Torbay and South Devon NHS
NHS Foundation Trust

Leflunomide Shared Care Guideline for GPs

Indication:

Active rheumatoid arthritis and other types of inflammatory arthritis

Specialist Responsibility:

- Assess patient for co-morbidities
- Request baseline tests including FBC, U+Es and eGFR, LFTs (and chest X-ray and lung function tests in high risk patients)
- Counsel patient on benefits, side effects, frequency of dosing and monitoring requirements and provide written information
- **Treatment with these drugs will be initiated by the specialist, who is responsible for prescribing until shared care is agreed. Any GP who does not feel confident to undertake the clinical and legal responsibility for a shared care drug is not obliged to undertake the prescribing and should discuss this with the specialist.**
- Specify target doses, monitoring and review dates at clinically relevant time intervals for both the GP and specialist team and any other patient specific information.
- **Initiate therapy and provide at least the first 6 weeks of Leflunomide and until GP has confirmed willingness to share care.**
- Provide advice as required by the GP and review patient as necessary

GP responsibility

- On-going prescription of Leflunomide
- Monitoring as per instructions below
- Report adverse events to specialist team and to the MHRA via the yellow card scheme
- Report and seek advice from the specialist team on any aspect of patient care which is of concern and may affect treatment
- Inform specialist team if treatment is stopped for any reason

Dosage

- The **starting dose is usually 20 mg on alternate days**.
- The dose range for Leflunomide is 10-20mg daily.
- Dose should be increased as set out in the dosing letter. This is usually an increase from 20mg on alternate days to 20mg daily after 4-8 weeks.
- Leflunomide is available as 10 and 20mg tablets.
- In common with other 2nd line agents, Leflunomide will take 10-12 weeks to have any effect.

- **Monitoring:Required tests:**
    - **FBC, U+Es and eGFR, LFTs and albumin**
    - **Blood pressure**
- **Frequency:**
    - **Every 2 weeks for 6 weeks,**
    - **Then monthly for 3 months**
    - **Then 12 weekly there after unless there are exceptions as detailed below**
- **For dose increases monitor blood tests every 2 weeks until stable dose for 6 weeks**
- **Exceptions to monitoring rules**
    - Monthly monitoring required if:
        - Leflunomide taken in combination with methotrexate, azathioprine or mycophenolate
        - High risk or significant co-morbidities that would affect monitoring results. i.e. co-existing liver or renal disease, highly fluctuant blood results.
    - The specialist will inform the GP if this is required
- Consider stopping Leflunomide and seek advice (e-mail tsdft.rheumatologydmards@nhs.net or **01803-654939**) if any of the following occur:
    - WCC or platelet count falls on 3 successive occasions
    - Total WCC <3.5 or
    - Neutrophils < 1.6
    - Isolated lymphopenia is not usually an indication for cessation of Leflunomide therapy
    - Platelet count < 140
    - MCV >105
    - Unexplained eosinophilia >0.5
    - ALT or AST >100 U/l
    - Unexplained drop in albumin <30g/l
    - Creatinine >30% above baseline +/- eGFR <60
    - Uncontrolled hypertension
- The MCV may rise on Leflunomide – if >105, consider checking B12 / folate if patient is anaemic.
- The patient should be advised to report signs of infection (e.g. persistent sore throat, fever) or easy bruising.

Side effects:

- This list is not exhaustive, for additional information please consult the BNF and product SPCs

Common	• **Diarrhoea** - can occur at any stage. Advise patient to take Leflunomide with food and in the evening. May resolve with Leflunomide dose reduction. Withhold treatment if does not resolve or is severe and discuss with specialist.
Less common	• **Alopecia rash** • **Hypertension** • **Mild Leucopenia -** may occur abruptly; concomitant use of Methotrexate may increase risk. The patient should be advised to report easy bruising or infection. • **LFT abnormalities** • **Headache** • **Mouth ulcers**
Uncommon	• **Pulmonary symptoms (~0.1%) - I**ndicated by persistent dry cough or shortness of breath. Patient should report these symptoms, stop Leflunomide and urgent specialist advice should be sought. • **Bone marrow suppression** • **Hepatitis**

NB The active metabolite or Leflunomide has a very long half-life and a washout procedure may be required if significant side effects/haemotoxicity/hepatotoxicity.

Drug interactions:

- This list is not exhaustive, for additional information please consult the BNF and product SPCs

Cholestyramine	**Avoid**	Effect of Leflunomide significantly decreased
Methotrexate		Increased risk liver/haemotoxicity
Phenytoin	**Caution**	Plasma concentration of phenytoin potentially increased
Tolbutamide		Hypoglycaemic effect enhanced
Warfarin		Monitor INR closely – anticoagulant effect enhanced

Cautions and Contraindications

Alcohol:

- There is a theoretical risk of liver toxicity with Leflunomide and alcohol and there are no specific national guidelines. We recommend limiting intake to 14 units per week and not taking this in one go.

Vaccines:

- **Pneumococcal vaccination** (Pneumovax® II) every 10 years and **annual influenza vaccinations** are strongly recommended for patients with inflammatory arthritis
- Live vaccinations are contraindicated until 3 months after cessation of Leflunomide.
- The shingles (Zostavax) vaccine is a live attenuated vaccine and treatment with Leflunomide 10-20mg/day as monotherapy is considered a **relative contraindication** to administering the vaccine. This should be agreed with Rheumatology and microbiology on a case by case basis
- Passive immunisation may be given with varicella zoster immunoglobulin (VZIg) in non-immune patients exposed to chicken pox or shingles. Contact specialist for advice.

Pregnancy, breastfeeding and fertility:

- Leflunomide is **contraindicated** in pregnancy and in breastfeeding women
- Reliable and effective **contraception** must be practised by **female** patients during treatment. Female patients should cease Leflunomide therapy and commence cholestyramine washout prior to conception**.**
- In accidental pregnancy, Leflunomide should be stopped and cholestyramine given under specialist support.
- Breast feeding is not advisable given a lack of data on excretion of Leflunomide into breast milk.
- Limited evidence suggests that Leflunomide may be compatible with paternal exposure. Seek specialist advice

Elective surgery

- Continue Leflunomide but consider infection risk and drug interactions

Infection

- Leflunomide can be continued while patient receiving oral antibiotics
- Leflunomide should be stopped in the acutely unwell older person or while receiving IV antibiotics.
- Please seek advice if there are recurrent infections

Advice and Support

- Rheumatology.sdht@nhs.net
- Nurses helpline: 01803 654939
- Rheumatology secretaries: 01803 655897/54832/55759

References

1. BNF 74. September 2017-March 2018

2. SPC Azathioprine 50mg tablets. Accessed via www.medicines.org.uk June 2018

3. Ledingham J et al. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. *Rheumatology*, Volume 56, Issue 6, 1 June 2017, Pages 865–868

4. Flint J et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. *Rheumatology*, Volume 55, Issue 9, 1 September 2016, Pages 1693–1697