NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Selpercatinib for advanced thyroid cancer with RET alterations that has not been treated with systemic therapy

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using selpercatinib in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: April 2024

Note that this document is not NICE's final guidance on selpercatinib. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using selpercatinib in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 23 May 2024
- Second evaluation committee meeting: 12 June 2024
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Selpercatinib is not recommended for:

- advanced RET-mutant medullary thyroid cancer that has not been treated with systemic therapy in people 12 years and older
- advanced RET fusion-positive thyroid cancer that has not been treated with systemic therapy, and is refractory to or not suitable for radioactive iodine in people 12 years and older.

1.2 This recommendation is not intended to affect treatment with selpercatinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For young people, this decision should be made jointly by the clinician, the young person, and their parents or carers.

Why the committee made these recommendations

This evaluation considered selpercatinib for thyroid cancer that has not been treated with systemic therapy. NICE has already evaluated selpercatinib for thyroid cancer that has been treated with systemic therapy (see NICE technology appraisal guidance 742).

Usual treatment for RET-mutant medullary thyroid cancer that has not been treated with systemic therapy is cabozantinib or best supportive care (BSC, which includes routine care and monitoring). For RET fusion-positive thyroid cancer that has not been treated with systemic therapy, and is refractory to or not suitable for radioactive iodine, usual treatment is sorafenib, lenvatinib or BSC.

The main clinical trial did not directly compare selpercatinib with usual treatment. Indirect comparisons suggest that people having selpercatinib live for longer and have longer before their cancer gets worse than people having usual treatment. But this is uncertain.

There were no cost-effectiveness estimates that compared selpercatinib with sorafenib. All of the cost-effectiveness estimates that compared selpercatinib with the other usual treatments are above what NICE considers an acceptable use of NHS resources. So selpercatinib is not recommended.

2 Information about selpercatinib

Marketing authorisation indication and anticipated marketing authorisation indication

2.1 Selpercatinib (Retevmo, Eli Lilly) is indicated for 'the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer'.

2.2 Selpercatinib also received a marketing authorisation by the European Commission for 'the treatment of adults and adolescents 12 years and older with advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate)', but it does not have a marketing authorisation in Great Britain for this indication yet.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for selpercatinib.

Price

2.3 The list price for selpercatinib is £2,184 per pack of 56 40-mg capsules, and £4,368 per pack of 56 80-mg tablets.

2.4 The company has a commercial arrangement. This makes selpercatinib available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The evaluation committee considered evidence submitted by Eli Lilly, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Effects on quality of life

3.1 Thyroid cancer has a number of different subtypes. RET-activating fusions and mutations are important in many cancer types, including different types of thyroid cancer. The clinical experts explained that medullary thyroid cancer, in which RET mutations are relatively common and are associated with poorer outcomes, accounts for approximately 4% of thyroid cancers. RET fusions in other thyroid cancers are less common and it is unclear whether they are associated with poorer outcomes. The patient organisation submissions explained that the symptoms associated with thyroid cancer, such as diarrhoea, bone pain, fatigue and weight loss, can prevent people from leaving the house and have a significant impact on quality of life. Currently available treatment options can cause significant side effects that also affect the ability to continue usual daily activities. The committee concluded that there is an unmet need for more treatment options for thyroid cancer that are effective and well tolerated.

Clinical management

Comparators

3.2 For RET-mutant medullary thyroid cancer, after a partial or full thyroidectomy or radiotherapy, most people have cabozantinib as recommended in NICE's technology appraisal guidance on cabozantinib for treating medullary thyroid cancer. Some people will have best supportive care (BSC), for example if they cannot have cabozantinib, including people aged 12 to 17. For differentiated RET fusion-positive thyroid cancer, after a partial or full thyroidectomy, followed by radioactive

iodine, NICE's technology appraisal guidance on lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine recommends lenvatinib and sorafenib. For people who cannot have lenvatinib or sorafenib, including people aged 12 to 17 and people with undifferentiated RET fusion-positive thyroid cancer, the only treatment option is BSC. For RET fusion-positive thyroid cancer, the company stated that lenvatinib was the main comparator, because it had received clinical advice that about 5 to 10% of people would have sorafenib in NHS clinical practice. The clinical experts agreed that most people would have lenvatinib, because clinicians perceive it to be more effective than sorafenib and offer treatment with lenvatinib first. But the committee considered that sorafenib should be included as a comparator because some people do have it, it is recommended by NICE technology appraisal guidance, and it was unclear why lenvatinib was preferred over sorafenib. The committee also felt that to assess whether a new treatment was cost effective, it was important to include all relevant treatments that are currently used in the NHS as comparators. The committee concluded that the most relevant comparators for RET-mutant medullary thyroid cancer were cabozantinib and BSC, and that the most relevant comparators for RET fusion-positive thyroid cancer were lenvatinib, sorafenib and BSC.

Clinical effectiveness

Data sources

3.3 The company's evidence for selpercatinib came from the phase 1 and 2 single-arm trial LIBRETTO-001. The company also highlighted a phase 3 trial, LIBRETTO-531, which compared selpercatinib with cabozantinib or vandetanib in untreated locally advanced or metastatic medullary thyroid cancer with a RET alteration. Both trials included adults, but people aged 12 and over could be included where permitted by local regulatory authorities. The company stated that the data from LIBRETTO-531 was too immature to be used in this evaluation.

Indirect treatment comparisons

3.4 To compare selpercatinib with cabozantinib and BSC in RET-mutant medullary thyroid cancer, the company did a matched-adjusted indirect treatment comparison. This used any-line data (that is, from people whose cancer had been previously treated with a systemic therapy and those whose cancer was untreated with systemic therapy) from LIBRETTO-001 and from the EXAM trial. The EXAM trial compared cabozantinib with placebo, and the company used the placebo arm as a proxy for BSC in its analysis. The results suggested that progression-free survival and overall survival were improved with selpercatinib compared with cabozantinib (hazard ratio for progression-free survival 0.08, $p<0.001$; hazard ratio for overall survival 0.20, $p<0.001$) and compared with BSC (hazard ratio for progression-free survival 0.05, $p<0.001$; hazard ratio for overall survival 0.11, $p<0.001$). The EAG highlighted a number of uncertainties in the company's matched-adjusted treatment comparison, including that:

- the company could not adjust for many of the important prognostic factors and effect modifiers it had identified because of a lack of data
- overall survival data was only available for the RET M918T mutation-positive subgroup in EXAM (a specific type of RET mutation)
- the matched-adjusted treatment comparisons were not done in the relevant population for this evaluation (cancer untreated with systemic therapy)
- 21.5% of people having cabozantinib in the EXAM trial had had previous kinase inhibitor treatment
- using the placebo arm from EXAM as a proxy for BSC was not reasonable for overall survival because 49.5% of people received subsequent systemic therapies.

To compare selpercatinib with lenvatinib, sorafenib and BSC in RET fusion-positive thyroid cancer, the company did a naive, unadjusted indirect comparison using any-line data from LIBRETTO-001, and data from the SELECT and DECISION trials. SELECT compared lenvatinib

with placebo, and DECISION compared sorafenib with placebo. The company used the placebo arm data from SELECT as a proxy for BSC, and because 87.8% of people in the placebo arm crossed over to receive lenvatinib, it adjusted the Kaplan–Meier overall survival curves for crossover. The results from the indirect treatment comparison in RET fusion-positive thyroid cancer suggested that progression-free and overall survival were improved with selpercatinib compared with lenvatinib, sorafenib and BSC. The company considers the exact results to be confidential so they cannot be reported here. But the EAG cautioned that the populations in LIBRETTO-001, SELECT and DECISION were very different, particularly in the number of previous treatments, time from diagnosis and severity of disease, and that the RET fusion status was unknown in SELECT and DECISION. The indirect treatment comparison did not account for any of these differences. The EAG also highlighted that some of the proportional hazards assumptions appeared violated, so the reported hazard ratios may not be accurate. The committee concluded it was likely that selpercatinib improved progression-free and overall survival compared with cabozantinib, lenvatinib, sorafenib and BSC, but that it was uncertain by how much, because of the many uncertainties in the 2 indirect treatment comparisons.

Economic model

Comparators in the model

3.5 For RET-mutant medullary thyroid cancer, the company included cabozantinib and BSC as comparators in the economic model. For RET fusion-positive thyroid cancer, the company included lenvatinib and BSC as comparators. It did not include sorafenib because it considered that only a small number of people would have sorafenib in NHS clinical practice. The committee noted that the company's model had been built with some functionality to include sorafenib, and that overall survival with sorafenib in the model was better than with lenvatinib, although this was based on a naive comparison of treatment arms across studies. The

committee understood the uncertainties in the indirect comparisons (section 3.4) but considered sorafenib to be a relevant comparator (section 3.2), and therefore concluded that it would like to see analyses including sorafenib.

Overall survival estimates with selpercatinib

3.6 The company presented a partitioned survival model with 3 health states: progression-free, progressed disease and death. To model overall survival for selpercatinib, the company fitted 19 parametric distributions to the overall survival curve for selpercatinib from the matched-adjusted indirect comparison. It elicited clinical expert opinion on the proportions of people likely to be alive at 10 and 20 years after each treatment. The clinical experts provided ranges of plausible values; the company considers the figures to be confidential so they cannot be reported here. The company selected a stratified Weibull function for selpercatinib in RET-mutant medullary thyroid cancer. It applied an adjustment factor of 2 at 5 years, so that the values predicted by the model for 10-year and 20-year survival matched the clinical experts' opinion. The EAG provided optimistic and pessimistic scenarios that aligned the predicted 10- and 20-year survival from the model with the upper (adjustment factor of 1.5 at 5 years) and lower (adjustment factor of 3.5 at 5 years) limits of the clinical experts' plausible range. To model overall survival for selpercatinib in RET fusion-positive thyroid cancer, the company fitted 20 parametric distributions to the overall survival data from LIBRETTO-001 for the any-line RET fusion-positive thyroid cancer population. The company chose a piecewise exponential distribution, and applied a 1.2 adjustment factor at 5 years, to be consistent with its approach for RET-mutant medullary thyroid cancer. The EAG provided optimistic and pessimistic scenarios that aligned the predicted 10- and 20- year survival from the model with the upper (adjustment factor of 0.9 at 60 months) and lower (adjustment factor of 1.5 at 18 months) limits of the clinical experts' plausible range. At the committee meeting, the company explained that it had applied the adjustment factor at 5 years because that was the end of the trial data.

The EAG explained that it had applied the adjustment factor at 18 months so that the function better fitted the Kaplan–Meier data. The clinical experts at the committee meeting explained that it was difficult to estimate the 10- and 20-year overall survival for people having the different treatments because the treatments were relatively new and the disease is rare. The committee was concerned that the company's method of adjusting the survival curves was crude and not based on trial data, although it noted that the adjustments did reduce the estimates of overall survival with selpercatinib to be more in line with expert opinion. It concluded that the overall survival extrapolations were uncertain, but that the company's extrapolations were in line with the clinical experts' estimations and therefore could be used for decision-making. The committee also agreed that the EAG's optimistic and pessimistic scenarios showed the plausible range of uncertainty.

Overall survival estimates with cabozantinib

3.7 To extrapolate overall survival for BSC in RET-mutant medullary thyroid cancer, the company used placebo arm data from the RET M918T population from EXAM and fitted a stratified Weibull distribution to the Kaplan–Meier curve. The company then generated an overall survival curve for cabozantinib by applying the hazard ratio from EXAM (in the RET-mutant medullary thyroid cancer population) to the BSC extrapolation. The company consulted clinical experts to elicit a range of survival estimates at 10 and 20 years for people with RET-mutant medullary thyroid cancer having cabozantinib. The EAG preferred to apply the same hazard ratio from EXAM to the stratified spline 1 knot extrapolation for BSC to obtain an overall survival curve for cabozantinib. It considered that this predicted a 10-year overall survival that was more in line with the values suggested by clinical experts. The committee agreed that the EAG's extrapolation of cabozantinib was more in line with the clinical experts' estimates of overall survival. It therefore concluded that it was more appropriate to use the EAG's method of generating an overall survival curve for cabozantinib.

Utility values

Source of utility values

3.8 The company sourced utility values for the economic model from a vignette study by Fordham et al. (2015). The mean health state utility value was 0.8 in the progression-free state and 0.5 in the progressed disease state. The EAG thought that the value of 0.8 seemed high for the progression-free health state and that it was close to general population values. When age- and sex-matched to the RET-mutant medullary thyroid cancer population, the general population utility value was 0.845. When matched to the RET fusion-positive thyroid cancer population, the general population utility is 0.857. The EAG also thought that the utility value of 0.5 for the progressed disease health state seemed low. It preferred to use utility values mapped from the RET fusion-positive thyroid cancer population from LIBRETTO-001. The company considers these values to be confidential so they cannot be reported here, but the utility value for the progression-free state was lower than the company's, and the utility value for the progressed disease state was higher than the company's. The company noted that the EAG's method was based on very small numbers of people from the trial with a small number of assessments. And for the progressed disease health state, people were still taking selpercatinib when the assessments were done. It also noted that the utility values from Fordham 2015 had been accepted in NICE's technology appraisal guidance on cabozantinib for treating medullary thyroid cancer. The committee considered that the large reduction in the utility value between the progression-free and the progressed disease health states in the company's model was implausible. The clinical experts explained that after progression, symptoms such as diarrhoea and bone pain can return. The committee agreed that quality of life would be worse in the progressed disease state but did not consider it had been presented with evidence for a reduction as large as that in the values from Fordham 2015 that were included in the company's model. The committee also noted that the utility value used in NICE's technology appraisal guidance on

selpercatinib for treating advanced thyroid cancer with RET alterations was 0.8 for people whose cancer had progressed after treatment with a systemic therapy. Although the committee acknowledged that the utility values from Fordham 2015 had been accepted in previous NICE evaluations, it was aware that EQ-5D methods are preferred in the NICE health technology evaluations manual, where available. The committee also agreed that the utility values mapped from LIBRETTO-001 were more plausible. So the committee concluded that the utility values mapped from LIBRETTO-001 should be used in the model.

Costs

Relative dose intensity

3.9 The company included a relative dose intensity multiplier in the model, to reflect dose reductions because of treatment toxicity. The EAG thought that because cabozantinib and lenvatinib have a flat price for all recommended doses, the costs of these treatments should have instead been adjusted for dose adherence, that is, the proportion of days on which people had treatment. This data was not available, so the EAG provided scenarios in which the relative dose intensity was removed for cabozantinib, lenvatinib and selpercatinib, or just for cabozantinib and lenvatinib. When the relative dose intensity was removed, dose reductions did not result in treatment cost reductions. The committee agreed that because selpercatinib has different prices for different doses, dose reductions would result in treatment cost reductions. So it concluded that in the absence of adherence data, relative dose intensity should be removed in the model for cabozantinib and lenvatinib, but not for selpercatinib. The committee also noted that an analysis comparing selpercatinib with sorafenib in the RET fusion-positive thyroid cancer population should not include relative dose intensity for sorafenib.

Severity

3.10 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight (a severity modifier) to quality-adjusted life years (QALYs) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. For RET-mutant medullary thyroid cancer, the company considered that a severity modifier of 1.2 should be applied to the comparisons with BSC and cabozantinib. But when including the utility values mapped from LIBRETTO-001 (section 3.8) or using its preferred method of modelling cabozantinib overall survival (section 3.7), the EAG calculated that the QALY shortfall changed such that a severity modifier should not apply for the comparison with cabozantinib. The committee noted that both of these amendments were its preferred assumptions. For RET fusion-positive thyroid cancer, the company considered that a severity modifier would apply to the comparison with BSC but not with lenvatinib. The committee's preferred assumptions did not change the calculations of QALY shortfall enough to change the conclusions about whether a severity modifier would apply. The committee was not presented with calculations of QALY shortfall for the comparison with sorafenib. So, the committee concluded that in a pairwise analysis, a severity modifier of 1.2 could be applied to the comparisons with BSC for both populations, but not to the comparisons with cabozantinib or lenvatinib. It also concluded that it was unknown whether a severity modifier would apply to a comparison with sorafenib.

Cost-effectiveness estimates

Acceptable ICER

3.11 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an

effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically that:

- the main evidence presented did not directly compare selpercatinib with the relevant comparators (section 3.3)
- for RET-mutant medullary thyroid cancer, the indirect treatment comparison did not adjust for many of the key prognostic factors and effect modifiers, was not done in the population relevant to this evaluation, and previous treatments were inconsistent across the trials (section 3.4)
- for RET fusion-positive thyroid cancer, the indirect treatment comparison was naive and unadjusted and did not account for fundamental differences between the trials (section 3.4)
- overall survival estimates for selpercatinib and cabozantinib were uncertain because of the simplistic modelling methods for selpercatinib and uncertainty in the data from the indirect treatment comparisons (section 3.6 and section 3.7).

The committee acknowledged that thyroid cancer is quite rare, and that the population that could be eligible for selpercatinib included children and young people. However, the committee noted that there was no indication that evidence generation was especially difficult in the relevant population and data from 2 trials was available. So, the committee concluded that an acceptable ICER would be around £20,000 per QALY.

Preferred assumptions

3.12 The committee's preferred assumptions differed from the company's base case in the following ways:

- using utility values mapped from LIBRETTO-001 (section 3.8)
- basing cabozantinib overall survival extrapolation on a stratified spline 1 knot distribution for BSC (RET-mutant medullary thyroid cancer only) (section 3.7)
- removing relative dose intensity for cabozantinib, lenvatinib and sorafenib (section 3.9)
- applying a severity modifier of 1.2 only to the comparisons with BSC (section 3.10).

The committee also agreed that sorafenib should be included in the model for RET fusion-positive thyroid cancer (section 3.5) but that it did not have this analysis at the first committee meeting. The committee preferred to base its decision on a fully incremental analysis, including all relevant comparators. The cost-effectiveness estimates are confidential because of confidential commercial discounts for selpercatinib, cabozantinib and lenvatinib. For RET-mutant medullary thyroid cancer, the most plausible ICERs were all above £20,000 per QALY gained. For RET fusion-positive thyroid cancer, a fully incremental analysis that included sorafenib, as was the committee's preference, was not presented. The most plausible ICERs for selpercatinib compared with lenvatinib and BSC were all above £20,000 per QALY gained. The ICERs from the EAG's optimistic and pessimistic overall survival scenarios (section 3.6) were also above £20,000 per QALY gained in both populations.

Other considerations

Managed access

3.13 The company did not present a full managed access proposal. The committee noted that the ongoing LIBRETTO-531 trial could provide relevant evidence for the RET-mutant medullary thyroid cancer population (section 3.3). At the committee meeting, the company explained that LIBRETTO-531 currently had limited follow-up and that median progression-free survival would be unlikely to be reached within the period of managed access. The committee considered that further survival data collected through a managed access arrangement would be valuable in reducing the uncertainty in the evaluation, even if median progression-free or overall survival was not reached. It also agreed that more data on quality of life in this population would help to inform the choice of utility values. But it noted that there was no plausible potential for selpercatinib to be cost effective in any of its preferred scenarios. So the committee concluded that the criteria for managed access were not met.

Equality

3.14 Stakeholders stated that women are more likely to be diagnosed with thyroid cancer than men, that children should have access to selpercatinib, and that there could be regional variation in molecular testing for RET alterations. Age and sex are protected under the Equality Act 2010. The committee noted that it could only evaluate selpercatinib within its marketing authorisation indications, which were for people aged 12 and over. The committee noted that issues related to differences in regional availability of genetic testing cannot be addressed in a technology appraisal. The committee did not consider that its recommendations had a different impact on people protected by the equality legislation than on the wider population. So the committee concluded that these were not potential equality issues.

Further benefits not captured in the modelling

3.15 The committee considered if selpercatinib was innovative. It did not identify additional benefits of selpercatinib not captured in the economic modelling. So the committee concluded that all additional benefits of selpercatinib had already been taken into account.

Conclusion

Recommendation

3.16 For the RET-mutant medullary thyroid cancer population, the committee agreed that the most likely cost-effectiveness estimates were above the range that NICE considers to be a cost-effective use of NHS resources. For the RET fusion-positive thyroid cancer population, the committee noted that it had not been presented with cost-effectiveness results for its preferred analysis, but that the cost-effectiveness results presented were above the range that NICE considers to be a cost-effective use of NHS resources. So it did not recommend selpercatinib for untreated advanced thyroid cancer with RET alterations in people 12 years and older.

4 Evaluation committee members and NICE project team

Evaluation committee members

This topic was evaluated as a single technology evaluation by the highly specialised technologies evaluation committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Paul Arundel

Chair, highly specialised technologies evaluation committee

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Kirsty Pitt

Technical lead

Christian Griffiths

Technical adviser

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ISBN: [to be added at publication]