

RGH Pharmacy E-Bulletin

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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.

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Vemurafenib for metastatic melanoma

Melanoma is the fourth most common cancer affecting Australians, accounting for 9.5% of all cancers in this country, with more than 10,300 new cases diagnosed annually. While melanoma is the least common dermatological cancer, it is associated with the highest rates of mortality and accounts for around 75% of all skin cancer related deaths.

Vemurafenib (Zelboraf®) is a targeted new oral therapy for metastatic and unresectable melanomas which carry the BRAF-V600E gene mutation. This BRAF-kinase inhibitor was approved by the US FDA as well as the European committee for medical products for human use in 2011 after publication of a phase 3 efficacy study: the BRIM-3 trial (n = 675). The trial showed a greater overall survival rate at six months (84% vs. 64%) and greater mean progression-free survival (5.3 months vs. 1.6 months) with vemurafenib when compared to the standard first line chemotherapy agent dacarbazine.

Approximately 50% of melanoma patients have tumours which express the targeted BRAF-V600E gene. As such a companion diagnostic test (the Cobas 4800 BRAF V600 mutation test) has been developed in composite with vemurafenib to ensure that only those patients whose tumours are most likely to respond to the mechanism of the drug are treated. Thus vemurafenib, when used together with the diagnostic test, allows for a highly individualised and targeted approach to chemotherapy.

Adverse effects associated with vemurafenib caused 38% of patients participating in the BRIM-3 trial to require a dose reduction. Cutaneous squamous cell carcinomas were a reported adverse effect in 18% of Vemurafenib treated patients and were dealt with by simple excision of the lesion. As such patients treated with vemurafenib are encouraged to regularly check their skin for new lesions or changes to moles. Other adverse effects of vemurafenib include severe skin reactions (such as Stevens Johnson Syndrome and Toxic Epidermal Necrolysis), increased photosensitivity, QT prolongation, abnormal liver function tests, blurred vision and other eye problems. Common adverse effects noted in the BRIM-3 trial were arthralgia, rash, fatigue, nausea, alopecia, diarrhoea, vomiting and headache. Haematological adverse effects such as neutropenia seemed to be minimal (affecting only one study patient) and aside for the increased incidence of squamous cell carcinomas, no other secondary neoplasias were detected.

Vemurafenib is a substrate of the cytochrome P450 isoenzyme CYP3A4 and thus interacts with both potent inhibitors (protease inhibitors, azole antifungals etc) and inducers (phenytoin, rifamycin antibiotics, carbamazepine etc). Vemurafenib is also a moderate inhibitor of CYP1A2 and a weak inhibitor of CYP2D6 and thus caution should be used in patients treated with low therapeutic index drugs metabolised by these enzymes (including warfarin). The recommended dose of vemurafenib is 960 mg twice daily, and this is reduced in increments of 240 mg according to adverse effects.

In May of this year, the Australian Therapeutic Goods Administration approved the use of vemurafenib in Australia for patients with metastatic melanoma. A submission to have vemurafenib and its companion diagnostic test subsidised under the Pharmaceutical Benefits Scheme and Medicare respectively is currently under review. Vemurafenib is also currently being investigated as a potential treatment option for thyroid cancers.

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FOR FURTHER INFORMATION – CONTACT THE PHARMACY DEPARTMENT ON 82751763 or email: chris.alderman@rgh.sa.gov.au
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