A.4	**BRAF/MEK inhibitors –unresectable or metastatic melanoma with a BRAF V600 mutation** **dabrafenib plus trametinib; vemurafenib plus cobimetinib; encorafenib plus binimetinib**
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Recently the incidence of melanoma has increased. The number of newly diagnosed melanomas worldwide is expected around 280,000, and it is estimated that about 67,809 people will die from this disease.
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	Nivolumab is included in the EML. This is monoclonal antibody used in the treatment of different kinds on cancer including melanoma and metastatic melanoma.
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included:
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). Initial studies showed that BRAF 600 inhibitors were effective in the treatment of advance melanoma but due to resistance they were combined with MEK inhibitors. Combinations are associated with OS of 34% and complete response of 19%. They are an effective option even for patients with brain metastasis. There is no head to head comparison between BRAF/MEK inhibitors and checkpoint inhibitors such as nivolumab Outcomes are similar with the 3 combinations Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? Studies were developed in adults >18 years old in multiple centres around the world.

Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Side effects include ophthalmic and cardiovascular toxicity. Both of them could be severe and require dose adjustment or treatment discontinuation. Other side effects include pyrexia and cutaneous toxicity
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Patients should be monitored for ophthalmologic toxicity. A cardiological assessment is needed prior to treatment initiation due to cardiovascular toxicity; once treatment is started monitoring is required as well.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	I consider the profile of these combinations is favourable. As most drug used in the management of cancer side effects can be severe and many of them require monitoring. Considering the mortality associated with metastatic melanoma I believe that the potential benefits justify the risks.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Evidence is moderate to high quality. It is based on double blind RTCs with consistent results.
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: In order to use BRAF/MEK inhibitors testing for BRAF V600 mutation is required. Additionally, as mentioned previously, monitoring for side effects is also needed. Physicians managing g patients using these medications need to be familiar with the toxicity profile and dose adjustment schemes.
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments:

Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments:
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	These medications are extremely expensive. Even when effective, cost can results prohibitive for many LMICs. The cost of treatment also includes testing for BRAF V600 mutation and adverse event monitoring. This is supported by the fact that economic evaluation concluded that targeted combinations were not cost effective at current prices using data for the US, UK and Canada and Australia Italy, Portugal, Italy and Norway.
Any additional comments	
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	I consider BRAK/MEK inhibitors should not be included in the EML for the following reasons: -High cost and studies show they are not cost-effective -The EML already includes a drug for the treatment of metastatic melanoma and there is no evidence that BRAF/MEK inhibitors are a better option -Additional testing in required (VRAF 600 mutation, not needed for checkpoint inhibitors)
References (if required)	