Central Manchester University Hospitals NHS
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Greater Manchester Interface Prescribing Group Shared Care Template

Shared Care Guideline for **Leflunomide for Rheumatological Conditions**		**Reference Number** **CMFT-SCG-005**
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Date approved by Commissioners: **January 2013**	**Review Date:** **January 2015**	

Please complete all sections

1. Licensed Indications	*Leflunomide is indicated for treatment of adult patients with active rheumatoid arthritis as a disease-modifying anti-rheumatic drug and active psoriatic arthritis.*
2. Therapeutic use & background	*Leflunomide is a disease-modifying anti-rheumatic agent with antiproliferative properties. It has immunomodulating/ immunosuppressive characteristics, acts as an antiproliferative agent, and displays anti-inflammatory properties. A771726, the active metabolite of leflunomide, inhibits the human enzyme dihydroorotate dehydrogenase (DHODH) and exhibits antiproliferative activity.*
3. Contraindications (please note this does not replace the SPC or BNF and should be read in conjunction with it).	*Contraindications: severe immunodeficiency, serious infections, impaired liver function due to any cause, severe unexplained hypoproteinaemia, renal impairment (moderate to severe).* *Cautions: Localised or systemic infection including hepatitis B or C and history of tuberculosis. Drug potentiation- haematotoxic or hepatotoxic drugs such as methotrexate, caution if used together. Impaired bone marrow function including anaemia, leucopenia or thrombocytopenia (avoid if significant and due to causes other than rheumatoid arthritis).*
4. Prescribing in pregnancy and lactation	*This drug should not be prescribed during pregnancy and or while breastfeeding.* *It is important that women of childbearing potential do not start leflunomide until pregnancy has been excluded and both men and women must use reliable contraception. If, during treatment, there is a delay in onset of menstruation or other reason to suspect pregnancy then the patient must notify their GP and Consultant as soon as possible. Pregnancy is not recommended during treatment and for 2 years after stopping leflunomide and if the patient wants to conceive then blood metabolite levels need to be checked and a wash out organised if necessary.*

	Blood metabolite A77 1726 please contact Dr Gwendolen Ayers Consultant Clinical Biochemist for blood test (secondary care responsibility). *It is possible that rapidly lowering the blood level of the active metabolite through the drug washout procedure the risk to the foetus may be reduced. Male and female patients should not plan a pregnancy within two years of discontinuing leflunomide. Blood concentrations of its active metabolite should be measured two years after discontinuation (should be < 20µg/L on two occasions, 14 days apart) before pregnancy occurs (this waiting time may be reduced by using the drug washout procedure).* *Women must not breastfeed while they are taking leflunomide.*		
5. Dosage regimen for continuing care	Route of administration	*oral*	
	Preparations available (include in this section any necessary information relating to availability of special preparations for children or those with swallowing difficulties) *Tablets can be dispersed in water for swallowing difficulties and enteral feeding.*		
	Dose to be prescribed including units, frequency and duration of treatment. *Started by Hospital and supplied by hospital for the 1st 3 months.* Please prescribe: *10mg-20mg per day depending on disease severity.*		
	Is titration required	**Yes (complete the following section) Yes**	
	Titrate dosage up by *10mg* according to response. Maintenance dosage up to a maximum *20mg/day*		
	Adjunctive treatment regime *No adjunctive treatment*		
	Conditions requiring dose reduction *Not to be used in impaired liver function, moderate/severe renal impairment.*		
	Usual response time *8-12 weeks*		
	Duration of treatment *ongoing*		
	Treatment to be terminated by *healthcare professional in consultation with Rheumatology Team.*		
	NB. All dose adjustments will be the responsibility of the initiating specialist care unless directions have been specified in the medical letter to the GP.		
6.Drug Interactions ***For a comprehensive list consult the BNF or Summary of Product***	The following drugs must <u>not</u> be prescribed without consultation with the specialist: *Live vaccines (e.g. oral polio, oral typhoid, MMR, BCG, yellow fever, varicella zoster) are contraindicated.*		

Characteristics	The following drugs may be prescribed with caution: *Leflunomide may inhibit the metabolism of warfarin, phenytoin and tolbutamide. It has an extremely long elimination half life and interactions with these drugs and with other DMARDs may occur even after leflunomide has been discontinued.* *Alcohol should be avoided (or limited to max. 8 units weekly) due to an increased risk of hepatotoxicity.* *The effect of leflunomide is significantly decreased by colestyramine (enhanced elimination), avoid unless drug elimination desired.*

7. Adverse drug reactions

For a comprehensive list (including rare and very rare adverse effects), or if significance of possible adverse event uncertain, consult Summary of Product Characteristics or BNF

Specialist to detail below the action to be taken upon occurrence of a particular adverse event as appropriate. Most serious toxicity is seen with long-term use and may therefore present first to GPs.

Adverse event System – symptom/sign	**Action to be taken** Include whether drug should be stopped prior to contacting secondary care specialist	**By whom**
WBC<3.5 x 10^9/l Neutrophils< 2.0 x 10^9/l Platelets<150 x 10^9/l	*Withhold until discussion with Rheumatology Team*	*GP*
AST,ALT between two and three times the upper limit of reference range *AST, ALT more than three times the upper limit of reference range*	*If the current dose is more than 10mg daily reduce the dose to 10mg daily and recheck weekly until normalised. If the AST and ALT is returning to normal, leave on 10mg daily. If LFTs remain elevated withdraw the drug and discuss with Rheumatology Team* *Recheck LFTs within 72 hrs, if still more than three times the reference range, withhold until discussion with Rheumatology Team*	*GP*
Rash or Itch	*Consider dosage reduction with or without antihistamines if severe, withhold until discussion with Rheumatology Team*	*GP*
Hair Loss	*Consider dosage reduction if severe, withhold until discussion with Rheumatology Team as risk of alopecia*	*GP*
Abnormal bruising or severe sore throat	*Check FBC immediately and withhold until results are available as risk of bone marrow suppression*	*GP*
Hypertension	*If BP > 140/90 treat in line with NICE guidance. If BP remains uncontrolled, withhold until discussion with Rheumatology Team*	*GP*
Headache	*If severe, consider dosage reduction. If headaches persist, withhold until discussion with Rheumatology Team*	*GP*
Weight Loss	*If >10% weight loss with no other cause identified reduce dosage or withhold until discussion with Rheumatology Team as risk of anorexia*	*GP*
Breathlessness	*If increasing shortness of breath occurs withhold until discussion with Rheumatology Team as risk of interstitial lung disease*	*GP*

	The patient should be advised to report any of the following signs or symptoms to their GP without delay: *Leflunomide may also cause mouth ulcers, skin rash (including Stevens–Johnson syndrome and toxic epidermal necrolysis), gastrointestinal upset, headaches, dizziness, tenosynovitis and hair loss. If a severe undesirable side effect of leflunomide occurs or for any other reason rapid removal of its active metabolite is required a washout procedure with cholestyramine 8 grams three times a day or activated charcoal 50 grams four times a day, each for 11 days is available. Leflunomide increases susceptibility to infections which should be treated promptly.*
	Other important co morbidities (e.g. Chickenpox exposure). Include advice on management and prevention and who will be responsible for this in each case: *Pneumovax and annual 'flu vaccine should be given. Passive immunisation should be carried out using Varicella zoster immunoglobulin (VZIG) in non-immune patients if exposed to chickenpox or shingles.*
	Any adverse reaction to a black triangle drug or serious reaction to an established drug should be reported to the MHRA via the "Yellow Card" scheme.
8.Baseline investigations	*List of investigations / monitoring undertaken by secondary care* *FBC* *U&Es* *LFTs* *BP: If >140/90 on two consecutive readings 2 weeks apart treat hypertension before commencing the drug* *Weight: To allow assessment of weight loss, this may be attributable to leflunomide*

9. Ongoing monitoring requirements to be undertaken by GP	**Is monitoring required?**	**Yes or No (if yes complete following section)** *Yes*		
	Monitoring	**Frequency**	**Results**	**Action**	**By whom**
	FBC, U&E, LFT, (ESR desirable but not essential)	***Dose during titration**: Every 2 weeks for 6 months, if stable,* ***Maintenance Dose**: when stable every 2 months thereafter*	*See Section 7: Adverse drug reactions above*		*GP*
	Blood pressure	*Once every month*	*See Section 7: Adverse drug reactions above*		*GP*
	Weight	*Once every month*	*See Section 7: Adverse drug reactions above*		*GP*

10. Pharmaceutical aspects	*e.g. special storage requirements, washout periods Or where there are "no special considerations"* *no special requirements*
11. Secondary care contact information	**If stopping medication or needing advice please contact:**
	To contact The Kellgren Centre Rheumatology Manchester Royal Infirmary: **Enquiries regarding blood monitoring and results please contact the specialist nurses below:**

	Specialist Nurse Jane Hawthorne 0161 276 4688 **Specialist Nurse Melissa Aris 0161 701 1454** **Specialist Nurse Carole Hill 0161 701 1454** **Fax number for GP blood results 0161 276 8690** **Consultant contact details below:** **Professor Ian Bruce 0161 276 4626** **Professor Ann Barton 0161 276 4626** **Dr Kimme Hyrich 0161 276 4627** **Dr Pauline Ho 0161 276 4397** **Dr Rachel Gorodkin 0161 276 4628** **To contact Rheumatology Department Trafford General Hospital:** **Trafford Rheumatology helpline number 0161 746 2162** **Consultant contact details below:** **Dr Frank McKenna 0161 746 2395** **Dr Preeti Shah 0161 746 2395**
12. Criteria for shared care	Prescribing responsibility will only be transferred when ▪ Treatment is for a specified indication and duration. ▪ Treatment has been initiated and established by the secondary care specialist. ▪ The patient's initial reaction to and progress on the drug is satisfactory. ▪ The GP has no objection in each individual case that shared care is appropriate. ▪ The patient's general physical, mental and social circumstances are such that he/she would benefit from shared care arrangements
13. Responsibilities of initiating specialist	Initiate treatment and prescribe treatment for the 1st 3 months. Undertake baseline monitoring. Advise GP of any dose adjustments. Monitor patient's initial reaction to and progress on the drug. Ensure that the patient has an adequate supply of medication until GP supply can be arranged. Continue to monitor and supervise the patient according to this protocol, while the patient remains on this drug, and agree to review the patient promptly if contacted by the GP Provide GP with diagnosis, relevant clinical information and baseline results, treatment to date and treatment plan, duration of treatment before consultant review. Provide GP with details of outpatient consultations, ideally within 14 days of seeing the patient *or* inform GP if the patient repeatedly does not attend appointment. Provide GP with advice on when to stop this drug. Provide patient with relevant drug information to enable Informed consent to therapy. Provide patient with relevant drug information to enable understanding of potential side effects and appropriate action.

	Provide patient with relevant drug information to enable understanding of the role of monitoring. Provide patient with monitoring booklet. Provide patient with rheumatology nurse helpline contact number.
14. Responsibilities of the GP	Continue treatment as directed by the specialist Ensure no drug interactions with concomitant medicines. To monitor and prescribe in collaboration with the specialist according to this protocol. To ensure that the monitoring and dosage record is kept up to date in the shared care booklet. To ensure blood monitoring is carried out once dose stable and responsibility transferred from secondary care. To inform Rheumatology Team if patient repeatedly does not attend routine blood monitoring. To undertake vaccination as directed by the initiating consultant, the BNF or Green Book Symptoms or results are appropriately actioned, recorded and communicated to secondary care when necessary.
15. Responsibilities of the patient	--- To take medication as directed by the prescriber, or to contact the GP if not taking medication To attend hospital and GP clinic appointments, bring monitoring booklet. Failure to attend will result in medication being stopped (on specialist advice). To report adverse effects to their Specialist or GP.
16. Supporting documentation	The SCG must be accompanied by a patient information leaflet. Patient Information Leaflet EMC medicines Leflunomide Arthritis Research UK Patient Information Leaflet Leflunomide
17. Patient monitoring booklet	The patient must receive a monitoring booklet from the specialist upon initiation of treatment. The patient must bring this booklet to all specialist and GP appointments where it will be updated by the health professional conducting the appointment. The patient must also produce the booklet to any health professional involved in other aspects of their care e.g. pharmacists and dentists.