NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Proposed Health Technology Appraisal

Dabrafenib for the treatment of unresectable, advanced or metastatic BRAF V600 mutation-positive melanoma

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of dabrafenib within its licensed indication for the treatment of unresectable, advanced or metastatic BRAF V600 mutation-positive melanoma.

Background

Malignant melanoma is a type of skin cancer which in its early stages is normally asymptomatic and, if detected early, before it has spread, can be curable. However, at presentation, around 10% of malignant melanomas will have metastasised. Melanoma can spread to nearby lymph nodes (stage III, of which stage IIIc disease includes tumours of varying size with extensive lymph node involvement but no metastases) or to other parts of the body (stage IV). It occurs more commonly in fair-skinned people and there is strong evidence that ultra violet exposure is causal. People with an above-average mole count, sun-sensitive skin, or a strong family history of melanoma are at greatly increased risk.

The incidence of malignant melanoma is increasing in England and Wales with rates doubling approximately every 10-20 years. There were 11,877 new diagnoses of malignant melanoma and 2203 deaths registered in the UK in 2010. In the UK, melanoma is diagnosed at a mean age of around 50 years but approximately 20% of cases occur in young adults aged between 15 and 39 years old. Five-year survival rates are approximately 20-30% for stage IIIc disease and approximately 7-20% for stage IV disease.

BRAF is part of the RAS/MAPK signalling pathway, which helps to control cell proliferation, differentiation and death. The mutated form BRAF V600 is found in approximately 50% of malignant melanomas.

Early recognition of malignant melanoma and accurate diagnosis presents the best opportunity for cure by surgical resection of the tumour. A very small minority of people with advanced disease can still have their tumour removed. People with unresectable stage III or IV (metastatic) disease are usually managed by a specialist oncologist and first-line standard care normally involves the administration of dacarbazine. Radiotherapy, immunotherapy and combination chemotherapy have also been studied in randomised clinical trials. A NICE technology appraisal of vemurafenib for previously untreated advanced or metastatic BRAF V600 mutation-positive melanoma is currently ongoing. Also ongoing is the appraisal of ipilimumab for the treatment of previously treated unresectable stage III or IV malignant melanoma. The

treatment options currently available for advanced or metastatic malignant melanoma are limited.

The technology

Dabrafenib (Brand name unknown, GlaxoSmithKline) is a selective ATP-competitive BRAF (serine/threonine-protein kinase BRAF) inhibitor. When the activity of mutant protein kinase is blocked, the cancer cells stop growing and die. It is administered orally.

Dabrafenib does not currently have a UK marketing authorisation for the treatment of metastatic melanoma. It is being studied in clinical trials compared with dacarbazine in adults with unresectable Stage IIIc or IV (metastatic) BRAF V600E/K mutation-positive cutaneous melanoma who have not received prior treatment. It is also being studied in combination with trametinib compared with dabrafenib alone in adults with metastatic BRAF V600 mutation-positive melanoma who have not received prior systemic chemotherapy.

Intervention(s)	Dabrafenib
Population(s)	Previously untreated adults with advanced or metastatic BRAF V600 mutation-positive melanoma
Comparators	• dacarbazine • vemurafenib (subject to ongoing NICE appraisal)
Outcomes	The outcome measures to be considered include: • progression-free survival • overall survival • response rate • adverse effects of treatment • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.

Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Cost of any additional mutational testing required for this treatment should be considered.
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal in Preparation, 'Vemurafenib for the treatment of unresectable locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma'. Earliest anticipated date of publication October 2012. Technology Appraisal in Preparation, 'Ipilimumab for previously treated unresectable stage III or IV malignant melanoma'. Earliest anticipated date of publication TBC. Technology Appraisal in Preparation, 'Ipilimumab in combination with dacarbazine for previously untreated unresectable stage III or IV malignant melanoma'. Earliest anticipated date of publication TBC. Suspended Technology Appraisal, 'Temozolomide for the treatment of advanced and metastatic melanoma'. Related Guidelines: Clinical Guideline 104, Jul 2010, 'Diagnosis and management of metastatic malignant disease of unknown primary origin'. Clinical Service Guidance CSGSTIM, May 2010, 'Skin tumours including melanoma'.

Questions for consultation

Is dabrafenib likely to also be used as a second-line or subsequent treatment in clinical practice?

Have the most appropriate comparators for dabrafenib for the treatment of advanced or metastatic BRAF V600 mutation-positive melanoma been included in the scope? Are the comparators listed routinely used in clinical practice?

Are there any subgroups of people in whom dabrafenib is expected to be more clinically effective and cost effective or other groups that should be examined separately?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the

proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which dabrafenib will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider dabrafenib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of dabrafenib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

Another treatment, trametinib, is also in development for BRAF V600 mutation-positive metastatic melanoma (alone and in combination with dabrafenib), and is likely to receive regulatory approval at a similar time to dabrafenib monotherapy. NICE welcomes comments on whether both treatments should be appraised together as a Multiple Technology Appraisal (MTA) or if dabrafenib should be considered alone through the Single Technology Appraisal (STA) Process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp)