



Commissioning Support
Appraisals Service

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21 June 2012

National Institute for Health and Clinical Excellence



RE: Vemurafenib for the treatment of locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma

On behalf of the Commissioning Support, Appraisals Service (CSAS), Solutions for Public Health, I would like to submit our comments on the appraisal consultation document for Vemurafenib for the treatment of locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. We are in agreement with the recommendations in the ACD not to recommend vemurafenib for this indication as on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective in real life clinical practice.

- **Vemurafenib represents a step change in the management of advanced malignant melanoma.** Treatment options for advanced metastatic melanoma are limited. The Appraisal Committee agreed that vemurafenib represents a valuable new therapy and that its mechanism of action is novel. The Appraisal Committee agreed that vemurafenib represents a step change in the management of advanced malignant melanoma.
- **An interim analysis in one trial found that vemurafenib is an effective therapy for the management of advanced BRAF V600 mutation-positive malignant melanoma.** The effectiveness of vemurafenib was investigated in an open-label RCT that compared vemurafenib to standard treatment with dacarbazine in patients with previously untreated advanced BRAF V600 mutation-positive metastatic melanoma (BRIM3 trial). The study ended early (December 2010) after the pre-planned interim analysis, and cross-over onto vemurafenib was permitted. At the interim analysis, vemurafenib treatment led to a statistically significant reduction in death, a significant increase in overall survival at six months, and a statistically significant reduction in tumour progression. The manufacturer submitted some follow-up data from this trial (March 2011 and October 2011).
- **There is uncertainty over the long-term survival benefit of vemurafenib.** Due to the premature termination of the BRIM3 trial and the permitted crossover onto vemurafenib, there is uncertainty over the estimation of the overall survival benefit with vemurafenib. The Evidence Review Group (ERG) and the manufacturer modelled overall survival differently.
- **There is uncertainty over the cost-effectiveness of vemurafenib.** The uncertainty over long-term survival benefit of vemurafenib was a major source of uncertainty during ICER calculation.
- **The manufacturer has agreed a patient access scheme.** This was taken into account during ICER calculation.

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- **There is no RCT data for previously treated patients.** The scope for the technology appraisal and marketing authorisation specify the eligible population for treatment with vemurafenib as all patients with unresectable locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. The BRIM3 trial only included previously untreated patients. The results of a single arm phase II trial on the effectiveness of vemurafenib in previously treated individuals were presented.
- **Treatment with vemurafenib will require mutation testing.** This testing is being offered free of charge by the manufacturer. In the manufacturer's economic model, they estimate the BRAF testing cost (per test) at £95. However, the Appraisal Committee concluded that BRAF V600 mutation testing is likely to become part of routine management for people with advanced melanoma.
- **In the BRIM3 trial 38% of patients receiving vemurafenib required dose modification because of toxic effects which included photosensitivity, arthralgia rash, fatigue and development of keratoacanthoma or well differentiated squamous cell carcinoma of the skin.** Few patients stopped the drug due to toxicity, all secondary skin cancers were resected and there have been no cases of metastatic secondary cancer.
- **Vemurafenib meets all end-of-life criteria.** The Appraisal Committee concluded that vemurafenib met all criteria for being a life-extending end-of-life treatment, and that the evidence presented for this consideration was robust.
- **Funding for vemurafenib may be available through the Cancer Drugs Fund.** The fund may be used to pay for drugs recommended by oncologists that have either been appraised by NICE and not recommended on the basis of cost effectiveness, only recommended in a smaller group of patients than specified in the marketing authorisation, or drugs that have yet to be appraised. The fund is for the purchase of medicines, although it may also be used for molecular diagnostic testing. £200 million is being made available in 2012-2013.

If you require any further information please contact me directly: Phone: 01865 334 723, email

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Yours sincerely

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