National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Encorafenib with binimetinib for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma [ID923]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	-	-	-
Wording	NCRI-ACP-RCP	Yes	Comment noted. No action required.
	Novartis Pharmaceuticals Ltd	The wording of the remit is appropriate and reflects the clinical and cost-effectiveness issues that the technology should consider	Comment noted. No action required.
	Pierre Fabre Ltd	The anticipated licensed indication for encorafenib in combination with binimetinib is for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation	Comment noted. No action required.
Timing Issues	NCRI-ACP-RCP	Medium	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Novartis Pharmaceuticals Ltd	Despite the introduction of multiple new therapies for metastatic melanoma in recent years and the evolution of the treatment landscape, there is urgency for the institute to review this topic to ensure that patients receive access to effective medicines in an area where there remains a unmet need for further effective treatments.	Comment noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10217. No action required.
	Pierre Fabre Ltd	In order to ensure the Appraisal Committee are provided with the full dataset for encorafenib in combination with binimetinib we had requested consideration of a submission date of August 2018 which has now been provisionally agreed.	Comment noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10217. No action required.
Additional comments on the draft remit	Novartis Pharmaceuticals Ltd	None	Comment noted. No action required.
	Pierre Fabre Ltd	None	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	NCRI-ACP-RCP	Accurate	Comment noted. No action required.
	Novartis Pharmaceuticals Ltd	The background information states that a mutated form of the BRAF gene is found in approximately 50% of melanomas. We believe this figure to be an over-estimate, with more recent sources reporting a BRAF mutation rate of 40%[1] **References** Long GV, Hauschild A, Santinami M, Atkinson V, Mandalà, M, Chiarion‐Sileni, V, Larkin J, Nyakas M, Dutriaux C, Haydon A, Robert C, Mortier L, Schachter J, Schadendorf D, Lesimple T, Plummer R, Ji R, Zhang P, Mookerjee B, Legos J, Kefford R, Dummer R, Kirkwood J.M: Adjuvant dabrafenib plus trametinib in Stage III BRAF-mutated melanoma. N Eng J Med. 2017 Sep 10.	Comment noted. This section has been amended to "A mutated form of the BRAF gene is found in 40% to 60% of melanomas; 80% to 90% of these are BRAF V600 mutations."
	Pierre Fabre Ltd	Within the paragraph on treatment options the addition of the following text would be helpful in order to highlight the current standard of care following the NICE recommendation for dabrafenib in combination with trametinib. 'Following TA396 dabrafenib in combination with trametinib is considered the standard of care in clinical practice and is replacing the use of BRAF V600 monotherapy'.	Comments noted. This section of the scope has been amended.
The technology/ intervention	NCRI-ACP-RCP	Yes	Comment noted. No action required.
	Novartis Pharmaceuticals Ltd	No comment	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Pierre Fabre Ltd	The anticipated licensed indication for encorafenib in combination with binimetinib is for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation. The anticipated brand names are as follows: [redacted]	Comments noted. No action required.
Population	NCRI-ACP-RCP	Yes	Comment noted. No action required.
	Novartis Pharmaceuticals Ltd	The population is appropriately defined, reflecting the population in COLUMBUS[2] the pivotal trial for this intervention. Since this trial included both previously untreated and previously treated patients who had progressed on or after prior first line immunotherapy, it may be of interest to consider these sub-groups separately **References** Study Comparing Combination of LGX818 Plus MEK162 Versus Vemurafenib and LGX818 Monotherapy in BRAF Mutant Melanoma (COLUMBUS) https://clinicaltrials.gov/ accessed 16/10/17	Comment noted. The subgroups were added to the scope.
	Pierre Fabre Ltd	The population is defined appropriately and there are no sub groups within this population which need to be considered separately.	Comment noted. No action required.
Comparators	NCRI-ACP-RCP	Yes	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action

	Novartis Pharmaceuticals Ltd	BRAF V600 mutation testing is standard for people with melanoma, and dabrafenib in combination with trametinib (BRAF and MEK inhibitor combination therapy) is considered the standard of care for treating advanced (unresectable or metastatic) BRAF V600 mutation-positive melanoma.
		
		It should also be noted that although dabrafenib in combination with trametinib is the standard of care, BRAF monotherapies represent relevant treatment options for those who may be intolerant to MEK inhibitors. In addition, it should also be noted that the NICE pathway[3] and clinical guidelines for melanoma[4] recommend immunotherapies as potential treatment options for this population. As such all the following technologies could be considered as relevant comparators for encorafenib in combination with binimetinib:
		• Targeted BRAF inhibitor monotherapies
		  ○ Dabrafenib
		  ○ Vemurafenib
		• Immunotherapies:
		  ○ Ipilimumab
		  ○ Nivolumab
		  ○ Ipililmumab in combination with nivolumab Pembrolizumab
		References
		1. NICE Pathways- Melanoma https://pathways.nice.org.uk/pathways/melanoma accessed 16/10/17
		2. NICE Guidelines NG14 Melanoma: assessment and management (2015)
			Comment noted. People receiving encorafenib with binimetinib must be able to have a MEK inhibitor, thus BRAF inhibitor monotherapy is not a suitable comparator. Immunotherapies are not considered an appropriate comparator for this population and were not included in any previous scopes in this disease area. No action required.
			
			In addition, if evidence allows, subgroups of people with previously untreated disease and people with previously treated disease that has progressed on or after first line immunotherapy will be considered separately.

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	Pierre Fabre Ltd	Trametinib in combination with dabrafenib is the only appropriate comparator. In clinical practice many melanoma patients with metastatic or unresectable melanoma who have a high burden of disease and are BRAF-mutant are treated with a combination of a BRAF-inhibitor/MEK-inhibitor (targeted therapy) first-line. At present the only licensed and NICE recommended combination product is dabrafenib/trametinib. Following first line therapy with targeted therapy patients whose disease progresses go on to receive immunotherapy second-line. Most melanoma patients with a low burden of disease receive immunotherapy used first-line and targeted therapy second-line. In clinical practice encorafenib in combination with binimetinib will offer an alternative to the current combination of trametinib and dabrafenib in the existing NICE Melanoma pathway. No change to the existing NHS infrastructure will be required	Comment noted. No action required. In addition, if evidence allows, subgroups of people with previously untreated disease and people with previously treated disease that has progressed on or after first line immunotherapy will be considered separately.
Outcomes	NCRI-ACP-RCP	Yes	Comment noted. No action required.
	Novartis Pharmaceuticals Ltd	The outcomes are appropriate and reflect the endpoints of the COLUMBUS trial	Comment noted. No action required.

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	Pierre Fabre Ltd	Yes – all the outcomes listed are appropriate	Comment noted. No action required.
Economic analysis	NCRI-ACP-RCP	Appropriate	Comment noted. No action required.
	Novartis Pharmaceuticals Ltd	The economic analysis is appropriate and consistent with the NICE reference case.	Comment noted. No action required.
	Pierre Fabre Ltd	The economic model submitted will be in line with other melanoma models submitted to NICE.	Comment noted. No action required.
Equality and Diversity	NCRI-ACP-RCP	No issues	Comment noted. No action required.
	Novartis Pharmaceuticals Ltd	No Comment	Comment noted. No action required.
	Pierre Fabre Ltd	No issues identified.	Comment noted. No action required.
Innovation	NCRI-ACP-RCP	Dabrafenib+trametinib was the innovation. This new combination offers an alternative which is not expected to be more effective but could be an option if dabrafenib+trametinib was not tolerated by an individual patient. The QALY will be set by the costs of the drugs and whether this becomes a more cost effective option to prescribing dabrafenib+trametinib.	Comments noted. Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an

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			opportunity to provide evidence on the innovative nature of its product in its submission. No action required.
	Novartis Pharmaceuticals Ltd	No Comment	Comment noted. No action required.
	Pierre Fabre Ltd	Not applicable.	Comment noted. No action required.
Other considerations	NCRI-ACP-RCP	Nil	Comment noted. No action required.
	Novartis Pharmaceuticals Ltd	No Comment	Comment noted. No action required.
	Pierre Fabre Ltd	No issues identified.	Comment noted. No action required.
Questions for consultation	Novartis Pharmaceuticals Ltd	**Which treatments are considered to be established clinical practice in the NHS for unresectable or metastatic BRAF V600 mutation-positive melanoma?** As mentioned previously in the comparators section of the scope, dabrafenib in combination with trametinib is considered established clinical practise for unresectable/metastatic BRAF V600 mutation positive	Comment noted. People receiving encorafenib with binimetinib must be able to have a MEK

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		melanoma, however according to the NICE clinical guidelines and pathway[3, 4], the following technologies are also potential treatment options: • Dabrafenib • Vemurafenib • Ipilimumab • Nivolumab • Ipililmumab in combination with nivolumab • Pembrolizumab This was supported by the NICE committee in the recent appraisal for cobimetinib in combination with vemurafenib in V600 BRAF positive mutation melanoma[5] (the same population for which encorafenib plus binimetinib is indicated). The NICE committee noted that although ipilimumab, pembrolizumab or nivolumab may be used as a first line treatment in some people with BRAF mutations whose disease is not progressing rapidly and who are relatively fit, BRAF inhibitors are the preferred first treatment for people with BRAF V600 mutations[6] **Is BRAF inhibitor monotherapy used in clinical practice in this population? If yes, is BRAF inhibitor monotherapy an appropriate comparator for combination therapy with encorafenib and binimetinib?** Market research/IMS data estimates [redacted][7] of patients are currently receiving BRAF monotherapy. The majority of patients with unresectable metastatic BRAF mutant melanoma now receive BRAF and MEK inhibition combination therapy (i.e. dabrafenib and trametinib), however BRAF monotherapies	inhibitor, thus BRAF inhibitor monotherapy is not a suitable comparator. Immunotherapies are not considered an appropriate comparator for this population and were not included in any previous scopes in this disease area. No action required. In addition, if evidence allows, subgroups of people with previously untreated disease and people with previously treated disease that has progressed on or after first line immunotherapy will be considered separately.

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		represent relevant treatment options for those who may be intolerant to MEK. **Have all relevant comparators for encorafenib in combination with binimetinib been included in the scope?** Please refer to previous comments on comparators **Are the outcomes listed appropriate?** Please refer to previous comments on outcomes. **Are there any subgroups of people in whom encorafenib in combination with binimetinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?** Since there are limited data in support optimal treatment strategies, it may be of interest to examine previously untreated and previously treated patients separately since the COLUMBUS trial included patients who were treatment naïve as well as those who had progressed on or after prior first line immunotherapy. **Where do you consider encorafenib in combination with binimetinib will fit into the existing NICE pathway, Melanoma?**	

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		Encorafenib in combination wth binimetinib should be considered alongside dabrafenib in combination with trametinib and NICE approved therapies in the existing pathway. **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 in combination with trametinib 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**. No comment. **Do you consider encorafenib in combination with binimetinib 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**	

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		current need is met (is this a 'step-change' in the management of the condition)? No comment **Do you consider that the use of encorafenib in combination with binimetinib 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.** No comment **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** No comment **References** 3. NICE Pathways- Melanoma https://pathways.nice.org.uk/pathways/melanoma accessed 16/10/17 4. NICE Guidelines NG14 Melanoma: assessment and management (2015)	

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		5. Cobimetinib in combination with vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma (2016) NICE technology appraisal guidance 414 6. https://www.nice.org.uk/guidance/ta414/documents/committee-papers accessed 16/10/17 7. Novartis Data On File 2017: Market Research	
	Pierre Fabre Ltd	All responses to the consultation questions are covered in the above sections with the exception of the questions relating to the appropriateness and suitability of the cost comparison methodology to this topic which are addressed below. • *Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?* In clinical practice encorafenib in combination with binimetinib will offer an alternative to the current combination of trametinib and dabrafenib in the existing NICE Melanoma pathway. In the absence of a direct head-to-head clinical trial a network meta-analysis will be utilised to demonstrate at least equivalent efficacy, and comparable resource use. • *Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?* Yes, the primary outcome is relevant.	

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		• *Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?* Not applicable On the basis of the above responses and depending on the interim overall survival data to become available, as well as the outcomes from the network meta-analysis, a cost comparison may be appropriate and we would like to request that this approach is given consideration.	
Additional comments on the draft scope	Novartis Pharmaceuticals Ltd	None	Comment noted. No action required.
	Pierre Fabre Ltd	None	Comment noted. No action required.