National Institute for Health and Care Excellence

Multiple Technology Appraisal (MTA)

Cabozantinib and vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer

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	Ipsen	Metastatic medullary thyroid cancer is a rare type of cancer. In 2013, as stated in the draft scope, there were only 80 new cases in England. Currently cabozantinib is available via the Cancer Drugs Fund for the treatment of adults with progressive unresectable locally advanced or metastatic medullary thyroid carcinoma and for the period March 2014 - June 2015 only eight patients were receiving treatment, funded by the CDF. Given the ultra-orphan nature of cabozantinib in this indication, the size of the patient population and the nature of the new transition framework for CDF funding using NICE appraisal processes, we would welcome a discussion with NICE as to whether MTA is the most appropriate route of assessment for the drug and the best use of NICE resources. Our concern would be that the MTA methodology is not appropriate for this population size and would appreciate clarification from NICE.	Thank you for your comments. The different appraisal processes were considered at the scoping workshop and the attendees agreed that a multiple technology appraisal was the most suitable process to appraise these interventions.
	SanofiGenzyme	While SanofiGenzyme fully supports technology appraisals, we would request consideration that the MTA is not the optimal assessment process given the	Thank you for your comments. The

Section	Consultee/ Commentator	Comments [sic]	Action
		patient population of approximately 80 patients in England. We would request that consideration is given to reviewing these products through either the new Abbreviated Technology Assessment or the Highly Specialised Technology process	different appraisal processes were considered at the scoping workshop and the attendees agreed that a multiple technology appraisal was the most suitable process to appraise these interventions.
	NCRI/RCP/RCR /ACP	This is an appropriate topic for NICE. Over the last 4 years two drugs (vandetanib and cabozantinib) have shown efficacy in advanced medullary thyroid cancer where the previous option has been best supportive care alone. Currently both drugs are funded in the first line by the CDF in England. Cabozantinib is funded in Wales. Therefore there is disparity across England and Wales. Neither are funded as second line and this needs to be addressed as there is an unmet need for patients progressing through first line treatment.	Thank you for your comments. The interventions are appraised within their marketing authorisations. No action required.
	Healthcare Improvement Scotland	Metastatic medullary thyroid cancer (MTC) is chemoresistant therefore the introduction of two new agents has had a major impact as they are active against MCT especially in some genotypes such as 918 and 634 codons. Previously patients would be referred for phase 1 studies once symptomatic progressive disease stage had been reached. It is highly appropriate for NICE to consider and review	Thank you for your comments. No action required.
Wording	Ipsen	Yes	Thank you for your comments. No action

Section	Consultee/ Commentator	Comments [sic]	Action
			required
	SanofiGenzyme	Yes	Thank you for your comments. No action required
	NCRI/RCP/RCR /ACP	This is appropriate	Thank you for your comments. No action required
	Healthcare Improvement Scotland	Yes it would appear appropriate.	Thank you for your comments. No action required
Timing Issues	Ipsen	As stated above, we are unclear if an MTA is the best assessment route and use of NICE resources given the nature and number of eligible patients.	Thank you for your comments. The different appraisal processes were considered at the scoping workshop and the attendees agreed that a multiple technology appraisal was the most suitable process to appraise these interventions.
	SanofiGenzyme	Non-Urgent	Thank you for your comments. No action required

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	NCRI/RCP/RCR /ACP	This is an issue that needs to be clarified. There is disparity in access to the drugs across England and Wales with both vandetanib and cabozantinib available as first line treatment in England and only cabozantinib in Wales. Neither drug are currently funded in the second line setting and many patients are reaching this situation since the licensing and subsequent availability of these two drugs over the last 4 years.	Thank you for your comments. The interventions are appraised within their marketing authorisations. No action required.
	Healthcare Improvement Scotland	These drugs are licenced and available. They are approved by EMA and maybe obtainable on Individual patient treatment applications in some circumstances.	Thank you for your comments. No action required.
Additional comments on the draft remit		No	Thank you for your comments. No action required
	SanofiGenzyme	None	Thank you for your comments. No action required
	Healthcare Improvement Scotland	Only to reiterate the timeliness and clinical need	Thank you for your comments. No action required

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Ipsen	Further information on the mortality associated with metastatic disease would be helpful in order to demonstrate the high mortality rate and the following additional text is proposed: 'Metastatic disease is the most common cause of death in patients with medullary thyroid cancer, and approximately 90% of patients with metastatic disease die of progressive cancer1'. Reference 1. European Medicines Agency. Assessment Report Cometriq. December 2014.	Thank you for your comments. The background section of the scope provides an overview of the disease area. More detailed information can be presented in the companies' evidence submissions. No action required
	SanofiGenzyme	No comment	Thank you for your comment. No action required
	NCRI/RCP/RCR/ACP	Paragraph 3 of the Background states that chemotherapy is one of the treatment options. This is incorrect. Conventional chemotherapy is not used routinely in the management of medullary thyroid cancer (MTC). Radioiodine is not used in MTC. (radioiodine is only used for differentiated thyroid cancer ie papillary and follicular which arise from thyroid follicle cells which are able to take up iodide; medullary thyroid cancer arises from parafollicular or 'C' cells which do not take up iodide). Radioisotope therapies in the form of MIBG or peptide receptor radionuclide therapy (PRRT) e.g. Lutathera have been used in MTC but with limited efficacy and vandetanib and cabozantinib would be considered first line therapies based on evidence.	Thank you for your comments. The background section of the scope has been updated to reflect the treatment options currently used in clinical practice in the NHS.
	Healthcare Improvement	It describes the clinical failings with currently available treatments. New and effective treatments are required for this condition.	Thank you for your comments. No action

Section	Consultee/ Commentator	Comments [sic]	Action
	Scotland		required
The technology/ intervention	Ipsen	Cabozantinib has orphan designation and we recommend that the current text is revised as follows: 'Cabozantinib, designated as an orphan medicinal product, has a marketing authorisation in the UK.....'	Thank you for your comments. The technology section provides an overview of the technology and is not designed to provide an in-depth description. No action required
	SanofiGenzyme	Yes	Thank you for your comment. No action required
	NCRI/RCP/RCR /ACP	It is incorrect to say that patients harbouring a RET mutation do not respond as well as those without. These drugs are multikinase inhibitors blocking more targets than RET. Neither phase III study for vandetanib or cabozantinib, have yielded evidence to select patients based on RET mutation status. Indeed both somatic RET mutation positive and negative cases responded to both drugs. Confusion often arises between germline RET mutation and somatic RET mutations and care should be used to clarify this in any statements.	Thank you for your comments. The scope reflects the marketing authorisation for each intervention. No action required.
	Healthcare Improvement Scotland	Yes, it seems accurate	Thank you for your comment. No action required.
Population	Ipsen	The population is appropriately defined.	Thank you for your comment. The

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			population reflects that of the marketing authorisations for the interventions. No action required.
	SanofiGenzyme	The population appropriately defined	Thank you for your comment. The population reflects that of the marketing authorisations for the interventions. No action required.
	NCRI/RCP/RCR /ACP	The statement re population is correct	Thank you for your comment. The population reflects that of the marketing authorisations for the interventions. No action required.
	Healthcare Improvement Scotland	These are rare tumours, i think the numbers slightly underestimate. I quote 5% not 3% and also there will be queuing patients who have advanced disease and are awaiting approval since there is no alternative effective therapy.	Thank you for your comment. The population reflects that of the marketing authorisations for the interventions. No action required

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Comparators	Ipsen	The appropriate relevant comparators are: • Vandetanib • Palliative care Palliative care Palliative care is currently considered standard of care in patients with unresectable locally advanced or metastatic medullary thyroid cancer and should be included as a comparator along with vandetanib. Radiotherapy Based on its indication and current treatment guidelines, cabozantinib is positioned after surgery or radiotherapy: • It is licensed for use in patients with unresectable locally advanced or metastatic medullary thyroid cancer[1]. • In this group of patients, current treatment guidelines recommend radiotherapy for palliative use only.[2] Radiotherapy is not, therefore, an appropriate comparator and should be excluded from the list. Chemotherapy We would also highlight that chemotherapy (including doxorubicin and cisplatin) is rarely used for the treatment of persistent or recurrent medullary thyroid cancer[2]. We would therefore recommend that consideration be given to excluding chemotherapy from the list of comparators. References 1. COMETRIQ Summary of Product Characteristics, 2015	Thank you for your comments. The comparators section of the scope has been updated in line with the discussions at the scoping workshop to reflect the treatment options currently used in clinical practice in the NHS.

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		2. Guidelines for the management of thyroid cancer. Third edition. British Thyroid Association. February 2014	
	SanofiGenzyme	Best supportive care and cabozantinib are the most appropriate comparators for vandetanib	Thank you for your comments. The comparators section of the scope has been updated in line with the discussions at the scoping workshop to reflect the treatment options currently used in clinical practice in the NHS.
	NCRI/RCP/RCR /ACP	Best supportive care is the comparator. There are no other therapies that have been shown to alter the natural history of the disease	Thank you for your comments. The comparators section of the scope has been updated in line with the discussions at the scoping workshop to reflect the treatment options currently used in clinical practice in the NHS.
	Healthcare Improvement Scotland	There are no effective comparators. Best supportive care would be only comparator. Chemotherapy considered pretty ineffective and as a result is very rarely used and only as a last resort. Patients will be counselled about	Thank you for your comments. The comparators section of

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		very low success rate.	the scope has been updated in line with the discussions at the scoping workshop to reflect the treatment options currently used in clinical practice in the NHS.
Outcomes	Ipsen	All the outcomes listed are appropriate but please note that clinical trial quality of life data is not currently available for cabozantinib and published data will need to be utilised.	Thank you for your comments. No action required
	SanofiGenzyme	Yes	Thank you for your comment. No action required
	NCRI/RCP/RCR /ACP	Outcome measures are appropriate although symptom relief should also be reviewed if possible	Thank you for your comments. The scoping workshop attendees agreed that the outcomes in the scope are appropriate. No action required
	Healthcare Improvement Scotland	PFS, quality of life, return to work/functionality. Time taken before next treatment. Standard RECIST criteria of limited value, tumours may show tumour blood flow changes with DWI MRI for example without actually shrinking; and	Thank you for your comments. The scoping workshop attendees agreed that the outcomes in the scope

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		calcitonin also shown to be unreliable after vandetanib. Also accept stable disease as a ”response”. Many patients with stable disease have long durations of response leading to significant clinical benefit	are appropriate. No action required
Economic analysis	Ipsen	A lifetime time horizon should be considered.	Thank you for your comment. No action required
	SanofiGenzyme	Given the small size of the patient population there will be data limitations that compromise the veracity of any economic modelling. Another limitation in the modelling and extrapolation of survival data relates to treatment cross-over in the pivotal Phase III trial for vandetanib, allowing patients on placebo to be treated with the active comparator once unblended. However, aside from the limited data package and the issue of patient cross-over, typical modelling techniques could be applied	Thank you for your comments. No action required
Equality and Diversity	Ipsen	Not applicable	Thank you for your comment. No action required
	SanofiGenzyme	None Known	Thank you for your comment. No action required
	NCRI/RCP/RCR /ACP	It is very concerning that the draft scope is focussing on RET status for treatment selection. There is no evidence that patients without a somatic RET mutation do not benefit from these drugs. There is very little evidence about the heterogeneity of somatic RET mutation status throughout locally advanced and metastatic medullary thyroid cancer.	Thank you for your comment. The remit of the appraisal is to appraise the technologies within their marketing

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		None of the National guidelines on management of MTC advocate the selection of treatment based on RET mutational status.	authorisations. Therefore, the population broadly reflects the marketing authorisations for the interventions. No action required
	Healthcare Improvement Scotland	There are no equality issues that I am aware of in this context. Do not make genetic testing mandatory but should be encouraged. RET negative patients can still respond although clearly there is evidence of some codon types will do better.	Thank you for your comments. No action required
Innovation	Ipsen	Cabozantinib and vandetanib provide a treatment option for patients with unresectable locally advanced or metastatic thyroid cancer who previously would have received palliative care only. In both applications to CDF, the decision panel deemed both should be available 1st line in the absence of alternative treatments and that NHSE requested urgent review under NICE.	Thank you for your comments. The innovative nature of cabozantinib and vandetanib will be considered by the appraisal committee. No action required
	SanofiGenzyme	The progression free survival (PFS) benefit reported for vandetanib in the Zeta clinical trials indicates an oncology treatment that would be considered a ‘step-change’ in cancer care. While this is a surrogate endpoint for overall survival (OS), a PFS gain of this magnitude is promising for OS outcomes.	Thank you for your comments. The innovative nature of cabozantinib and vandetanib will be considered by the appraisal committee.

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			No action required
	Healthcare Improvement Scotland	Highly innovative novel targeted agents especially for some subtypes where very high responses are seen. This meets an area of unmet demand	Thank you for your comments. The innovative nature of cabozantinib and vandetanib will be considered by the appraisal committee. No action required
Other considerations	Ipsen	<u>Sub Group</u> The sub group of people in whom RET mutation status is not known or is negative is appropriate. Current treatment guidelines recommend that RET mutation analysis is performed in all confirmed cases of medullary thyroid cancer even in the absence of a positive family history to establish the possible genetic basis of the disease within an individual or kindred1. However, RET mutation status is not yet tested for routinely within the NHS. Reference 1. Guidelines for the management of thyroid cancer. Third edition. British Thyroid Association. February 2014.	Thank you for your comments. No action required
	SanofiGenzyme	None	Thank you for your comment. No action required
	Healthcare	This undoubtedly falls into the ultra orphan status	Thank you for your

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	Improvement Scotland		comment. No action required
Questions for consultation	Ipsen	<u>NICE Pathway</u> The NICE pathway for head and neck cancer does not currently include an arm for thyroid cancer and in the event an MTA is completed a treatment pathway detailing the place of cabozantinib (and vandetanib) after surgery and radiotherapy in patients with unresectable locally advanced or metastatic thyroid cancer will need to be added.	Thank you for your comments. The pathway will be updated once final guidance is published. No action required.
	SanofiGenzyme	1) Comparators See response above 2) Which treatments are considered to be established clinical practice in the NHS for unresectable locally advanced or metastatic medullary thyroid cancer? Having been available in the NHS via the Cancer Drug Fund, vandetanib and cabozantinib are considered established clinical practice. Prior to the introduction of these products, patients would have been treated with Best Supportive Care and palliative care. 3) Are the outcomes listed appropriate? Yes, the outcomes listed are appropriate to this technology 4) Are there any subgroups of people in whom cabozantinib and	Thank you for your comments. The comparators section of the scope has been updated in line with the discussions at the scoping workshop to reflect the treatment options currently used in clinical practice in the NHS. Thank you for your comment. No action required

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		vandetanib are expected to be more clinically effective and cost effective or other groups that should be examined separately? a. Should Rearranged during Transfection (RET) mutation status be a subgroup? The effect of a patients' RET mutation should be considered in the HTA. However, due to the small number of patients with negative status in the ZETA trial. There is a high degree of uncertainty in drawing conclusions about patients with RET negative mutation status. 5) Is Rearranged during Transfection (RET) mutation status routinely tested for in clinical practice? The clinicians have advised they follow the BTA guidelines for the management of Thyroid Cancer (July 2014) which states (section 17.2, page 70 – 'in all confirmed cases of MTC, RET mutation analysis to establish the possible genetic basis for the disease within an individual or kindred, should be performed even in the absence of a positive family history.' This is a key recommendation and good practice point. 6) Where do you consider cabozantinib and vandetanib will fit into the existing NICE pathway head and neck cancer? It is currently unclear where cabozantinib and vandetanib would fit into the existing NICE pathway. From their CDF status they are currently used in NHS England as first line tyrosine kinase therapy for patients with unresectable, locally advanced cancer. Various international guidelines support thyroid oncology treatment practice in the UK: the American Thyroid Association (ATA) Medullary Thyroid Cancer Guidelines 2009,1 the European Thyroid Association (ETA) Guidelines for Metastatic Medullary Thyroid Cancer 2012,2	Thank you for your comment. No action required Thank you for your comment. No action required Thank you for your comment. No action required.

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		and the National Comprehensive Cancer Network (NCCN) Thyroid Carcinoma Guidelines 2013.3 The current British Thyroid Association Guidelines refer to surgery, chemotherapy and radiotherapy as treatment options for MTC. However, the sequencing within a standard treatment pathway is not clear. 7) Equality issues None 8) Do you consider cabozantinib and vandetanib to be innovative in their potential to make a significant and substantial impact on health-related benefits and how they might improve the way that current need is met (are these a 'step-change' in the management of the condition)? The trial PFS data for vandetanib suggest it is an innovative cancer treatment (>10months versus placebo). 9) Do you consider that the use of cabozantinib and vandetanib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? No, the benefits of vandetanib are likely to be well captured in the QALY measure, notwithstanding usual concerns about the sensitivity of standard measures of utility: EQ5D/SF36 in cancer technology appraisals	Thank you for your comment. No action required. Thank you for your comments. The innovative nature of cabozantinib and vandetanib will be considered by the appraisal commitee. No

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			action required.
		10) Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. For vandetanib, the main data source is the ZETA trial, randomized, double-blind, placebo-controlled trial of 331 patients. This is supported by Phase II data	Thank you for your comments. No action required.
		11) NICE intends to appraise this technology through its Multiple Technology Appraisal (MTA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction Given the burden and duration associated with the MTA process, and the small patient population associated with this disease area, SanofiGenzyme would ask that alternative assessment approaches be considered.	Thank you for your comments. The different appraisal processes were considered at the scoping workshop and the attendees agreed that a multiple

Section	Consultee/ Commentator	Comments [sic]	Action
			technology appraisal was the most suitable process to appraise these interventions.
	NCRI/RCP/RCR /ACP	In answer to the 'Questions for consultation' not dealt with above: The scope has omitted radiolabelled MIBG and octreotide as possible comparators. Established practice other than vandetanib or cabozantinib would be best supportive care.	Thank you for your comments. The comparators section of the scope has been updated in line with the discussions at the scoping workshop to reflect the treatment options currently used in clinical practice in the NHS.
		The existing NICE pathway for head and neck cancer does not mention thyroid cancer at all.	Thank you for your comments. No action required.
		Patient experience would contribute to the committee's understanding of the impact of these therapies	Thank you for your comments. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Yes, we consider cabozantinib and vandetanib to be innovative in their potential to make a significant and substantial impact on health-related benefits and provide a 'step-change' in the management of advanced and metastatic medullary thyroid cancer.	Thank you for your comments. The innovative nature of cabozantinib and vandetanib will be considered by the appraisal committee. No action required.
		The use of these drugs may lead to reduced inpatient stays, better palliation of symptoms without the requirement for other interventions such as palliative external beam radiotherapy. Improved symptom, control may improve the ability of patients to work and care for their families.	Thank you for your comments. No action required
		We note that the American Thyroid Association nor the European Thyroid Association guidelines on the management of medullary thyroid cancer have not been referenced. These should be added.	Thank you for your comments. The background section provides an overview of the disease area. No action required
Additional comments on the draft scope	Ipsen	None	Thank you for your comment. No action required

Section	Consultee/ Commentator	Comments [sic]	Action
	SanofiGenzyme	None	Thank you for your comment. No action required
	Healthcare Improvement Scotland	Nothing else, I hope I have covered all the points in sufficient detail.	Thank you for your comment. No action required

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Janssen
Pfizer
The Royal College of Pathologists