THE SHEFFIELD AREA PRESCRIBING GROUP

Prescribing Guideline

For

Leflunomide

Prescribing guideline developed by:

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- Approved by consultants within the Rheumatology Team at STH

Based on the SCP for the monitoring of leflunomide developed, November 2012 and updated in April 2015.

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Prescribing Guideline for Leflunomide

Statement of Purpose

This prescribing guideline has been written to enable the continuation of care by primary care clinicians of patients initiated on leflunomide by the rheumatology department at Sheffield Teaching Hospitals. Primary care will only be requested to take over prescribing of leflunomide within its licensed indication.

Indication

Leflunomide is indicated for the treatment of adult patients with:
- active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD)
- active psoriatic arthritis (not all brands are licensed for this indication)

Selection of patients

All adult patients will be treated and stabilised on leflunomide by a secondary care specialist. Once stabilised patients are suitable for referral to a primary care service – this will usually take 6 months.

The following patients are excluded from this Shared Care arrangements:
- Moderate or severe renal impairment;
- Significant hepatic impairment;
- Severe pleural effusion or ascites;
- Children under 16 years;
- Pregnancy

Dosage

Oral
Maintenance dose of leflunomide: 10mg – 20mg daily

Continue NSAIDs or analgesics at least until treatment response

Contra-indications

- Hypersensitivity to the active substance (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) or to any of the excipients
- Severe hypoproteinaemia
- Impairment of liver function
- Moderate or severe renal impairment (eGFR <60mL/minute/1.73 m²)
- Pregnancy, breast-feeding and women of child bearing potential not using reliable contraception (see under additional information)
- Severe immunodeficiency states/serious infections.
- Patients with significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid or psoriatic arthritis.
- Live vaccines, e.g. Rubella, BCG, small pox, yellow fever, etc, should not be given to patients taking leflunomide (refer to Green Book for further advice on vaccines).
- Patients on leflunomide for the management of inflammatory conditions may not be sufficiently immunosuppressed to contraindicate administration of zoster vaccine. The degree of immunosuppression should be assessed on a case by case basis. Specialists with responsibility for patients in the vaccine eligible age cohorts should include a statement of their opinion on the patient's suitability for Zostavax® in their correspondence with primary care. If clinicians administering the vaccine have concerns about the degree of immunosuppression they should contact the relevant
specialist.

- Live oral polio should not be given to patient or household contacts. **NB. Pneumococcal polysaccharide vaccine & annual flu vaccine should be given.**
- Patients with serious infections

**Side effects**

The details below are not a complete list and the **BNF** and the **SPC** remain authoritative.

- Common - nausea, anorexia, weight loss, oral ulceration, minor hair thinning, abdominal discomfort, diarrhoea, headaches, leucopenia, hypertension*, rash, elevation of liver parameters.
- Uncommon – thrombocytopenia and anaemia**. Patients should be warned to report a sore throat and abnormal bleeding/bruising
- Rare –hepatotoxicity and pulmonary toxicity

*Hypertension: consider dose reduction, introduction of anti-hypertensive agent in line with **NICE CG127** - discontinuation of treatment if no response. **NB Hypertension should be controlled prior to commencing treatment.**

**MCV>105fl: check B12 and folate, if low discuss with secondary care and prescribe as appropriate

**Monitoring**

**Secondary care** – At baseline: quantiferon and pregnancy test (if clinically indicated), LFTs (including GGT), U&Es, creatinine, FBC, CRP, CXR, PFTs, body weight and BP (if BP raised above 140/90 mm/Hg a further three readings need to be taken before commencing leflunomide) and the patient will undergo further monitoring in line with the local procedure at STH. The patient will then be transferred to shared care with primary care when stable.

**Primary Care** - FBC, LFTs, U&Es, creatinine and CRP, two monthly, as recommended in the SPC. Weight and BP should be checked at each medication review, i.e every 6 – 12 months. Also remind patient to report any side effects at each medication review.

If any increase in dose revert to initial monitoring advice.

**Stop Leflunomide and contact helpline if:**

- WBC <3.5 x 10⁹/l
- Neutrophils <2 x 10⁹/l
- Platelets <150 x 10⁹/l
- AST/ALT >2 times increase on two occasions, or significant rise from baseline; If >3 times, do not wait to retest, stop and contact helpline.
- New rash, photosensitivity, nausea, alopecia;
- Mouth ulceration, sore throat with ulceration, unexplained bruising/bleeding, unexplained fever, any infections where antibiotics are needed. Check FBC and withhold treatment until results are available – discuss with STH
- (Leflunomide may cause patients to be more susceptible to infections, including opportunistic infections. If a patient suffers from an infection where antibiotics are needed the WCC should be checked and action taken should be in line with advice above (under monitoring section). Infections may be more severe in nature and may, therefore, require early and vigorous treatment. In the event that severe, uncontrolled infections occur, it may be necessary to interrupt leflunomide treatment and administer a washout procedure as described under additional information).
- Chicken pox/varicella zoster can be fatal in immunosuppressed patients: if contact suspected check antibody status. Stop leflunomide and contact rheumatology department. Follow current advice in the **Green Book**
- Deterioration in renal function (creatinine >10% of normal), creatinine >300micromol/l
- Increasing shortness of breath or cough
- Unexplained, >10% weight loss
- Uncontrolled hypertension >140/90 mm/Hg, despite standard anti-hypertensives
- If CRP is significantly and persistently raised above what is normal for that patient and infection is ruled out, treatment does not need to be stopped but consider referring patient back to rheumatology for further review.
- If a patient taking leflunomide develops a peripheral neuropathy, consider discontinuing leflunomide therapy and performing the drug elimination procedure

**Interactions**

The details below are not a complete list and the current BNF and the SPC remain authoritative.

Other hepatotoxic drugs, other myelotoxic drugs, colestyramine, phenytoin, tolbutamide, warfarin, live vaccines

Concomitant methotrexate is not advisable except on advice of rheumatologist

Leflunomide has a very long half-life (2 weeks) and therefore potential interactions may take time to become clinically apparent. Extra monitoring is needed if starting or stopping leflunomide in a patient also taking warfarin, phenytoin or tolbutamide.

**Smokers, psoriatic arthritis:** careful observation and monitoring:
The SPC states to avoid alcohol consumption whilst taking leflunomide, due to additive hepatotoxic effects. If patients do consume alcohol the Arthritis Research UK states patients should discuss with their doctor or rheumatology nurse specialist and only drink in small amounts (no more than 4 units per week). If concerned with alcohol consumption, watch LFTs and discuss with secondary care.

**Additional information**

If a stable patient on leflunomide is considering conception (or becomes pregnant) refer them to secondary care. Note: Both men and women receiving leflunomide must use contraception throughout the treatment period, and for at least two years in women (3 months in men) after discontinuation of treatment. Alternatively a washout period can be undertaken; either colestyramine - 8g TDS for 11 days or activated charcoal - 50g QDS for 11 days. The concentration of the active metabolite after washout should be less than 20 micrograms/litre (measured on 2 occasions 14 days apart) in men or women before conception. A waiting period of one and a half months between the first occurrence of a plasma concentration below 20 micrograms/litre and fertilisation is required. For more information consult product information. Please note that washout will inhibit action of oral contraceptives and therefore alternative contraception is required.

Animal studies indicate that leflunomide or its metabolites pass into breast milk. Breast-feeding women must, therefore, not receive leflunomide.

**Responsibilities of consultant clinician**

- To discuss benefits and side effects of treatment with the patient/carer and obtain informed consent.
- To undertake pre-treatment tests
- To initiate leflunomide in appropriate patients and issue patient with patient information leaflet and counsel on contraceptive advice, if applicable
- To prescribe leflunomide until the patient is stable, for a minimum of 6 months
- To contact patient’s GP to request prescribing under shared care using Shared Care Transfer Form. Send a link to or copy of the prescribing guideline to the patients GP.
- To advise the GP regarding continuation of treatment, including the length of treatment
- To discuss any concerns with the GP regarding the patient’s therapy
Responsibilities of the primary care clinician

- To refer appropriate patients to secondary care for assessment
- To agree to prescribe for patients in line with the shared care agreement and return completed Shared Care transfer form to the rheumatology department.
- To report any adverse reaction to the CHM and the referring consultant
- To continue to prescribe for the patient as advised by the consultant
- To undertake monitoring as stated above and transcribe results clearly into the patients individual management plan (a ‘blue book’ which the patient will have been given from STH)
- To inform the consultant if the patient discontinues treatment for any reason
- To seek the advice of the consultant if any concerns with the patient’s therapy
- To conduct an annual face to face medication review or more frequent if required
- In the event that the GP is not able to prescribe, or where the prescribing guideline is agreed but the consultant is still prescribing certain items e.g. Hospital only product; the GP will provide the consultant with full details of existing therapy promptly by fax on request.
- Check for possible drug interactions when newly prescribing or stopping concurrent medication
- For medication supplied from another provider GPs are advised to follow recommendations for Recording specialist issued Drugs on Clinical Practice Systems – see link

Responsibilities of patients/carers

- To attend hospital and GP clinic appointments and to bring monitoring booklet (if required). Failure to attend will potentially result in the medication being stopped.
- Present rapidly to the GP or specialist should their clinical condition significantly worsen.
- Report any adverse effects to their specialist or GP whilst taking leflunomide.
- To read the drug information given to them
- To take leflunomide as prescribed
- Inform the specialist, GP or community pharmacist dispensing their prescriptions of any other medication being taken – including over-the-counter medication.
- To take responsibility for appropriate contraceptive precautions
- To restrict alcohol intake as advised in the patient information literature

Re-Referral guidelines

See under monitoring section above
Pregnancy
Deterioration of disease

Financial implications

Prescribing of leflunomide will move from secondary to primary care. Prescribing in primary care will be on FP10 prescriptions. There will be an increase in payments to GPs under the DMARD Local Commissioned Service.

Support, education and information

A drug information sheet and shared care booklet has been issued to your patient.

If any problems occur or you have any concerns please contact relevant specialist:

Rheumatology help line (Mon-Fri 0900-1600) (0114) 2713086 (option 3)
On call specialist via STH NHS Foundation Trust switchboard: (0114) 2711900

Secondary care assumes responsibility for the monitoring and re-prescription of leflunomide until stable dosage has been successfully achieved.
Patient information leaflets

These are provided to patients by secondary care, but can also be downloaded here
http://www.arthritisresearchuk.org/arthritis-information/drugs/leflunomide.aspx

References

http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/l/lfltabsscg.doc

Full list of side-effects is given in the leflunomide summary of product characteristics (SPC), available from
www.emc.medicines.org.uk .
https://www.medicinescomplete.com/mc/bnf/current/

London and South East Regional Medicines Information Service. Suggestions for Drug Monitoring in Adults in Primary Care
Appendix 1

Shared Care Transfer forms can be found here:
To follow