

New drugs

Apremilast

Approved indications: psoriasis, psoriatic arthritis

Otezla (Celgene)

30 mg film-coated tablets

Australian Medicines Handbook Appendix A

Psoriatic arthritis affects at least 25% of patients with psoriasis. Although there may be differences in the pathogenesis, both conditions involve immune-mediated inflammation. Immunosuppressant drugs such as methotrexate and cyclosporin have therefore been used to treat severe cases.

Phosphodiesterase 4 is an enzyme involved in inflammatory processes. When it is inhibited by apremilast there is a decrease in pro-inflammatory cytokines, such as tumour necrosis factor, and an increase in anti-inflammatory cytokines such as interleukin 10. In psoriatic skin, this results in less infiltration by inflammatory cells and reduced epidermal thickness.

The dose of apremilast is increased over six days from 10 mg on the first day to reach the recommended dose of 30 mg every 12 hours. The tablets can be taken with food, but should not be divided. After the drug is absorbed it is extensively metabolised. Some of the metabolic pathways involve the cytochrome P450 (CYP) system including CYP3A4. The concentration of apremilast will be reduced by inducers of CYP3A4, such as phenytoin, rifampicin and St John's wort, but inhibitors of CYP3A4, such as ketoconazole, do not significantly increase the concentration. Most of the metabolites are excreted in the urine. A dose reduction is required in severe renal impairment (creatinine clearance <30 mL/min). The elimination half-life is about nine hours.

Apremilast has been studied in moderate to severe psoriasis and in psoriatic arthritis but, at the time of writing, not all of the phase III trials have been published in full.

In a phase II placebo-controlled, dose-ranging study, 88 patients were randomised to take apremilast 30 mg twice daily. The outcome of this study was the proportion of patients who had at least a 75% improvement on the Psoriasis Area and Severity Index (PASI 75). After 16 weeks, 41% of the patients had this response compared with 6% (5/88) of the patients given a placebo.¹

Two phase III trials enrolled 1257 patients with moderate to severe plaque psoriasis. Results at

16 weeks showed that the PASI 75 outcome was achieved by 28.8–33.1% of the patients taking apremilast, but only by 5.3–5.8% of those taking a placebo. In one of the trials 77 patients, who had achieved a PASI 75 response, continued treatment for 52 weeks. This response was sustained in 47 of these patients.²

There were four main trials of apremilast in psoriatic arthritis. They had similar designs with 24 weeks of placebo-controlled treatment followed by at least 28 weeks of active treatment for all patients and then an open-label safety phase. The primary outcome of these trials was the proportion of patients having a 20% improvement in their condition as assessed by the American College of Rheumatology criteria (ACR 20).

The first of these trials (PALACE 1) randomised 168 patients who had experienced an inadequate response to disease-modifying antirheumatic drugs, to take apremilast 30 mg twice daily and 168 to take a placebo. After 16 weeks an ACR 20 response had been achieved by 38.1% of those taking apremilast and 19% of the placebo group. For the patients who had psoriasis affecting at least 3% of their skin surface there was some improvement – a 75% reduction in the PASI was achieved by 21% of patients taking apremilast 30 mg twice daily and 4.6% of the placebo group.³ The two other trials of previously treated patients had similar ACR 20 results (see Table).

A fourth trial with a similar design studied 528 patients with psoriatic arthritis who had not previously been treated with a disease-modifying drug. At 16 weeks an ACR 20 response had been achieved by 30.7% of the patients taking apremilast and 15.9% of the placebo group.

The advantage of apremilast over placebo was sustained in patients who continued to take it for psoriatic arthritis. In the PALACE 1 trial, 130 of the 168 patients randomised to take apremilast 30 mg twice daily continued it for a year. An ACR 20 response was achieved by 54.6%.⁴ In the other two trials of previously treated patients the response was 52.6–63% while for untreated patients it was 57%.

Adverse events with apremilast led to 5.2% of the patients dropping out of the psoriasis studies and 4.9% dropping out of the psoriatic arthritis studies. Common adverse effects included diarrhoea, nausea, upper respiratory tract infections and headaches. Over a year there was an average weight loss of



Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Table Efficacy of apremilast in psoriatic arthritis

Trial	Response rates at 16 weeks †	
	Placebo	Apremilast 30 mg 12-hourly
PALACE 1 ⁵	19% (32/168)	38.1% (64/168)
PALACE 2	18.9% (30/159)	32.1% (52/162)
PALACE 3	18.3% (31/169)	40.7% (68/167)

† Proportion of patients previously treated with a disease-modifying antirheumatic drug who had at least a 20% improvement in the criteria of the American College of Rheumatology

1.86 kg. There is a question about whether there is an increased incidence of depression with apremilast.

Apremilast is contraindicated in pregnancy. It is unknown if the drug is excreted in human breast milk.

While apremilast is more effective than a placebo for patients with moderate to severe plaque psoriasis, it needs to be compared to other oral therapies. It is unknown whether apremilast has a disease-modifying effect in joints affected by psoriatic arthritis. Until more data are available, it would seem prudent to reserve apremilast for patients with active psoriatic arthritis who do not respond or cannot tolerate other drugs, however this restriction has not been included in the marketing approval.

T T manufacturer provided additional useful information

REFERENCES *†

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3. Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis* 2014;73:1020-6.
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Ibrutinib

Approved indication: chronic lymphocytic leukaemia, mantle cell lymphoma

Imbruvica (Janssen-Cilag)

140 mg tablets

Australian Medicines Handbook section 14.2.3

Ibrutinib is an oral small-molecule drug for B-cell malignancies. It works by binding to Bruton's tyrosine kinase and blocking signalling through the B-cell receptor and cytokine receptor pathways. This inhibits the proliferation of B cells.

Ibrutinib has been registered for the following indications:

- first line for chronic lymphocytic leukaemia in patients with the 17p deletion
- second line for chronic lymphocytic leukaemia and small lymphocytic lymphoma (after at least one previous therapy)
- second line for mantle cell lymphoma (after at least one previous therapy).

Ibrutinib should be taken once a day. The recommended daily dose is 420 mg for chronic lymphocytic leukaemia and small lymphocytic lymphoma, and 560 mg for mantle cell lymphoma.

The safety and efficacy of ibrutinib were assessed in several trials.¹⁻³ In general, patients were heavily pre-treated (2-4 previous therapies) and their median ages were 66-68 years. Patients taking warfarin were excluded.

Chronic lymphocytic leukaemia and small lymphocytic lymphoma

The approval is based on a single-arm phase II trial¹ and a comparative phase III trial with ofatumumab.² Most enrolled patients had chronic lymphocytic leukaemia with only 5% having small lymphocytic lymphoma. Approximately a third of those in each trial had an abnormal chromosome 17 (17p deletion), which is associated with a poorer prognosis.