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Commissioning Support
Appraisals Service

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15th August 2012

National Institute for Health and Clinical Excellence

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RE: Vemurafenib for the treatment of locally advanced or metastatic BRAF V600 mutation-positive 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 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 cost effective in real life clinical practice.

- **There is uncertainty about the longer term clinical effectiveness of vemurafenib because the BRIM3 trial was ended early.** An open-label RCT investigated the effectiveness of vemurafenib compared to standard treatment with dacarbazine in patients with previously untreated advanced BRAF V600 mutation-positive metastatic melanoma (BRIM3 trial). The study ended early after the planned interim analysis, and cross-over onto vemurafenib was permitted. At this point, vemurafenib led to statistically significant reductions in death and tumour progression and a statistically significant increase in overall survival at six months. The manufacturer later submitted follow-up evidence from February 2012. At this point 34% of patients had crossed over from dacarbazine to vemurafenib. Despite potential confounding due to cross-over onto vemurafenib or treatment with other investigational treatments, vemurafenib led to statistically significant increases in progression free survival, reduction in tumour progression and median overall survival. The difference in median survival was increased when the manufacturer adjusted for switching using the rank preserving structural failure time (RPSFT) method. NICE has asked for details of the assumptions made and the parameter values used in the RPSFT model.
- **There is uncertainty about the overall survival benefit of vemurafenib.** The manufacturer's submission is based on the results of one open-label RCT(BRIM3), which was halted after the pre-planned interim analysis (December 2010). The manufacturer has also submitted some follow-up data from this trial (March 2011, October 2011 and February 2012). 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.
- **Vemurafenib is an effective long-term therapy for some patients.** The number of people with a complete response increased from 0.9% in December 2010 to 5.6% in February 2012 in the vemurafenib group, demonstrating that vemurafenib can provide long term benefit for some patients (in February 2012 there was a complete response in 1.2% of the dacarbazine group).

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- **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 was also satisfied that the drug met all of the criteria for being a life-extending, end-of-life treatment. The trial evidence presented for this was robust.
- **Vemurafenib may cost about £49,000 per patient at full dose.** Assuming an average length of treatment of 28 weeks (7 months) and using list prices. An estimated 1 to 2 people per 100,000 would be eligible for treatment.
- **The manufacturer has agreed a confidential patient access scheme.**
- **There is uncertainty over the cost-effectiveness of vemurafenib but the ICER is likely to be higher than £50,000.** The ICER for vemurafenib was highly uncertain and likely to be considerably higher than £50,000 per QALY gained, despite a discounted price offered via a patient access scheme. The uncertainty over long term survival benefit of vemurafenib was a major source of uncertainty during ICER calculation. The Appraisal Committee has requested a cost-effectiveness estimate from the manufacturer in which exponential hazards are applied to each arm of the BRIM3 study from 14 months (the manufacturer had assumed that survival following disease progression at 14 months is equal in both groups).
- **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.
- **Despite toxicity few patients stop the drug.** 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.
- **Funding for vemurafenib may be available through the Cancer Drugs Fund.** If NICE were not to recommend vemurafenib for this indication, 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.

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