Table **Efficacy of apremilast in psoriatic arthritis**

Trial	Response rates at 16 weeks ‡	
	Placebo	Apremilast 30 mg 12-hourly
PALACE 1[3]	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

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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 trial[1] 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.

Patients were given daily ibrutinib until their disease progressed or they developed unacceptable adverse effects. In the phase II trial, patients were given 420 mg or 840 mg. Overall, 71% of patients responded to treatment (Table 1). These were mainly partial responses. At 26 months, the progression-free survival rate was estimated at 75% and overall survival was 83%.

In the phase III trial, ibrutinib 420 mg significantly improved rates of progression-free survival, overall survival and treatment responses compared to ofatumumab (Table 1).[2] The efficacy of ibrutinib was similar in patients with and without the 17p deletion.[1,2]

Mantle cell lymphoma

The approval of daily ibrutinib 560 mg for mantle cell lymphoma is based on an open-label, uncontrolled phase II trial of 111 patients with relapsed or refractory disease.[3] Over two-thirds of patients responded to ibrutinib – 23 patients had a complete response and 35 had a partial response (Table 2). The response rate seemed to be independent of age, previous bortezomib exposure and prognosis at baseline. The estimated median duration of response was 17.5 months and the estimated median progression-free survival was just under 14 months.

Adverse effects and precautions

In a cohort of 357 patients, 6% discontinued treatment because of an adverse event (including infection and subdural haematoma). The most common adverse events were diarrhoea, musculoskeletal pain, upper respiratory tract infection, bruising, rash, nausea, fever, neutropenia and constipation. These were reported in at least 20%

Table 1 **Efficacy of daily ibrutinib in chronic lymphocytic leukaemia and small lymphocytic lymphoma**

Phase II trial [1]	**Ibrutinib 420 mg (51 patients)**	**Ibrutinib 840 mg (34 patients)**
Response rate‡	71% (2 complete and 34 partial responses)	71% (24 partial responses)
Progression-free survival estimated at 26 months	75%	
Overall survival at 26 months	83%	
Phase III trial [2]	**Ibrutinib 420 mg (195 patients)**	**Ofatumumab§ (196 patients)**
Response rate‡	43% (all partial responses)	4% (all partial responses)
Progression-free survival at 6 months	88%	65%
Median duration of progression-free survival	Not reached (at 9.4 months)	8.1 months
Overall survival at 12 months	90%	81%

‡ Assessment included blood counts, physical and radiological examinations to determine lymph node, spleen and liver size, and bone marrow biopsy to confirm a complete response.

§ Intravenous ofatumumab 300 mg was given at week one followed by 2000 mg each week for seven weeks and then monthly for 16 weeks.

Table 2 **Efficacy of daily ibrutinib in mantle cell lymphoma** [3]

	Ibrutinib 560 mg (111 patients)
Overall response rate#	68% (23 complete responses, 52 partial responses)
Estimated median duration of progression-free survival	17.5 months
Estimated median progression-free survival	13.9 months
Estimated overall survival at 18 months	58%

Response was assessed by regular physical and radiological examinations (CT and PET scans) and bone marrow biopsy. A PET scan was needed to confirm complete responses.

of patients. Anaemia, neutropenia, pneumonia and thrombocytopenia were the most common serious adverse effects (grade 3 or 4) and occurred in 5% or more of patients.

In total, 26 patients died during the trials. Apart from progressive disease, causes included pneumonia (5 patients), sepsis (2 patients), secondary malignancy (2 patients), cardiac arrest (1 patient) and hypovolaemic shock (1 patient).

Bleeding-related adverse events were common with ibrutinib and ranged from bruising and nosebleeds to blood in the urine, gastrointestinal bleeding and intracranial haemorrhage. Warfarin, fish oil and vitamin E should not be given concomitantly with ibrutinib.

Atrial fibrillation is a risk with ibrutinib, particularly during acute infections or in people with a history of atrial fibrillation or other cardiac risk factors. Regular cardiac monitoring is recommended. Alternatives to ibrutinib should be considered in patients who need oral anticoagulants.

Blood counts should be monitored every month as severe neutropenia, thrombocytopenia and anaemia can occur. Skin cancers have been reported with ibrutinib so regular skin examination is important.

Ibrutinib caused a transient increase in lymphocyte count at the beginning of treatment in 75% of patients with chronic lymphocytic leukaemia and 35% of patients with mantle cell lymphoma. Lymphocytosis often occurred at the same time as a reduction in lymph node and spleen size and is thought to be a pharmacodynamic effect unrelated to progressive disease. Leukostasis (clumping of white blood cells) was occasionally reported and may be related to an increase in circulating lymphocytes. It can cause local hypoxaemia and bleeding which can present as headache, blurred vision, transient ischaemia, cerebrovascular accident and dyspnoea. Patients should be monitored closely and ibrutinib may need to be interrupted if this occurs.

Pharmacology and drug interactions

Ibrutinib is rapidly absorbed after oral administration and metabolised in the liver by cytochrome P450 (CYP) 3A4. The half-life is 4–6 hours and metabolites are eliminated in the faeces (90%) and urine (10%).

Co-administration of moderate or strong CYP3A4 inhibitors such as ketoconazole, clarithromycin, erythromycin or verapamil should be avoided. If they are needed, the ibrutinib dose should be reduced to 140 mg or interrupted for up to a week. Avoid grapefruit and Seville oranges as they can inhibit CYP3A4.

Strong CYP3A4 inducers and drugs that increase the pH of the stomach can decrease ibrutinib concentrations and are not recommended. St John's wort should also be avoided. As ibrutinib could theoretically inhibit intestinal P-glycoprotein, substrates of this transporter with a narrow therapeutic index (e.g. digoxin) should be taken at least six hours before or after the ibrutinib dose.

Conclusion

Ibrutinib offers another option for people with chronic lymphocytic leukaemia or mantle cell lymphoma, particularly those who have relapsed after previous treatments. Adverse effects are common and sometimes severe so patient monitoring is very important with this drug.

T T manufacturer provided additional useful information

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Pembrolizumab

Approved indication: metastatic melanoma
Keytruda (MSD)
vials containing 50 mg powder
Australian Medicines Handbook section 14.2.1

Along with vemurafenib[1], dabrafenib[2] and trametinib[3], pembrolizumab is approved for metastatic melanoma. Like ipilimumab[4], it is an immune checkpoint inhibitor that works by modulating the patient's own immune response to tumour cells.[5]

Pembrolizumab was formerly known as MK3475 and lambrolizumab. It is a humanised monoclonal antibody that blocks the interaction between programmed death 1 (PD-1) on T cells with its ligands PD-L1 and PD-L2 on immune and tumour cells. Blocking this interaction boosts the immune response and potentially leads to tumour regression.

This antibody is indicated as monotherapy for inoperable or metastatic melanoma. It is given intravenously (over 30 minutes) every three weeks. The drug's terminal half-life is approximately 26 days. The drug is catabolised and its clearance is not affected by mild–moderate renal impairment or mild hepatic impairment. Pembrolizumab has not been studied in patients with more severe renal or hepatic impairment.