A.4	**BRAF/MEK inhibitors - unresectable or metastatic melanoma with a BRAF V600 mutation** **dabrafenib plus trametinib, vemurafenib plus cobimetinib, and encorafenib plus binimetinib**
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments:
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.	The submission seeks approval for three separate BRAF inhibitor plus MEK inhibitor two-drug combinations for the treatment of unresectable or metastatic melanoma where the role of the combinations is definite and for which no controversies exist. The three combinations are: dabrafenib plus trametinib; vemurafenib plus cobimetinib; and encorafenib plus binimetinib. All belong to the class of the mitogen-activated protein kinase (MAPK) pathway inhibitors, specifically they are BRAF/MEK inhibitors. All three combinations have been approved for the treatment of patients with irresectable or metastatic melanoma with a BRAFV600 mutation.
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable All relevant evidence has been addressed in the application. The relevant studies are cited and briefly summarized. The application leverages the review of data by ESMO in Europe and NCCN in the United States, noting “the majority of the data referred in this application, particularly for the clinical trials evaluating the three BRAF/MEK combinations proposed, has been referred in the ESMO and NCCN guidelines for the management of advanced melanoma”

Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable Three different two drug combinations of a BRAF inhibitor and a MEK inhibitor have received regulatory approvals worldwide for the treatment of patients with advanced melanoma. Four randomized phase III trials including coBRIM [vemurafenib plus cobimetinib], COMBI-d and COMBI-v [dabrafenib plus trametinib] and COLUMBUS [encorafenib plus binimetinib] compared the combinations with BRAF inhibitor monotherapy and showed improved survival outcomes in melanomas harboring BRAFV600 mutations. These results support the use of combined targeted therapy instead of monotherapy as targeted therapy in patients with whose melanoma harbors BRAFV600 mutations. The efficacy and survival outcomes are very similar with the three BRAF/MEK inhibitor combinations. There are no clinical trials evaluating the three combinations head-to-head making the choice of which combination to use an arbitrary one

Study	**Combination targeted therapy**				
	COMBI-d	COMBI-v	CoBRIM	COLUMBUS	
Agent(s)	D + T	D + T	V + C	E + B	E + B
Patients, n (study arm)	211	352	247	577 (1)	258 (2)
Follow up, months	≥ 36.0	23	21.2	36.8	---
Median OS, months	25.1	26.1	22.5	33.6	---
Median DOR, months	12	13.8	13.0	18.6	12.7
Related AEs, %	97	99	99	98	98
Discontinuation due to AE %	14	16	13	15	12
CTCAE grade 3/4 AEs, %	48	57	77	64	47
Median DOR, months	12	13.8	13.0	18.6	12.7
Related AEs, %	97	99	99	98	98
Discontinuation due to AE %	14	16	13	15	12
CTCAE grade 3/4 AEs, %	48	57	77	64	47
Median DOR, months	12	13.8	13.0	18.6	12.7
Related AEs, %	97	99	99	98	98
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D + T = Dabrafenib + Trametinib
V + C = Vemurafenib + Cobimetinib
E + B = Encorafenib + Binimetinib

<table>
<tr><td>Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?</td><td>☒ Yes
☐ No
☐ Not applicable
Comments: Sufficient data provided but clarity as to what toxicities are due to BRAF inhibitor alone or the combination of a BRAF inhibitor and a MEK inhibitor is wanting

<table><tr><th>Adverse Event</th><th>D + T</th><th>V + C</th><th>E + B</th></tr><tr><td>Photosensitivity</td><td><10</td><td>47 / 4</td><td><10</td></tr><tr><td>Keratoacanthoma / SCC</td><td>1-3</td><td>6</td><td><10</td></tr><tr><td>Arthralgia</td><td>28 / <1</td><td><10</td><td>26 / 1</td></tr><tr><td>Pyrexia</td><td>63 / 5</td><td>28 / 2</td><td>18 / 4</td></tr><tr><td>Fatigue</td><td>59 / 5</td><td><10</td><td>43 / 3</td></tr><tr><td>Chills</td><td>37 / 1</td><td>10 / 0</td><td><10</td></tr><tr><td>Rash</td><td>37 / <1</td><td>16 / 1.6</td><td>22 / 1</td></tr><tr><td>Headache</td><td>39 / 1</td><td><10</td><td>22 / 2</td></tr><tr><td>Nausea</td><td>40 / <1</td><td>41 / 1</td><td>41 / 2</td></tr><tr><td>Diarrhea</td><td>33 / <1</td><td>60 / 6</td><td><10</td></tr><tr><td>Vomiting</td><td>28 / <1</td><td>24 / 1</td><td>30 / 2</td></tr><tr><td>Blurred vision</td><td>6</td><td>15 / <1</td><td><10</td></tr><tr><td>Decreased ejection fraction</td><td>5</td><td>-26-</td><td><10</td></tr></table>SCC = squamous cell carcinoma
Toxicity reported as All grades / >G3. Single number if no breakdown
Note: <10 when data reported only if ≥10% All Grades toxicity
D + T = Dabrafenib + Trametinib [COMBI-d and COMBI A/D data]
V + C = Vemurafenib + Cobimetinib [coBRIM data]
E + B = Encorafenib + Binimetinib [COLUMBUS data]]</td></tr>
<tr><td>Are there any adverse effects of concern, or that may require special monitoring?</td><td>☒ Yes
☐ No
☐ Not applicable
Comments: May need to ensure access to specialized support for: (1) ophthalmology for blurred vison a category that includes amongst others uveitis and retinal detachment; (2) cardiology for decreased ejection fraction; and (3) dermatology for the occasional SCC</td></tr>
<tr><td>Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)</td><td>Combinations of a BRAF inhibitor with a MEK inhibitor [dabrafenib plus trametinib, vemurafenib plus cobimetinib, and encorafenib plus binimetinib] for the treatment of “adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation” are effective and reasonably well tolerated although by no means devoid of toxicity. In the clinical trials their benefit has been measured in very modest prolongation of survival compared to single agent BRAF inhibitors. An important attribute that has emerged from these studies is the amelioration of some toxicities seen at higher rates with single agent BRAF inhibitors with the combinations. They also remain as the single example where two small molecule targeted therapies have been successfully combined. Overall, the benefit to risk ratio can be regarded favourable</td></tr>
<tr><td>Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)</td><td>The overall quality of the individual evidence is very good coming from large prospectively randomized multi-institutional trials. The data suffers in that there are no head-to-head comparisons leaving one to make cross-trial comparisons that are always difficult. However, at the same time, the redundancy of some of the data contributes to its validity.</td></tr>
<tr><td>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)</td><td>☒ Yes
☐ No
☐ Not applicable
Comments: As noted above, may need to ensure access to specialized support for: (1) ophthalmology for blurred vison a category that includes amongst others uveitis and retinal detachment; (2) cardiology for decreased ejection fraction; and (3) dermatology for the occasional SCC</td></tr>
</table>

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.	All three two-drug combinations currently retain patent protection, and this makes their costs prohibitive. Recognizing the difficulties of cross-trial comparisons, in large, randomized trials they have demonstrated similar degrees of efficacy. Additionally, while they have some differences in their toxicity profiles, this too is more similar than different. This precludes any recommendation for the approval of a best or a more tolerable combination. Thus, in choosing which to provide, cost should be a principal if not the principal consideration.
Any additional comments	Mature OS data has been reported for the three two-drug combinations in this submission. While in both the e**ncorafenib + binimetinib [E + B]** and the **cobimetinib + vemurafenib [C + V]** studies the vemurafenib control achieved very similar outcomes, the better results with the **encorafenib + binimetinib** combination and slightly better HR must be interpreted with caution. At the present time the safest conclusion is to consider the efficacy of all three two-drug combinations comparable **Dabrafenib plus Trametinib [D +T]** A total of 563 patients were randomly assigned to receive dabrafenib plus trametinib (211 in the COMBI-d trial and 352 in the COMBI-v trial). **The median overall survival duration was 25.9 months (95%CI, 22.6 to 31.5).** The overall survival rates were 37% (95%CI, 33 to 42) at 4 years and 34% (95%CI, 30 to 38) at 5 years. In multivariate analysis, several baseline factors (e.g., performance status, age, sex, number of organ sites with metastasis, and lactate dehydrogenase level) were significantly associated with both progression-free survival and overall survival. A complete response occurred in 109 patients (19%) and was associated with an improved long-term outcome, with an overall survival rate of 71% (95%CI, 62 to 79) at 5 years. *Author Conclusions:* First-line treatment with dabrafenib plus trametinib led to long-term benefit in approximately one third of the patients who had unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation. **Encorafenib + Binimetinib [E + B]** **The median OS in the COLUMBUS trial was 33.6 months (95%CI, 24.4-39.2) for the combination of encorafenib plus binimetinib,** 23.5 months (95%CI, 19.6-33.6) for encorafenib alone and 16.9 months (95%CI, 14.0-24.5) for vemurafenib alone. **The hazard ratio [HR] was 0.61 (95%CI, 0.48-0.79)** for the comparison of encorafenib plus binimetinib versus vemurafenib alone. *Author Conclusions:* Updated PFS and OS results for COMBO450 from the COLUMBUS trial demonstrate a long-term benefit in patients with advanced BRAF V600-mutated melanoma. **Cobimetinib + Vemurafenib [C + V]** 495 eligible adult patients were randomly assigned to the cobimetinib plus vemurafenib group (n=247) or placebo plus vemurafenib group (n=248). **Median overall survival was 22·3 months (95%CI 20·3-not estimable) for cobimetinib and vemurafenib** versus 17·4 months (95 CI 15·0-19·8) for placebo and vemurafenib **(HR 0·70, 95%CI 0·55-0·90; p=0·005).**

	Author Conclusions: These data confirm the clinical benefit of cobimetinib combined with vemurafenib and support the use of the combination as a standard first-line approach to improve survival in patients with advanced BRAF(V600)-mutant melanoma.
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.	The submission understandably advocates recommending all three BRAF inhibitor plus MEK inhibitor combinations - dabrafenib plus trametinib, vemurafenib plus cobimetinib, and encorafenib plus binimetinib. Were inclusion in the WHO Model list of ESSENTIAL MEDICINES for cancer for the treatment of "adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation" be recommended, it should include all three two-drug combinations. However, at this time, we await clarification of the role of these two-drug combinations in patients previously treated with an immune checkpoint inhibitor. Pending that clarification, a delay in recommending their inclusion is wise.
References (if required)	