

New drugs

Vismodegib

Approved indication: basal cell carcinoma

Erivedge (Roche)

150 mg capsules

Australian Medicines Handbook section 14.2.4

Basal cell carcinomas are generally caused by exposure to ultraviolet radiation. They are very common, with half of all Caucasian Australians developing a lesion before the age of 70 (Aust Prescr 2011;34:6-7). However, metastatic disease is rare. Vismodegib is a new oral treatment for patients with metastatic or locally advanced basal cell carcinoma.

Most basal cell carcinomas have mutations in the hedgehog signalling pathway. These alterations up-regulate the pathway and cause unrestrained proliferation of basal cells. Vismodegib is a small molecule which inhibits the hedgehog pathway by blocking the expression of one of its signalling molecules.

After showing anticancer activity in a small trial,¹ vismodegib 150 mg given once a day was assessed in an open-label trial which included Australian patients. After a median of 10 months treatment, a third of patients with metastatic disease and 43% of patients with locally advanced disease had responded (Table). While almost half of the responders with locally advanced disease had a complete response, patients with metastatic disease had only partial responses. The median duration of response was 7.6 months in both groups of patients.²

Another study compared vismodegib to placebo in 41 patients with the rare basal cell naevus (Gorlin) syndrome. Because of a defect in a gene encoding an inhibitor of the hedgehog signalling pathway, patients can develop numerous basal cell carcinomas. Patients took vismodegib 150 mg once a day and were followed for a mean of eight months. Vismodegib significantly reduced the number of new lesions compared to placebo (2 vs 29 per patient per year). It also reduced the mean diameter of existing lesions compared to placebo (by 65% vs 11%).³

In a safety cohort of 138 patients, the most common adverse events with vismodegib were muscle spasms (71.7%), alopecia (63.8%), dysgeusia (55.1%), decreased appetite (25.4%), weight loss (44.9%), fatigue (39.9%), nausea (30.4%), vomiting (13.8%), diarrhoea (29%) and constipation (21%). In the

basal cell naevus syndrome trial, 54% of patients discontinued treatment because of an adverse event.³ There were seven deaths in the open-label trial – three of unknown cause, one each from hypovolaemic shock, acute myocardial infarction, ischaemic stroke and meningeal disease.²

Vismodegib may affect fertility as amenorrhoea has been observed. It is not known if this effect is reversible.

The hedgehog pathway is involved in embryonic development so it is not surprising that vismodegib causes birth defects and fetal death in animals. It is contraindicated in pregnancy (category X) and barrier contraception with spermicide is recommended for men and women during treatment and for seven months after stopping it. As exposure via seminal fluid can occur, this also applies to men who have had a vasectomy. A second form of contraception is recommended in women. Vismodegib is also contraindicated during breastfeeding because of the risk of irreversible effects on an infant's development.

Steady-state plasma concentrations of vismodegib are reached seven days after a daily oral dose. Its half-life is approximately four days and most of the dose is excreted in the faeces. Vismodegib is a substrate of P-glycoprotein in vitro, so co-administration with a P-glycoprotein inhibitor may increase vismodegib concentrations and consequently adverse events. Drugs that reduce gastric pH such as proton pump



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.

Table The efficacy of vismodegib in patients with advanced basal cell carcinoma in an open-label trial²

	Patients with metastatic basal cell carcinoma 33 patients	Patients with locally advanced basal cell carcinoma 63 patients
Complete‡ or partial§ response	10 (30%)	27 (43%)
Stable disease¶	21 (64%)	24 (38%)
Progressive disease#	1 (3%)	8 (13%)

‡ disappearance of all target lesions

§ at least 30% decrease in size of target lesions

¶ no change in size of target lesions

at least 20% increase in size of target lesions

NEW DRUGS

inhibitors, H2-receptor antagonists and antacids may reduce vismodegib's solubility and therefore bioavailability.

Vismodegib is the first systemic treatment for patients with advanced basal cell carcinoma who cannot have surgery or radiation. It is modestly effective in metastatic or locally advanced basal cell carcinoma and very effective in basal cell naevus syndrome. However, adverse effects such as muscle spasms, dysgeusia and gastrointestinal problems are very common and more than half of patients with basal cell naevus syndrome could not tolerate ongoing treatment. Rapid rebound of lesions after stopping vismodegib has been reported in a patient with basal cell naevus syndrome.⁴

T manufacturer provided the product information

REFERENCES *

1. Von Hoff DD, LoRusso PM, Rudin CM, Reddy JC, Yauch RL, Tibes R, et al. Inhibition of the hedgehog pathway in advanced basal-cell carcinoma. *N Engl J Med* 2009;361:1164-72.
2. Sekulic A, Migden MR, Oro AE, Dirix L, Lewis KD, Hainsworth JD, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med* 2012;366:2171-9.
3. Tang JY, Mackay-Wiggan JM, Aszterbaum M, Yauch RL, Lindgren J, Chang K, et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. *N Engl J Med* 2012;366:2180-8.
4. Wolfe CM, Green WH, Cognetta AB Jr, Hatfield HK. Basal cell carcinoma rebound after cessation of vismodegib in a nevoid basal cell carcinoma syndrome patient. *Dermatol Surg* 2012;38:1863-6.

The Transparency score (**T**) is explained in 'New drugs: T-score for transparency', *Aust Prescr* 2011;34:26-7.

* 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).