RA)** (licensed). Can be used as monotherapy or in combination with another DMARD. (The use of one or more DMARDs is recommended in NICE guideline [NG100] on the management of adults with RA, published July 2018.)
- **Psoriatic arthritis** (licensed).
- **Systemic vasculitis** (unlicensed).

SUPPORTING INFORMATION

- Leflunomide is an established drug with a known side effect profile.

CONTRAINDICATIONS

- **Impaired liver function tests due to any cause**
- **Patients with significant impairment of bone marrow function or significant anaemia, leucopenia, neutropenia, thrombocytopenia due to causes other than underlying arthritis**
- **Moderate to severe renal insufficiency**
- **Severe hypoproteinemia**
- **Current infection**
- **Pregnancy:**
  - Leflunomide is not recommended in women planning pregnancy.
  - Women should be taking effective contraception whilst on treatment.
  - **Women on leflunomide considering pregnancy should be referred urgently to Rheumatology** for advice, including organising blood tests. Women should stop treatment and undergo cholestyramine washout which will be organised by Rheumatology. Before conception, two blood tests 14 days apart are required to check leflunomide plasma levels, which must drop below 0.02 mg/l. This is a free service available from Aventis Pharma. Ltd. To request a laboratory form call 01732 584493.
  - If accidental conception occurs on leflunomide, the drug should be stopped immediately and cholestyramine washout organised through rheumatology department until plasma levels are undetectable. There is no human evidence of increased congenital abnormalities on leflunomide if washout is given.
- **Breastfeeding:** Not recommended.
- **Male patients:** Based on limited evidence leflunomide may be compatible with paternal exposure. Please refer to the rheumatologist if planning a family.
- **Hypersensitivity:** To leflunomide, teriflunomide, peanut or soya.

PRECAUTIONS

- Alcohol intake should be limited (maximum 4 - 6 units per week).
- **Peri-operative management**. Leflunomide should NOT routinely be stopped in the peri-operative period. Attention to liver function tests (LFT) is important and combinations with other potentially hepatotoxic drugs avoided. In surgical settings where there is a high risk of infections please discuss with a Rheumatologist.
- **Intercurrent infections**. During a serious infection (i.e. requiring IV antibiotics or hospitalisation) leflunomide should be temporarily discontinued until the patient has recovered from the infection. Treatment can be continued in patients with minor infections requiring a short course of oral antibiotics.

- **Chickenpox/shingles**. Stop leflunomide if proven infection. For those with exposure to chickenpox or shingles and no history of infection/vaccination, check that immunity to varicella zoster virus (VZV) infection has been checked. If the patient is susceptible, a course of oral aciclovir or valaciclovir is recommended unless there are significant concerns of renal toxicity or malabsorption. Discuss with a Microbiologist.

DOSAGE

- Typical dosage is 10 - 20 mg PO daily.
- There is no dose adjustment in patients over 65 years of age or those with mild renal insufficiency.
- A dose of 10 mg PO daily is recommended if leflunomide is used in combination with another potentially hepatotoxic DMARD, e.g. methotrexate.
- Leflunomide has an elimination half-life of around 8 weeks. In cases of significant adverse reactions, 'washout' procedure to speed elimination may be necessary.

Prescribing points

Prescriptions must state the form, strength, dose and directions in full.

The use of 'as directed' in prescribing should be avoided. A specific dose must be applied to each prescription.

TIME TO RESPONSE

8 to 12 weeks. Symptoms may further improve after several months.

PRE-TREATMENT ASSESSMENT BY THE RHEUMATOLOGIST

- Weight and height.
- Full blood count (FBC), LFT, urea and electrolytes (U&Es), erythrocyte sedimentation rate ESR or C-reactive protein (CRP).
- Blood pressure (BP). If >140/90 on two consecutive readings, two weeks apart, refer back to GP for treatment of hypertension before commencing leflunomide.
- Assessment of comorbidities.
- Patients should be offered screening for occult viral infections including Hepatitis B, Hepatitis C and HIV in particular if they are at risk of occult viral infections.
- Recommend vaccinations for influenza and pneumococcus.

VACCINATION recommended by the Specialist to the patient and GP

- Pneumococcal vaccination should be administered as a single dose polysaccharide PPV-23 (Pneumovax), if possible, prior to initiation of leflunomide therapy or as soon as possible after.
- Annual influenza vaccine should be recommended to all patients.
- Live vaccines should not be given to patients who are receiving or have received immunosuppressive therapy in the past three months[6].
- Patients who have received a live vaccine should wait until their immune response has been established before commencing immunosuppressive therapy. For most viral live vaccines, a period of up to four weeks should be sufficient[6]. Inactivated polio vaccine is available although a sub-optimal response may be seen.

ROLES AND RESPONSIBILITIES

Shared care assumes communication between the specialist, GP and patient. The intention to share care should be explained to patients and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. Unless otherwise stated in the protocol, the responsibilities are as follows:

Specialist

- Initiate treatment and prescribe until the dose is stable and/or the GP formally agrees to shared care.
- Ensure the patient understands the nature and complications of drug therapy and their role in reporting adverse effects promptly.
- Where appropriate, provide advice to the patient on the impact of leflunomide on fertility, pregnancy and breastfeeding.
- Provide a copy of patient information leaflet and drug monitoring card where appropriate.
- Send a letter to the GP requesting shared care. Outline shared care protocol criteria and how often monitoring should be done.
- Liaise with the GP regarding changes in disease management, drug dose, missed clinic appointments.
- Be available to give advice to the GP and patient throughout treatment.

GP

- Prescribe medication once the dose is stable and shared care is agreed.
- Ensure all monitoring is completed in accordance with the specific shared care protocol.
- Check and record results then advise the specialist of any deteriorations or abnormal results.
- Notify the specialist regarding any changes in patient's condition, any adverse drug reactions or failure to attend tests.

Patient

- Agree to treatment and monitoring after making an informed decision.
- Agree to being under the shared care of the GP and specialist.
- Attend for blood tests and monitoring when required.
- Ensure monitoring card is kept up to date and is brought to all appointments.
- Report any side effects to the GP or a member of the specialist team.
- Be responsible for taking effective contraception whilst on leflunomide because it is not recommended for use during pregnancy.
- Inform the GP or specialist team urgently if pregnancy is being planned so that referral to Rheumatology can be arranged.

Note: If the patient does not attend blood monitoring, then treatment will be stopped. If the patient is more than 4 weeks late with their monitoring, then treatment should be stopped.

ONGOING MONITORING SCHEDULE

- **FBC, alanine transaminase (ALT), albumin (Alb), creatinine/calculated glomerular filtration rate (GFR)** every 2 weeks until dose remains unchanged for 6 weeks; thereafter every month for 3 months; thereafter every 3 months. More frequent monitoring is appropriate for patients at higher risk of toxicity i.e. on combination therapies. The specialist will advise the GP if this is necessary.
- **After dose increase**, blood tests should be monitored 2 weekly for 6 weeks followed by return to the previous schedule. This is organised by the GP on the advice of the specialist.
- Patients taking leflunomide in combination with methotrexate should have monthly blood tests. The specialist will advise the GP on the monitoring necessary when the patient is transferred to primary care.
- **BP and weight -** 3 monthly.
- **CRP or ESR** every 3 - 6 months depending on disease activity. The rheumatologist will advise on frequency.

SIDE EFFECTS AND ACTIONS TO BE TAKEN

SIDE EFFECTS	ACTION
White blood cell count (WBC) <3.5 x 10^9/l Neutrophils <1.6 x 10^9/l Platelets <140 x 10^9/l	Stop leflunomide and repeat WBC. If repeat count is normal continue. If abnormal discuss with rheumatologist.
Liver function tests ALT rise Mild <1.5 x upper limit of normal (ULN) Moderate 1.5 - 3 x ULN Severe >3x ULN (or ALT >100) or unexplained reduction in Alb <30 g/l	Check if there was a recent increase in dose, new medications added e.g. antibiotics, statins, recent viral or bacterial infection, Check for increased alcohol intake, increased use of non-steroidal anti-inflammatory drugs (NSAIDS), use of over the counter (OTC) products. Repeat in 2 weeks. If still raised, discuss with specialist. If on leflunomide 20 mg PO daily, reduce the dose to 10 mg PO daily and repeat in 1 - 2 weeks. If still raised stop leflunomide and contact Rheumatology. Withhold and discuss with specialist urgently. If persistent elevation after one week despite stopping the drug the specialist will consider washout.
Hypertension	If BP >140/90, treat according to NICE guidance.[4] If BP remains uncontrolled, consider drug discontinuation.
Rash or severe mouth ulcers	Consider dose reduction with or without antihistamines. If severe, stop and consider washout procedure.
Severe sore throat, abnormal bruising	Immediate FBC and withhold until result of FBC available.
GI upset/nausea, diarrhoea	Not uncommon. Usually settles but, if severe, may require reduction in dose/discontinuation of the drug with or without washout procedure.
Weight loss	If greater than 10% with no identified cause, reduce or discontinue with or without washout.
Headache	If severe consider dosage reduction.
Alopecia	Most cases are mild/moderate and resolve during treatment. If severe, consider dosage reduction.
Hypersensitivity pneumonitis/ reactions	Acute allergic reactions rarely occur. Patients should be made aware of this rare complication. If they do occur, withhold treatment and speak with rheumatologist.
Tenosynovitis and rarely tendon rupture	Discuss with rheumatologist.

Please note that in addition to absolute values for haematological indices, a rapid fall or a consistent downward trend in any value should prompt caution and extra vigilance. In order to monitor trends it is recommended that all blood test results are entered in the patient held monitoring booklet.

WASHOUT PROCEDURE IN SECONDARY CARE

To aid drug elimination in case of significant adverse effect, or before conception. After stopping leflunomide:

- Cholestyramine, 8 g PO three times daily for a period of 11 days, OR
- Activated charcoal, 50 g PO four times daily for a period of 11 days.

NOTABLE DRUG INTERACTIONS (See BNF and SPC)

- **Other haematotoxic and hepatotoxic drugs, e.g. methotrexate:** Reduce monitoring interval.
- **Warfarin:** Plasma levels may be increased by leflunomide. Monitor INR of warfarin treated patients more closely at the time of treatment initiation. Advise patient to inform anticoagulation clinic.
- **Phenytoin, phenobarbital and carbamazepine:** Plasma levels may be increased by leflunomide. Check phenytoin plasma levels of leflunomide treated patients if they develop signs of toxicity.
- **Tolbutamide:** Hypoglycaemic effects may be increased by leflunomide.
- **Rifampicin:** Increases leflunomide plasma levels.
- **Paclitaxel:** Concentrations increased with leflunomide therapy.

Leflunomide has a half-life of approximately 8 weeks and interactions with these drugs may continue for that time after leflunomide has been discontinued.

BACK-UP INFORMATION AND ADVICE

Contact Details	Wycombe and Amersham	Stoke Mandeville
Rheumatology	01296 315960 (specialist nurse helpline – may take 48 hours for response; not for urgent queries). In an emergency contact consultant rheumatologist of the week 01296 316664 Rheumatology Reg: Bleep 905/907 via switchboard E-mail: bht.rheumatology@nhs.net	01296 315960 (specialist nurse helpline – may take 48 hours for response; not for urgent queries). In an emergency contact consultant rheumatologist of the week 01296 316664 Rheumatology Reg: Bleep 905/907 via switchboard E-mail: bht.rheumatology@nhs.net
Medicines Resource Centre	Bucks.medicinesresourcecentre@nhs.net 01494 425355 (9am to 5pm).	

SHARED CARE AGREEMENT FORM

Available on DocGen. When not available, use the Word version linked here.

REFERENCES

1. Ledingham J et al. 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
2. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. https://academic.oup.com/rheumatology/article/55/9/1693/1744535
3. NICE NG100 updated 11 July 2018 Rheumatoid arthritis in adults: management https://www.nice.org.uk/guidance/ng100/chapter/Recommendations#initial-pharmacological-management
4. NICE NG 136 Hypertension in adults: diagnosis and management.: https://www.nice.org.uk/guidance/ng136
5. Leflunomide 20mg film coated tablets Arava® Summary of Product Characteristics last updated on the emc 15 August 2017 https://www.medicines.org.uk/emc/medicine/26344
6. Contraindications and special considerations: the green book chapter 6, page 5 updated April 2017. Gateway number 2017523 G https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/655225/Greenbook_chapter_6.pdf

See also:
Guideline 280FM Management of Patients on Immunosuppressants admitted with Suspected Infections

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Author/s	Karen Hills, Rheumatology SPN, Dr M Magliano, Consultant Rheumatologist, Shona Lockie, Clinical Director, Medicines Management Bucks CCG, Breda Cronnolly, Medicines Optimisation Pharmacist, Maire Stapleton, Formulary Manager.
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