

## NEW MEDICINES ON THE MARKET

Evaluated Information for NHS Managers, Budget Holders and Prescribers.

### LEFLUNOMIDE

#### Summary

- Leflunomide is an immunomodulatory agent licensed for rheumatoid arthritis. It has a different mechanism of action to other available disease-modifying agents.
- Three phase III comparative trials against methotrexate and sulphasalazine involving a total of 1839 patients have been conducted, two of which have been published in full. Withdrawal rates were high for leflunomide (30-47%) but comparable to those for other active treatments. Overall, leflunomide has been shown to have similar efficacy to methotrexate and sulphasalazine with improvements in joint swelling and tenderness, pain and retardation of disease progression compared with placebo. 51-55% of patients taking leflunomide met the American College of Rheumatology criteria of 20% improvement, response rates which were similar to comparator drugs and statistically significantly superior to placebo. Quality of life measures have shown improvements in functional ability with leflunomide which are at least comparable to sulphasalazine or methotrexate.
- Adverse effects in trials included pruritus, rash, gastrointestinal effects, weight loss and alopecia. Increases in liver function tests were also seen. Rarely, severe allergic, hepatotoxic or haematological reactions can occur. Patients should have their liver function, blood pressure and full blood count monitored before therapy and regularly thereafter. Leflunomide is teratogenic in animals and women of child-bearing potential must use reliable contraception. The active metabolite of leflunomide has a long half-life, usually one to four weeks, therefore adverse effects may still occur after stopping treatment.
- Leflunomide may offer a useful alternative disease-modifying agent for patients with rheumatoid arthritis. It is likely to be used as an alternative to sulphasalazine or methotrexate if these are ineffective or inappropriate. It is substantially more expensive than either of these options but less costly than cyclosporin.

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# LEFLUNOMIDE

<b>APPROVED NAME:</b>	Leflunomide	
<b>BRAND NAME:</b>	Arava (Hoechst Marion Roussel)	
<b>SYNONYMS:</b>	HWA 486	
<b>INDICATION:</b>	Treatment of adult patients with active rheumatoid arthritis	
<b>PRESENTATION:</b>	100mg tablets (packs of 3 as loading dose), 20mg, 10mg tablets (packs of 30 tablets).	
<b>THERAPEUTIC CLASS:</b>	Immunomodulatory agent BNF 10.1.3	
<b>DOSE:</b>	Loading dose of 100mg daily for 3 days, followed by a maintenance dose of 10mg or 20mg once daily.	
<b>COST PER COURSE:</b>	Leflunomide 10mg-20mg daily £43.40 (after 3 day loading dose = £23.25)	
<b>TREATMENT ALTERNATIVES:</b>	(Prices for 28 days from Drug Tariff/ MIMS February 2000)	
	Sulphasalazine 500mg qds (Salazopyrin EC)	£9.69
	Methotrexate 10mg weekly	£2.26
	Intramuscular gold 50mg monthly	£9.36 (in addition to administration costs)
	Chloroquine base 150mg daily	£1.34 (as Nivaquine)
	Cyclosporin 3mg/kg daily (assume 70kg person, equivalent to 200mg Neoral daily)	£142.48
<b>AREAS OF USE:</b>	Hospital [Y]	Community [Y] NB. SPC states leflunomide should be prescribed by specialists experienced in the treatment of rheumatoid diseases

## INTRODUCTION

Rheumatoid arthritis (RA) affects 1-2% of adults in the UK [1]. It is a chronic, progressive polyarthritis with a high chance of developing joint erosions and disability. Until quite recently initial treatment for RA consisted of NSAIDs, simple analgesics or physical methods, with disease-modifying antirheumatic drugs (DMARDs) being introduced when these agents failed. However, the recognition that irreversible joint damage commonly occurs early in the disease has led to DMARDs being initiated earlier in the course of RA [1]. Currently available DMARDs include sulphasalazine, methotrexate, intramuscular gold, penicillamine, antimalarials, cyclosporin and azathioprine. There is no consensus on which should be chosen although methotrexate or sulphasalazine are commonly used as first line DMARDs [1].

## PHARMACOLOGY

Leflunomide is an isoxazole derivative. Its exact mode of action is unclear. The active metabolite of leflunomide (A771726) binds to dihydro-oroate dehydrogenase, an enzyme involved in the synthesis of pyrimidines. As a consequence there is a reduction in uridine triphosphate levels and pyrimidine synthesis by lymphocytes and other rapidly dividing cells. The action of the enzyme tyrosine kinase is also reduced. These effects result in changes in DNA and RNA synthesis and T- and B-cell proliferation in addition to suppression of immunoglobulin production and interference with cell adhesion [2,3]. There is also a suggestion that its anti-inflammatory activity is due to its ability to inhibit histamine release and cyclooxygenase-2 in vitro [2].

## PHARMACOKINETICS

After absorption leflunomide is converted to its active metabolite A771726, a malononitrilamide [2]. Plasma concentrations of A771726 appear to be linear across the dosage range of 5-25mg daily [4]. Mean plasma half-life is 15-18 days on chronic dosing with total plasma clearance of 0.3ml/kg/hour. The active metabolite is extensively protein bound (>99%) and is cleared by biliary and renal excretion. Plasma levels of A771726 remain above 0.02mg/l (the level above which teratogenic effects could still occur) for up to two years after stopping leflunomide [5].

## CLINICAL EFFICACY

One large, dose-finding phase II study [4] and three large comparative phase III studies (against sulphasalazine or methotrexate) [6-8] have been completed. All studies were randomised, double-blind, multi-centre, parallel group design. All but one included a placebo group. All but one has

been published in full. Results are shown in Table 1. Because of the long half-life of leflunomide all studies utilised a loading dose of either a single dose of 50mg-100mg or three days of 100mg daily. It should be noted that the trials were designed to compare active treatments against placebo. Any statistical differences between active treatments should be viewed with this in mind. All analysis was on an intention-to-treat basis.

### *Outcome measures*

Primary outcome measures used in the trials included tender joint count, swollen joint count, tender joint score and swollen joint score using a scale of 0 (none) to 3 (severe) to assess degrees of swelling and tenderness. Patient and physician global assessments were also conducted using a 5-point Likert scale ranging from very poor to very good. Secondary outcome measures included duration of morning stiffness, grip strength, Health Assessment Questionnaire, patient pain score, ESR, C-reactive protein and rheumatoid factor. Responder rates were also assessed using the American College of Rheumatology (ACR) criteria requiring improvement of  $\geq 20\%$  in 5 of 7 measures (which must include tender and swollen joint counts). Some of the trials also monitored ACR50% response rates (i.e. an improvement of  $\geq 50\%$  in 5 of 7 measures). This has been suggested as a more appropriate goal if more complete suppression of active disease is the aim [1].

### *Clinical efficacy*

The phase III studies have involved a total of 1839 patients [6-8]. One has compared leflunomide with sulphasalazine (up to 2g daily) and placebo for 24 weeks, one methotrexate 7.5-15mg weekly and placebo for 12 months and one against methotrexate 7.5-15mg weekly for 12 months with no placebo group. The placebo-controlled methotrexate study also included a folate supplement, whereas in the active-controlled study, no folate supplement was given. Patients in trials had a mean age of 53-59 with a mean duration of RA of 3.7-7.4 years. 33-53% of patients had previously been prescribed a DMARD.

In the comparative study against sulphasalazine, all primary outcome measures (tender joint count, swollen joint count and physician and patient global assessments) were statistically significantly improved with both active drugs compared with placebo ( $P < 0.001-0.0001$  for leflunomide and  $p < 0.001-0.005$  for sulphasalazine) [6]. There were no significant differences between the drugs. Response rates using the ACR criteria of 50% improvement were also statistically significantly higher with active treatment (33% leflunomide, 30% sulphasalazine, 14% placebo,  $p < 0.01$  for both drugs vs placebo). 28% of leflunomide patients withdrew early compared with 45% of the placebo group and 38% of sulphasalazine patients. The majority of withdrawals in the active treatment groups were due to adverse events.

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7.5% of leflunomide patients discontinued due to lack of efficacy. Improvements were seen from the second week of treatment with leflunomide, whereas sulphasalazine showed statistically significant improvements over placebo from the twelfth week of treatment.

At the end of the six months, 197 patients voluntarily entered a 12 month extension study [9]. Patients on placebo were switched to sulphasalazine. Twelve month data is available in abstract form. Both drugs showed improvements in efficacy outcomes in the second six months of treatment. By 12 months, the ACR20% response rates were leflunomide 67%, sulphasalazine 69%, previous placebo group (now sulphasalazine) 65%. Similar efficacy results were seen in the placebo-controlled methotrexate study [7]. Primary outcome measures were ACR success rate (defined as completing 52 weeks of treatment and meeting the ACR20% response criteria), disease progression (assessed by x-ray films) and improvements in function and health-related quality of life. ACR success rates were leflunomide 41%, methotrexate 35% and placebo 19% ( $P < 0.001$  both drugs vs placebo, no significant differences between drugs). Withdrawal rates were 47% with leflunomide, 42% with methotrexate and 69% of placebo patients. Again, the majority of withdrawals with leflunomide were due to adverse events (22% of patients vs 17% due to lack of efficacy). There were no differences in response rates depending on duration of disease ( $\leq 2$  years or  $> 2$  years) prior to randomisation [10].

Methotrexate was statistically significantly superior to leflunomide in terms of ACR 20% responder rates in the second comparative study [8,11]. In this study response rates with methotrexate were higher than those seen in other studies (ACR 20% responder rate of 65%). It has been suggested that the increased response rate is due to patients not receiving folate supplements. It is postulated that folate can inhibit the efficacy of methotrexate. 30% of leflunomide patients discontinued treatment early (19% due to adverse events, 7% lack of efficacy) compared with 22% of methotrexate patients.

## Radiological findings

All phase III studies also assessed disease progression by radiological means utilising the Larsen or Sharp methods [6,7,12]. Both methods are reported to be reliable and effective in the assessment of disease progression and operate by comparing the initial and final x-rays of a number of joints by a scoring method [11]. The number of eroded joints was also counted. Only patients who had x-rays at baseline and at endpoint were included (this could include patients who withdrew early if endpoint x-rays were available). Results are summarised in Table 2.

**Table 2: Radiographic findings of disease progression**

Drug (no of patients)	Radiographic findings		
	Scoring method	Baseline score	Change from baseline
Leflunomide (91) Sulphasalazine (77) Placebo (60)	Larsen	1.48 1.39 1.49	0.01** 0.01** 0.05
Leflunomide (131) Methotrexate (138) Placebo (83)	Sharp	23.11 22.76 25.37	0.53***† 0.88* 2.16
Leflunomide (295) Methotrexate (315)	Larsen	1.25 1.29	0.03 0.03

\* $p=0.02$  vs placebo

\*\*  $p \leq 0.001$  vs placebo

†  $p=0.05$  vs methotrexate

## Quality of life measures

Quality of life, measured using the Health Assessment Questionnaire (HAQ) and SF-36 showed improvements in functional ability with leflunomide which were statistically significantly greater than placebo and sulphasalazine or methotrexate [13,14].

## Combination with other DMARDs

Combination therapy is increasingly being used in the management of RA. It has been suggested that leflunomide and methotrexate are a logical combination given their different pharmacological actions [15]. A small study assessed the combination of methotrexate and leflunomide in 30 patients who had not responded to methotrexate alone [16]. 23 patients completed the one year study, withdrawals were mostly due to raised liver enzymes. 16 (53%) patients met the ACR20% response criteria. The combination appears to warrant further study although adverse events may be more common and the Summary of Product Characteristics currently advises against combination with other DMARDs [5].

## PROMOTIONAL DATA

Leflunomide is the first new DMARD for a decade and is a valuable alternative to 'gold standard' agents such as methotrexate and sulphasalazine. It is as effective as sulphasalazine and methotrexate in retarding disease progression and improving signs and symptoms of RA. It significantly improves functional ability and health-related quality of life. It has a satisfactory tolerability profile with a low frequency of serious adverse events [17].

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## ADVERSE EFFECTS

The most common adverse effects with leflunomide are gastrointestinal symptoms (including diarrhoea, nausea and vomiting, abdominal pain and oral ulceration), allergic reactions (eg rash, pruritus and rarely anaphylaxis), alopecia and elevated liver function tests (LFTs) [5]. Anorexia, weight loss, headache, paraesthesia, hypertension and dizziness have also been reported. Infections may be more common. Rarely, severe haematological, hepatotoxic or allergic (eg severe skin reactions or anaphylaxis) reactions may occur. During post-marketing studies in the USA, 15 cases of pancytopenia were identified, mostly when leflunomide was used in combination with methotrexate or other DMARDs [18]. Patients should have LFTs, blood pressure and a full blood count taken before and during treatment (in the case of the blood count, every two weeks for the first 6 months, then every 8 weeks) [5]. If a severe reaction occurs, a washout procedure is described in the Summary of Product Characteristics to eliminate leflunomide rapidly from the body [5].

## PRECAUTIONS/CONTRA-INDICATIONS

Leflunomide has a prolonged half-life and once, stopped, plasma concentrations may not fall below minimal levels for up to 2 years. This should be considered when assessing a patient who has taken leflunomide within the previous two years.

Leflunomide is teratogenic in animals. It is therefore contraindicated in women of child-bearing potential who are not using a reliable contraceptive. Women or men taking leflunomide who wish to have a child must undergo a washout procedure to ensure plasma levels are minimal. Women should not breastfeed whilst taking leflunomide. It is also contraindicated in immunosuppressed patients, those with hepatic impairment or moderate/ severe renal impairment, or those with serious infections or severe hypoproteinaemia [5].

## INTERACTIONS

Cholestyramine significantly reduces the plasma concentration of leflunomide's active metabolite and the two should not be co-administered (unless as part of the washout procedure). Administration with other DMARDs or other hepato- or haematotoxic drugs may increase the risk of toxicity. If switching from leflunomide to another DMARD, a washout procedure should be considered. Alcohol should be avoided with leflunomide. Caution should be used if given concomitantly with phenytoin, warfarin, tolbutamide or rifampicin.

Patients should not be given live vaccination whilst taking leflunomide and for some time afterwards due to its long half-life [5].

## References

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**TABLE 1 Phase II and III clinical trials with leflunomide**

Drug / dose	Duration of study	No of patients randomised (evaluated for efficacy)	Tender joint count		Swollen joint count		% responders (measured by ACR20%)	Overall efficacy
			Baseline	Change from baseline (% change)	Baseline	Change from baseline (% change)		
<b>Comparison with placebo [4]</b>								
Leflunomide 5mg od	24 weeks	95 (95)	35	-10.5 (30%)	23	-7.6 (33%)	32%	LEF20mg>PI
Leflunomide 10mg od		101 (100)	35	-13.6 (39%)	24	-10.4 (43%)*	52%***	LEF10mg>PI
Leflunomide 25mg od		104 (101)	35	-16.5 (47%)*	24	-11.7 (49%)*	59%***	
Placebo		102 (102)	37	-9.7 (26%)	24	-6.5 (27%)	30%	
<b>Comparison with sulphasalazine [6]</b>								
Leflunomide 20mg od	24 weeks	133 (130)	18.8	-9.7 (52%)*	16.2	-7.2 (44%)*	55%***	LEF>Placebo
Sulphasalazine EC up to 2g daily		133 (132)	16.7	-8.1 (48%) (no statistical analysis vs placebo)	15.3	-3.4 (21%) (no statistical analysis vs placebo)	56%***	LEF=SSA
Placebo		92 (91)	16.3	-4.3 (26%)	15.8	-6.2 (40%)	29%	
<b>Comparison with methotrexate [7, 8, III]</b>								
Leflunomide 20mg od	12 months	182 (182)	15.5	-7.7 (50%)*	13.7	-5.7 (42%)*	52%**	LEF>Placebo
Methotrexate 7.5-15mg weekly		182 (180)	15.8	-6.6 (42%)*	13.0	-5.4 (42%)*	46%**	LEF=MTX
Placebo		118 (118)	16.5	-3 (18%)	14.8	-2.9 (20%)	26%	
Leflunomide 20mg od	12 months	501 (495)	16.9	-10.5 (62%)	16	-9.1 (57%)	64.3%	LEF=MTX
Methotrexate 7.5-15mg weekly		498 (489)	17.2	-10.9 (63%)	16.1	-10.3 (64%)†	71.1%†	

\* p<0/05 vs placebo

\*\*p≤0.001 vs placebo

\*\*\* p=0.0001 vs placebo

†p<0.05 vs leflunomide