Frimley Park Hospital NHS
NHS Foundation Trust

Shared Care Guideline for the use of *Leflunomide* for *Rheumatoid Arthritis*

Section 1: Agreement for transfer of prescribing to GP
Please sign this form and return it to the named consultant if you are willing to share care for the patient. Please also keep a signed copy for your records.

Patient details/addressograph

Name……

Address……
……..
……..
……..

DOB…… Hospital no…….

Drug name and dose:……

Desired clinical outcome as agreed with the patient/carer

……

Consultant

Address:……
……...
……...
……...

Contact no:……

Agreement to shared care, to be signed by GP and Consultant before transfer of care to GP

Consultant signature:

……

Date:……..

GP

Address:……
……..
……..

Contact no:……

GP signature:

……..

Date:……..

In case of emergency contact *Name:*……

Contact number:……

Prepared by: Jacqueline Kew in conjunction with Dr Lloyd Date: August 2007
Approved by: Prescribing Forum, FPH, January 2008 Review date: January 2010

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Responsibilities of the Consultant

- Assess the need and suitability for treatment with leflunomide (including exclusion of pregnancy in women of child bearing potential).
- Carry out relevant baseline investigations / tests
- Advise the patient regarding the possible side-effects of leflunomide and emphasize the importance of regular monitoring. Give the patient a patient information leaflet together with a hand held record book.
- Initiate patient on leflunomide and titrate dose as required in line with response/ tolerance.
- If patient does not respond/ tolerate leflunomide discontinuation of treatment.
- Continued prescription of leflunomide until patient is stabilised.
- Request GP to carry out shared care.
- Review results of safety monitoring at patient's follow up visits and request additional tests as required
- Review patient in clinic regularly to assess response to treatment and need to continue therapy, adjusting dose as necessary. The GP must be informed of the patient's progress after each outpatient clinic visit and the letter must include details of any changes to therapy and drug dosage.
- At any stage of treatment be available to advise GP of concerns regarding monitoring or potential adverse effects of treatment including giving advice on appropriate action if blood results are abnormal.

Responsibilities of the GP

- Initial referral to secondary care for management of moderate / severe rheumatoid arthritis.
- Continued prescription of treatment once patient is stabilised on medication and shared care is agreed under the guidance of the hospital consultant.
- Ensure the patient is receiving and attending regular reviews in outpatient clinic. Continued prescription is only appropriate for patients attending regular review.
- Regularly monitor the patient's overall health and reporting signs of deterioration to the consultant.
- Arrange ongoing monitoring and enter results in the patient handheld record book
- Give symptomatic treatment of minor adverse effects
- Report any serious adverse effects to the Rheumatology Department.
- Ensure no adverse drug interactions with other medication
- Modify the dose only on advice from the consultant.
- Report to and seek advice from the Rheumatology Department on any aspect of patient care which is of concern and may affect disease treatment.

*** Washout procedure is detailed in the drug interaction section***

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Section 2: Information

- Leflunomide decreases the autoimmune response and arrests activated autoimmune lymphocytes thought to be involved in the pathogenesis of rheumatoid arthritis
- The active metabolite (A771726) has a half-life of between 1 and 4 weeks

Licensed indications

Leflunomide is indicated for the treatment of adult patients with:
• Active rheumatoid arthritis as a "disease-modifying anti-rheumatic drug" (DMARD)
• Active psoriatic arthritis

Dose

Leflunomide is taken orally once a day. The dose is 10 or 20mg daily. Clinical improvement usually starts after 4 to 6 weeks. Further improvement may be seen after 4 to 6 months. Lower doses may be advisable in the elderly. A three day loading dose is referred to in product literature but is rarely used.

Recent or concurrent treatment with hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) may result in an increased risk of serious adverse reactions; therefore, the initiation of leflunomide treatment has to be carefully considered regarding these benefit/risk aspects.

Moreover, switching from leflunomide to another DMARD without following the washout procedure may also increase the risk of serious adverse reactions even for a long time after the switching.

Cautions

- **Alcohol:** patients are advised that alcohol consumption should be avoided or kept to a minimum due to potential for liver toxicity.
- **Vaccines:** Live vaccines should be avoided in patients taking leflunomide. Passive immunisation should be carried out using Varicella zoster immunoglobulin (VZIG) in non-immunised patients exposed to chickenpox or shingles.
- **Pneumococcal vaccine (IMPORTANT revaccination is not recommended see BNF) and 'Flu' vaccine are recommended.**

Contraception / Pregnancy: reliable contraception should be used by men and women whilst on leflunomide and for at least 2 years after discontinuing it. A washout procedure may reduce this period to 2 to 3 months. Patients discovered or planning to become pregnant should be referred to the rheumatologist at the earliest opportunity.

Contra-indications

- Severe renal or hepatic impairment
- Serious, chronic or recurrent infections
- Severe immunodeficiency
- Significantly impaired bone marrow function
- Severe anaemia, leucopenia, neutropenia or thrombocytopenia
- Uncontrolled hypertension
- Women at significant risk of becoming pregnant
- Breastfeeding

- Patients with severe hypoprotinaemia

Monitoring

INDICATION	Initial monitoring	Continuous monitoring	Comments
Rheumatoid arthritis	**Baseline** U&Es, creatinine & Blood Pressure, FBC, LFTs	**FBC, LFTs, ESR & Blood Pressure -** every 2 weeks during the first 6 months of therapy, then every 8 weeks thereafter. **U&Es & creatinine** – every 6-12 months	

If MCV >105fL check Vitamin B_{12} & folate levels and supplement if necessary

Withhold leflunomide and contact rheumatologist if:

- WBC < 4.0 x 10^9/L
- Neutrophils < 2.0 x 10^9/L
- Platelets <150 x 10^9/L
- ALT rising above double upper limit of FPH normal range **(40 iu/L)**
- Alk Phos rising above double upper limit of FPH normal range **(120 iu/L)**

****Please note increasing or decreasing trends in any values should prompt caution and extra vigilance****

Side effects

Patients must report mouth ulcers, sore throat, fever epistaxsis, unexplained bruising or bleeding and any unexplained illness/infection and should be seen urgently for full blood count and liver function tests

- **Common (1 in 10 to 1 in 100):** gastrointestinal effects (diarrhoea, nausea, vomiting, anorexia, mouth ulceration, abdominal pain), weight loss, headache, dizziness, paraesthesia, alopecia, eczema and mild allergic reactions including rash and pruritus, leucopenia, mild hypertension, alopecia.
- **Uncommon (1 in 100 to 1 in 1000):** anaemia, mild thrombocytopenia, hypokalaemia, disturbances, urticaria, anxiety, taste disturbances, tendon rupture
- **Rare (1 in 1000 to 1 in 10 000):** Severe infections, eosinophilia, leucopenia, pancytopenia, severe hypertension, interstitial lung disease (including interstitial pneumonitis), hepatitis, jaundice/cholestasis
- **Very rare (less than 1 in 10 000):** Agranulocytosis, vasculitis, peripheral neuropathy, pancreatitis, Stevens-Johnson Syndrome, toxic epidermal necrolysis, erythema multiform

Side effect	Action
Nausea	Can occur at any time during therapy. The symptoms may resolve with addition of anti-emetic medication. If no benefit gained may respond to dose reduction from 20mg to 10mg – discuss with rheumatologist.
Diarrhoea	Occurs in approx 20% of patients and is sometimes self-limiting. May respond to loperamide or codeine phosphate. If not consider dose reduction – contact rheumatologist
Hypertension (usually mild)	Mild increases in blood pressure are common. BP increases tend to affect those with pre-existing hypertension and may require additional antihypertensive therapy or cessation of therapy. In patients who become hypertensive, as defined by BHS, contact rheumatologist.

Side effect	Action
Decreased resistance to infection	Especially respiratory / urinary tract or shingles / chickenpox. Treat the infection – infections may be more severe and therefore require early and vigorous treatment. If severe withhold leflunomide and contact rheumatologist.
Alopecia	Diffuse hair loss may occur in up to 10% of patients. It is usually mild and is reversible on stopping medication. May respond to dose reduction - contact rheumatologist
Rash or skin itch	If mild, continue full dose and monitor. If moderate or severe withhold leflunomide and contact rheumatologist
Oral ulceration	Withhold leflunomide and contact rheumatologist
Macrocytosis	Check B12 / folate levels and treat accordingly if low

Interactions

The following drugs should not be initiated by a GP unless discussed with the specialist rheumatologist:

- **Phenytoin:** plasma concentration of phenytoin possibly enhanced by leflunomide
- **Tolbutamide;** leflunomide possibly enhances hypoglycaemic effect of tolbutamide.
- **Warfarin:** anticoagulant effect possibly enhanced by leflunomide.
- **Co-prescription of drugs with hepatotoxic or haematotoxic effects** is inadvisable and must be used with caution.
- **Washout period with Colestyramine or activated charcoal:** recommended in cases of significant drug toxicity, all women of childbearing potential after discontinuing leflunomide and males wishing to conceive due to its long half life– refer to rheumatologist
- **Live Vaccines:** see cautions

References

- SPC leflunomide tablets: www.medicines.org.uk **last accessed July 2007**
- BSR guidelines, July 2000
- BNF53, March 2007
- Shared Care Guideline, 'Leflunomide', Ashford & St Peter's Hospital, 2006

Contacts

- **Dr Lloyd & Dr Reilly – Consultant Rheumatologists - Tel: 01276 604 348**
- **Sara Burton – Rheumatology Specialist Nurse - Tel: 01276 526 131**

Shared care guidelines produced by Jacqueline Kew (Liaison Pharmacist) in conjunction with Dr Lloyd

This does not replace the SPCs, which should be read in conjunction with this guidance. Prescribers should also refer to the appropriate paragraph in the current edition of the BNF