



Midland Therapeutic Review
& Advisory Committee

VERDICT & SUMMARY

Leflunomide

(Arava[®])

For the treatment of rheumatoid and psoriatic arthritis

Committee's Verdict: RESTRICTED USE

BNF: 10.1.3

Leflunomide has been associated with potentially serious toxicity and the evidence base for psoriatic arthritis is currently limited. Leflunomide treatment should be initiated and stabilised in secondary care. It is then appropriate for GPs to prescribe leflunomide with the guidance of an ESCA. The Summary of Product Characteristics states that it should be prescribed by specialists experienced in the treatment of rheumatoid and psoriatic arthritis; however, this does not preclude follow-up prescribing by GPs with appropriate experience.

MTRAC updated the evidence for rheumatoid arthritis and evaluated that for the new indication of psoriatic arthritis.

Licensed indication

Leflunomide is licensed for the treatment of adult patients with active rheumatoid arthritis as a disease-modifying antirheumatic drug (DMARD) and for the treatment of active psoriatic arthritis.¹

Background information

Rheumatoid arthritis (RA) is an inflammatory disorder that affects about 1-2% of adults in the UK.² The clinical hallmark of RA is persistent synovial inflammation of peripheral joints which results in some degree of irreversible joint damage or erosion in most patients. In addition many other tissues may also be affected. The course of the disease is highly variable; in patients with severe disease or extra-articular symptoms, life expectancy may be reduced by up to 10 years.³

Psoriatic arthritis (PsA) occurs in about 15% of patients affected by psoriasis (2-3% of the general population),⁴ with a prevalence of about 0.1%.⁵ PsA has a characteristic clinical and radiological pattern of joint involvement, including inflammatory synovitis and destructive arthritis of the hands and feet, polyarthritis, and spondylitis.⁴

The long-term outcome in PsA is considered to be more favourable than in RA, but most patients who consult a rheumatologist continue to suffer progressive joint disease.⁴

Current treatment options

The objectives when treating patients with RA and PsA are to minimise pain, reduce inflammation, prevent or minimise joint destruction, and suppress progression of the disease.

Treatment is with simple analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), and disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate or sulfasalazine. Antimalarial drugs are contraindicated in patients with PsA because they may exacerbate the psoriasis.

Leflunomide is a more recently introduced DMARD that has immunosuppressant properties.

Dosage and administration

Leflunomide therapy is initiated with an oral loading dose of 100 mg/day for 3 days. The maintenance dose is 10-20 mg/day for RA and 20 mg/day for PsA.¹

Regular monitoring of liver function tests (LFTs), blood cell count and blood pressure is required.

A washout period should be followed when switching to another hepato- or haematotoxic drug, or in cases of acute leflunomide toxicity (see the Summary of Products Characteristics [SPC] for more details).

For Contraindications and Drug Interactions consult the SPC.

Clinical efficacy

Rheumatoid arthritis. Five randomised controlled trials (RCTs) (n = 2,808, duration 12 – 104 weeks) have evaluated the efficacy of leflunomide (20 mg/day) compared with placebo,⁶ methotrexate (15 mg/week)^{7,9} and sulfasalazine (2 g/day).¹⁰ Two trials were extended to 12 months (n = 396) and provide data over a total of 24 months.^{11,12} Four of these trials were included in a systematic Cochrane review and meta-analysis.¹³ A fifth trial was published later.¹¹ Response rates were assessed using multiple criteria as specified by the American College of Rheumatology. An improvement of 20% (ACR20) is taken to indicate a significant response, but improvements of at least 50% or 70% (ACR50 or ACR70) are more appropriate goals if complete suppression of active disease is the aim.

Compared with placebo, leflunomide treatment showed significant improvements in the numbers of tender and swollen joints, pain severity, X-ray measures of joint erosion and damage, erythrocyte sedimentation rate and C-reactive protein levels, and the number of patients achieving the ACR20.

Compared with methotrexate, there were no significant differences in the numbers of tender or swollen joints, or in the X-ray measures of joint erosion, with leflunomide treatment. Significant improvements for leflunomide treatment compared with methotrexate were noted in several outcomes at some but not all of

the time points (e.g. the number of patients meeting ACR70 response criteria).

Compared with sulfasalazine, leflunomide treatment had a better response rate (ACR20, ACR50 and ACR70) and fewer tender or swollen joints at 24 months. Leflunomide treatment also showed significant improvements in assessments of disease severity, pain, and quality of life scores compared with sulfasalazine. Five-year data¹⁴ from two of the studies^{9,10} showed that improvements in efficacy measures were sustained over the longer term.

Psoriatic arthritis. One RCT (n = 190, duration 24 weeks)¹⁶ evaluated the efficacy of leflunomide (20 mg/day) compared with placebo. A significantly greater number of the patients in the leflunomide group were classed as treatment responders compared with placebo, and this group showed significantly greater improvements in joint tenderness and swelling, and assessments of disease severity. Significantly more leflunomide-treated patients showed an ACR20 response (modified for PsA) compared with placebo.

Adverse effects

The most common adverse events with leflunomide treatment in clinical trials were gastrointestinal effects, pruritus, rash, hypertension, alopecia and liver enzyme elevations. Postmarketing, there have been rare reports of serious hepatic reactions and pancytopenia. See the SPC for more details on adverse events.¹

Costs

At current prices a year's treatment with:

- leflunomide (20 mg/day) costs £622
- methotrexate (7.5 mg/week) costs £16
- sulfasalazine (2 g/day) costs £110

Conclusions

Leflunomide was licensed for the treatment of rheumatoid arthritis in 1999 and for psoriatic arthritis in June 2004.

For the treatment of RA, five RCTs have evaluated the efficacy of leflunomide compared with placebo, methotrexate and sulfasalazine. Patients treated with leflunomide showed significantly greater improvements in outcome measures, including tender and swollen joint counts, pain severity and the ACR20 response, compared with placebo. Leflunomide showed comparable efficacy to methotrexate and sulfasalazine.

For the treatment of PsA, one RCT assessed leflunomide compared with placebo. Leflunomide treatment resulted in greater response to treatment and

greater improvements in joint counts and assessments of disease severity, compared with placebo.

References

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Launch date: November 1999

Manufacturer: Aventis

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WARNING: This sheet should be read in conjunction with the Summary of Product Characteristics
This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

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RELEVANT NICE GUIDANCE WAS NOT AVAILABLE AT THE TIME OF ISSUE OF THIS VERDICT

(THIS VERDICT SHEET REPLACES VS99/25)

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