National Institute for Health and Care Excellence

Single Technology Appraisal

Cabozantinib for previously treated differentiated thyroid cancer unsuitable for or refractory to radioactive iodine [ID4046]
Response to stakeholder organisation comments on the draft remit and draft scope

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 and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness	Ipsen Limited	Yes, it is appropriate for NICE to evaluate this topic.	Thank you for your comment. No action needed.
	NCRI-ACP-RCP-RCR	Yes. Treatment options for patients with this condition are limited.	Thank you for your comment. No action needed.
Wording	Ipsen Limited	Yes, the wording of the remit is appropriate in the draft scope. It should be noted though that the title of the draft scope is ambiguous and open to misinterpretation. It currently states: *"Cabozantinib for previously treated differentiated thyroid cancer after radioactive iodine (RAI)"*	Thank you for your comment. The title of the evaluation has been updated to "*Cabozantinib for previously treated differentiated thyroid cancer unsuitable for or refractory to radioactive iodine*".

Section	Stakeholder	Comments [sic]	Action
		This could be interpreted as cabozantinib as a first-line tyrosine kinase therapy post RAI for DTC. Maybe a better wording for the title could be more in line with the licensed indication i.e. *"Cabozantinib for adult patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy"*	
	NCRI-ACP-RCP-RCR	Yes	Thank you for your comment. No action needed.
Timing issues	Ipsen Limited	Currently there are no alternative treatments other than Best Supportive Care (BSC) in this disease area which still holds a poor prognosis.	Thank you for your comment. No action needed.
	NCRI-ACP-RCP-RCR	Patients (without targetable genetic alterations) who have progressed on first line multikinase inhibitors have an unmet clinical need as there is currently no approved second line treatment option.	Thank you for your comment. No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Ipsen Limited	NICE scope states "Differentiated thyroid cancers are the most common types of thyroid cancers, with papillary carcinomas responsible for 80% of cases." Cancer Research UK states this figure is 90%.	Thank you for your comment. The scope has been updated to include a range of possible values for the percentage of papillary carcinomas.

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	NCRI-ACP-RCP-RCR	Papillary thyroid cancer accounts for 80-90%, follicular thyroid cancer accounts for up to 10%.	Thank you for your comment. The scope has been updated to reflect the proportion of thyroid cancer that papillary carcinomas and follicular carcinomas account for.
		Radioactive iodine (post-operatively) is primarily used to ablate any residual thyroid tissue, and may also destroy any remaining cancer cells.	The scope has been updated to reflect that radioactive iodine is used to destroy any residual thyroid tissue and remaining cancer cells.
		External beam radiotherapy is used uncommonly in the adjuvant setting and there is no role for adjuvant chemotherapy. In the palliative setting radiotherapy can be useful for local control of individual lesions. If palliative systemic therapy is indicated standard practise would be targeted therapy (eg multikinase inhibitors) rather than palliative chemotherapy.	Thank you for your comment. It is acknowledged in the scope that the use of external beam radiotherapy and chemotherapy has begun to be superseded by targeted therapy.

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		In terms of timing of initiating systemic therapy, surveillance (as opposed to best supportive care) is often appropriate until the disease starts to progress more rapidly or the patient is imminently symptomatic.	The scope has been updated to include monitoring as an option before initiating systemic therapy.
The technology/ intervention	Ipsen Limited	Yes. Note it is now licensed – see Section 4 below.	Thank you for your comment. The scope has been updated in line with the marketing authorisation.
	NCRI-ACP-RCP-RCR	Yes	Thank you for your comment. No action needed.
Population	Ipsen Limited	Yes, but it should be noted it is limited to adult patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy.	Thank you for your comment. The population has been updated in line with the marketing authorisation.
	NCRI-ACP-RCP-RCR	Yes	Thank you for your comment. No action needed.
Comparators	Ipsen Limited	Yes, BSC is the only available treatment option in this setting currently i.e. post first-line systemic treatment with lenvatinib or sorafenib. NICE technology appraisal 535 (TA535) recommends lenvatinib and sorafenib, which inhibit multiple receptor tyrosine kinases including vascular endothelial growth factor (VEGF) receptors only for people who have not had tyrosine kinase inhibitors before, or who have to stop them early because of tolerability (specifically, toxicity that cannot be managed by dose delay or	Thank you for your comment. No action needed.

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		dose modification). This is because there is not enough clinical evidence and no cost-effectiveness evidence to determine whether the treatments are effective when used sequentially. NHS England Cancer Drugs Fund criteria for use state: *"Sequential use of lenvatinib and then sorafenib is only funded if the patient has to discontinue lenvatinib because of intolerance within 3 months of its start and if the disease has not progressed whilst the patient is on lenvatinib. The use of lenvatinib after disease progression on or after sorafenib is not funded and vice versa."* Therefore lenvatinib or sorafenib can only be used first-line in RAI refractory or ineligible patients.	
	NCRI-ACP-RCP-RCR	For patients who do not have a targetable genetic alteration (eg RET or NTRK fusion) best supportive care is an acceptable comparator. Patients with a RET fusion may have access to selpercatinib via the Cancer Drug Fund, and those with a NTRK fusion could be treated with larotrectinib	Thank you for your comment. Technologies that have been recommended by NICE with managed access (for example, in the Cancer Drugs Fund) are not considered established practice so selpercatinib and larotrectinib have not been included in the scope as comparators.
Outcomes	Ipsen Limited	The outcome measures to be considered are appropriate.	Thank you for your comment. No action needed.

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	NCRI-ACP-RCP-RCR	Yes	Thank you for your comment. No action needed.
Economic analysis	Ipsen Limited	The economic analysis is appropriate and consistent with NICE reference case. The analysis will include an appropriate time horizon to capture all the relevant costs and QALYs.	Thank you for your comment. No action needed.
Equality	Ipsen Limited	No comments.	No action needed.
	NCRI-ACP-RCP-RCR	No concerns	No action needed.
Innovation	Ipsen Limited	Cabozantinib is an innovative therapy in a disease area of high unmet medical need. It offers a treatment option to a patient population with poor prognosis where there is only BSC available after failure of sorafenib or lenvatinib in first line therapy.	Thank you for your comment. The appraisal committee will consider the innovative nature of the technology. No action needed.
	NCRI-ACP-RCP-RCR	Yes. At present patients with no targetable genetic alteration whose disease progresses after first line systemic therapy have no other active treatment options. As disease progresses it is likely that patients will develop more symptoms that require utilisation of NHS resources. Prolonging disease control by using a second line therapy may reduce the burden on other NHS services.	Thank you for your comment. The appraisal committee will consider the innovative nature of the technology. No action needed.
Questions for consultation	Ipsen Limited	*Are external beam radiotherapy (EBRT) and chemotherapy treatments considered to be established clinical practice in the NHS for previously treated radioiodine-refractory differentiated thyroid cancer?* EMSO guidelines state EBRT is not really used as treatment for previously treated radioiodine-refractory differentiated thyroid cancer, but it may still be	Thank you for your comment. No action needed.

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		used for locoregional symptomatic management of metastases. Therefore not a relevant comparator.	
		If chemotherapy is used in clinical practice, how is chemotherapy defined? ESMO guidelines state that the results of chemotherapy administration (e.g. doxorubicin) in RAI-refractory DTC are disappointing; therefore, it is not recommended unless TKI therapy is contraindicated. Therefore not a relevant comparator.	Thank you for your comment. No action needed.
		How should best supportive care be defined? BSC should be defined as no treatment as there are no therapy options in this setting currently i.e. post first-line systemic treatment with lenvatinib or sorafenib.	Thank you for your comment. No action needed.
		Where do you consider cabozantinib will fit into the existing care pathway for previously treated radioiodine-refractory differentiated thyroid cancer? *Would lenvatinib and sorafenib be considered comparators in clinical practice in the NHS?* See above.	Thank you for your comment. No action needed.
		Would cabozantinib be a candidate for managed access? No, we do not believe so.	Thank you for your comment. No action needed.
		Do you consider cabozantinib 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)?	Thank you for your comment. The appraisal committee will consider the innovative nature of the technology. No action needed.

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		See above.	
		Do you consider that the use of cabozantinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? No comment.	Thank you for your comment. No action needed.
		NICE intends to evaluate this technology through its Single Technology Appraisal process. Yes, the STA route is appropriate.	Thank you for your comment. No action needed.
		Would it be appropriate to use the cost-comparison methodology for this topic? No, as the comparator is BSC and not a NICE approved technology.	Thank you for your comment. No action needed.
		Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? Not applicable as BSC is the comparator.	Thank you for your comment. No action needed.
		Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? Not applicable as BSC is the comparator.	Thank you for your comment. No action needed.

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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 as BSC is the comparator.	Thank you for your comment. No action needed.
	NCRI-ACP-RCP-RCR	As mentioned above, palliative radiotherapy can be useful for local control of individual lesions in patients with metastatic/locally advanced unresectable radioiodine refractory disease. Palliative chemotherapy has really been superseded by more targeted therapy, so is not standard practice. Best supportive care implies that a decision has been made that active anti-cancer treatment is not planned, and management is instead focused on symptom control. Based on current evidence cabozantinib would fit in the second line setting after lenvatinib or sorafenib for patients with no targetable genetic alteration. Lenvatinib and sorafenib would not be suitable comparators as patients being considered for cabozantinib would have progressed on lenvatinib or sorafenib so these are not appropriate alternatives. Ideally cabozantinib would be NICE approved, but could be considered for managed access in the event that it is not approved.	Thank you for your comment. No action needed.
Additional comments on the draft scope	Ipsen Limited	No	No action needed.

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

None