Pharmacotherapeutic report, summary

Vemurafenib (Zelboraf®) for the indication 'BRAF V600 mutation-positive unresectable or metastatic melanoma'

Recommendation by CVZ[1] dated 29-07-2013, based on an evaluation by the WAR (Scientific Advisory Committee)

Medicine. Vemurafenib (Zelboraf®).

Registered indication. "In monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma."
Posology. The recommended dose of vemurafenib is 960 mg (4 tablets of 240 mg) twice daily (equivalent to a total daily dose of 1,920 mg).
Mechanism of action. Protein kinase inhibitor. Inhibits the v-raf mouse sarcoma oncogene homologue B1 (BRAF) serine-threonine kinase. Vemurafenib interrupts the formation of constitutively activated BRAF proteins that can cause cell proliferation in the absence of growth factors that would normally be required for proliferation; these proteins are formed by mutations in the BRAF gene which substitute the valine for another amino acid at position 600.
Specific details. Before taking vemurafenib, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test. It was designed to detect the predominant BRAF V600E mutation with high sensitivity. However, the test can also detect the less common BRAF V600D and V600K mutations with lower sensitivity.

Summary of the therapeutic value

Intended effects. In one phase III study with patients in a relatively good clinical condition (ECOG 0/1) with BRAF V600E mutation-positive unresectable or metastatic melanoma (mainly the V600E mutation) treatment with vemurafenib lengthened the duration of median survival in comparison to decarbazine. Based on a post hoc analysis, the extension in survival seems limited, i.e., 3.6 months. In view of the short follow-up duration of the studies, the long-term favourable effects of vemurafenib are as yet unknown.
Unintended effects. The most frequent side effects of vemurafenib are joint pain, skin rash, alopecia, fatigue, nausea and photosensitivity reactions. About 20% of the patients treatment with vemurafenib developed cutaneous tumours (squamous cell carcinomas, keratoacanthomas and benign skin lesions (e.g. keratosis)), which required treatment with local excision. In general the side effects were mild to moderate and manageable. The long-term side effects of vemurafenib are unknown.
Experience. Experience with vemurafenib is limited, while ample experience has been gained with decarbazine.
Applicability. Patients with BRAF V600-negative melanoma should not be treated with vemurafenib. The scope for using vemurafenib is not as broad as decarbazine.
Ease of use. The recommended dose of vemurafenib is 960 mg (4 tablets of 240 mg). The first dose should be taken in the morning and the second dose about 12 hours later. Vemurafenib may be taken with or without food, but consistent intake of both daily doses on an empty stomach should be avoided. Treatment should be continued until disease progression or the development of unacceptable toxicity.

Final conclusion on therapeutic value.
Vemurafenib has an added therapeutic value in comparison with decarbazine for the treatment of adult patients in a relatively good clinical condition (ECOG 0/1) with a BRAF V600 mutation-positive unresectable or metastatic melanoma.

*The original text of this excerpt from a **WAR-Report** of Zorginstituut Nederland was in Dutch. Although great care was taken in translating the text from Dutch to English, the*

[1] CVZ's name was altered to *Zorginstituut Nederland* as of 1 April 2014.

translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of Zorginstituut Nederland's WAR-Report.
Furthermore, Zorginstituut Nederland points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.