New drugs

Dabrafenib

Approved indication: metastatic melanoma
Taflinar (GlaxoSmithKline)
50 mg and 75 mg capsules
Australian Medicines Handbook section 14.2.4

Like vemurafenib (Aust Prescr 2012;35:128-35), dabrafenib is indicated for patients with inoperable or stage IV metastatic melanoma with a BRAF V600 mutation. These mutations are present in about half of people with melanomas. BRAF V600E accounts for most of them (80–90%) with BRAF V600K being less common. The mutations result in expression of an abnormal protein kinase which continuously stimulates tumour cell growth. Dabrafenib is thought to slow the growth and spread of cancer cells by competitively inhibiting the abnormal BRAF kinase.

The approval of dabrafenib (150 mg orally twice daily) is based on a pivotal open-label comparative trial with dacarbazine (1000 mg/m^2 intravenously every three weeks). Only people with previously untreated BRAF V600E-positive melanoma and no active brain metastases were enrolled. Treatment was given until disease progressed, the patient died or adverse events were intolerable. Patients in the dacarbazine arm were allowed to cross over after confirmation of disease progression. More patients responded to dabrafenib than to dacarbazine and progression-free survival was significantly longer (see Table 1A).[1]

Dabrafenib has also been investigated in patients with brain metastases (1–4 lesions) but no neurological symptoms.[2] There was no treatment comparator in the trial. Responses appeared to be better in patients with the BRAF V600E mutation compared to those with the V600K mutation. Response rates were similar regardless of whether the patient had received local treatment (brain surgery or radiotherapy) or not (see Table 1B).[2]

Adverse events with dabrafenib were more common in patients with brain metastases[2] compared to those without brain lesions[1] (82% vs 53% of patients), but discontinuations because of an event were similar (3% vs 2%). In a safety cohort of 187 patients, the most common adverse reactions were hyperkeratosis (37% of patients), headache (32%), fever (28%), arthralgia (27%), skin papilloma (24%), hair loss (22%), palmar–plantar erythrodysaesthesia (20%), fatigue (19%), nausea (19%), asthenia (18%), rash (17%), vomiting (12%), cough (12%), back pain (12%), constipation (11%) and diarrhoea (11%). Hypophosphataemia (37%) and increased alkaline phosphatase (19%) also occurred frequently.

Some patients (9%) developed cutaneous squamous cell carcinoma, often in the first 12 weeks of treatment. New primary melanomas were also reported so regular skin examination is recommended. Lesions should be excised and treatment can continue.

Uveitis and iritis have been reported with dabrafenib so vision should be monitored. Pancreatitis can occur and investigation of unexplained abdominal pain should include tests for serum lipase. Monitoring serum glucose is recommended for patients with diabetes or high blood sugar as hyperglycaemia was a problem in the trials. Treatment interruption is recommended if renal failure or fever develops.

Dabrafenib should be taken one hour before or two hours after a meal. If a dose is missed, it should not be taken within six hours of the next dose. Following oral administration, peak plasma concentrations of dabrafenib are reached after two hours. Its terminal half-life is eight hours and the dose is excreted in the faeces (71%) and urine (23%). Although there are no clinical data, dabrafenib exposure could potentially be increased in patients with moderate to severe hepatic impairment, and caution is urged.

Dabrafenib is metabolised by cytochrome P450 (CYP) 2C8 and 3A4 so inhibitors of these enzymes, such as ketoconazole and gemfibrozil, increase dabrafenib exposure. Potent CYP 2C8 inducers such as rifampicin, phenytoin and St John's wort should be avoided.

Dabrafenib induces UDP glucuronosyl transferase and numerous cytochrome enzymes (CYP3A4, 2C9, 2B6, 2C8 and 2C19) so it may lower serum concentrations of many drugs including midazolam, warfarin, hormonal contraceptives, dexamethasone and immunosuppressants. Drugs that increase gastric pH, such as proton pump inhibitors and H2 antagonists, could potentially reduce the bioavailability of dabrafenib.

Dabrafenib may prolong progression-free survival in patients with inoperable or metastatic melanoma. However, patients must have a confirmed BRAF V600 mutation before they can start treatment. It is not yet known how dabrafenib will compare to other treatments for this disease such as vemurafenib and ipilimumab.

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data 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. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

T T manufacturer provided additional useful information

REFERENCES *†

1. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380:358-65.
2. Long GV, Trefzer U, Davis MA, Kefford RF, Ascierto PA, Chapman PB, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:1087-95.

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).

Table 1 **Efficacy of dabrafenib in BRAF V600-positive metastatic melanoma**

A Patients without brain metastases – phase III trial [1]

	dabrafenib	dacarbazine
Mutation	BRAF V600E (187 patients)	BRAF V600E (63 patients)
Response rate	50% (6 complete responses, 87 partial responses)	7% (1 complete response, 3 partial responses)
Median progression-free survival	5.1 months	2.7 months
12-month overall survival	70%	63%

B Patients with brain metastases – phase II trial [2]

	dabrafenib			
Mutation	BRAF V600E		BRAF V600K	
Patients	untreated brain metastases (74 patients)	progressive brain metastases after local treatment (65 patients)	untreated brain metastases (15 patients)	progressive brain metastases after local treatment (18 patients)
Overall intracranial response rate	39.2% (2 complete responses, 27 partial responses)	30.8% (20 partial responses)	6.7% (1 partial response)	22.2% (4 partial responses)
Median progression-free survival	3.7 months	3.8 months	1.9 months	3.6 months
Median overall survival	7.6 months	7.2 months	3.7 months	5.0 months