Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2370

selpercatinib, 40mg and 80mg hard capsules (Retsevmo®)

Eli Lilly and Company Ltd

6 August 2021

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan equivalent process

selpercatinib (Retsevmo®) is accepted for use within NHSScotland on an interim basis subject to ongoing evaluation and future reassessment.

Indication under review:

Selpercatinib as monotherapy is indicated for the treatment of adults with advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib.

Selpercatinib as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.

In a phase I/II study, in previously treated patients with RET-fusion positive thyroid cancer or RET-mutant MTC, selpercatinib was associated with an objective response rate of 79% and 69% respectively.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Published 13 September 2021

Advice must be treated in strict confidence until published on the SMC website on **Monday 13 September 2021.**

Chairman
Scottish Medicines Consortium

Indication

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Selpercatinib as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and/or vandetanib.[1, 2]

Dosing Information

The recommended dose of selpercatinib based on body weight, taken orally (capsules swallowed whole) with or without food at approximately the same time every day is:

- Less than 50kg: 120mg twice daily.
- 50kg or greater: 160mg twice daily.

Treatment should be continued until disease progression or unacceptable toxicity.

The presence of a RET gene fusion or mutation should be confirmed by a validated test prior to initiation of treatment with selpercatinib.

Selpercatinib therapy should be initiated and supervised by physicians experienced in the use of anti-cancer therapies.

Please see the Summary of product characteristics (SPC) for further information.[1, 2]

Product availability date

March 2021

Selpercatinib has conditional marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) and meets SMC orphan equivalent and end of life criteria for these indications.

Summary of evidence on comparative efficacy

Selpercatinib is an inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase. Certain point mutations in RET or chromosomal rearrangements involving in-frame fusions of RET with various partners can result in constitutively activated chimeric RET fusion proteins that can act as oncogenic drivers by promoting cell proliferation of tumour cell lines. Selpercatinib inhibits wild-type RET and multiple mutated RET isoforms as well as vascular endothelial growth factor receptor (VEGFR) -1 and VEGFR-3. [1, 2]

The key evidence supporting the efficacy and safety of selpercatinib for the indications under review comes from LIBRETTO-001, an international, open-label, single-arm, phase I (dose escalation) and phase II (dose expansion) study. The study recruited patients aged ≥12 years with a locally advanced or metastatic solid tumour. Patients had progressed on or were intolerant to standard therapy, or no standard therapy existed, or they were not candidates for or were unlikely to tolerate or derive significant clinical benefit from, or they declined, standard therapy. For patients enrolled in phase II of the study, evidence of RET gene alteration in tumour and / or blood was required. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of ≤2 or a Lansky Performance Score (LPS) ≥40%.[3, 4]

In the phase II part of the study, selpercatinib was administered orally at a dose of 160mg twice daily. Treatment was to continue until disease progression, death, unacceptable toxic effects, or withdrawal of consent. Patients with documented disease progression could continue selpercatinib if they were deriving clinical benefit.[3, 4]

The primary outcome was objective response rate (ORR), assessed by independent review committee (IRC) using Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST v1.1). This was defined as the proportion of patients with best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR). BOR was defined as the best response designation for each patient that was recorded between the date of the first dose of selpercatinib and the data cut-off, or the date of documented disease progression per RECIST v1.1 or the date of subsequent therapy or cancer-related surgery.[3, 4]

RET-mutant MTC

The primary analysis set comprised the first 55 consecutively treated patients across both phase I and II who had RET-mutant MTC disease, a prospectively identified activating RET mutation, measurable disease, previous treatment with vandetanib and/or cabozantinib, and who had received at least one dose of selpercatinib. The integrated analysis set (IAS) comprised all primary analysis set patients and those treated after the 55th patient who met the primary analysis set criteria.[3, 4].

Results of the primary outcome and relevant secondary outcomes, which included duration of response, progression free survival (PFS) and overall survival, are detailed in Table 1 below for the RET-mutant MTC primary analysis set at data cut-off 16 December 2019.[4]

Table 1: Primary and relevant secondary outcomes of LIBRETTO-001 study. Previously treated RET-mutant MTC populations (data cut-off 16 December 2019) [4, 5]

	Previously treated RET-mutant MTC
	Primary analysis set (n=55)
ORR assessed by IRC per RECIST v1.1.	
ORR % (95% CI)	69% (55 to 81)
CR %	9.1%
PR %	60%
DOR by IRC	
Median duration of follow-up (months)	14.1
Patients with response	38
DOR events	6

Median DOR (95% CI)	NE (19.1 to NE)
KM estimate at 12 months	86%
PFS by IRC	
Median duration of follow-up (months)	16.7
Median PFS (95% CI)	NE (24.4 to NE)
KM estimate at 12 months	82%
Abbreviations: CI, confidence interval; CR, complete response; DOR, duration of response; DOR events, death or disease progression; IRC, independent review committee; KM, Kaplan Meier; NE, not evaluable; ORR, objective response rate; PFS progression-free survival; PR, partial response.	

In an updated analysis at data cut-off 30 March 2020 of the primary analysis set, there were no further ORR but one patient previously assessed as having a PR was upgraded to CR. In the updated primary analysis set, median duration of response was not estimable (NE); median PFS was NE; and median overall survival was 33.2 months (with 13 deaths). [3]

RET fusion-positive thyroid cancer

Results of the primary outcomes and relevant secondary outcomes at data cut-off 16 December 2019 in RET fusion-positive thyroid cancer patients, who had received at least one previous systemic therapy other than radioactive iodine, are detailed in Table 2 below. Of these, 68% had previously received sorafenib and/or lenvatinib.[4]

Table 2: Primary and relevant secondary outcomes of LIBRETTO-001 study. Previously treated RET fusion-positive thyroid cancer patients (data cut-off 16 December 2019) [4, 5]

	Previously treated RET fusion-positive thyroid cancer (n=19)
ORR assessed by IRC per RECIST v1.1.	
ORR % (95% CI)	79% (54 to 94)
CR %	5.3%
PR %	74%
DOR by IRC	
Median duration of follow-up (months)	17.5
Patients with response	15
DOR events	6
Median DOR (95% CI)	18.4 (7.6 to NE)
Rate of DOR at 12 months or more	71%
PFS by IRC	
Median duration of follow-up (months)	13.7
Median PFS	20.1
Rate of PFS at 12 months or more	64%
Abbreviations: CI, confidence interval; CR, complete response; DOR, duration of response; DOR events, death or disease progression; IRC, independent review committee; NE, not evaluable; ORR, objective response rate; PFS progression-free survival; PR, partial response.	

In an updated analysis at data cut-off 30 March 2020 of 22 patients with RET fusion-positive thyroid cancer previously treated with systemic therapy other than radioactive iodine, ORR was 77% (including 9.1% of CR and 68% of PR). [3]

The submitting company conducted unanchored matching-adjusted indirect comparisons (MAICs) for RET-mutant MTC to compare selpercatinib with placebo as a proxy for best supportive care

(BSC) and cabozantinib, and a naïve indirect treatment comparison (ITC) versus placebo as a proxy for BSC for RET-fusion-positive thyroid cancer. Two studies were included in the MAICs, LIBRETTO-001[4] (using data from the RET-mutant IAS and supplementary analysis set 1 [SAS1, which included patients who met the primary analysis set criteria but had not previously been treated with vandetanib or cabozantinib]) and EXAM (using data from the RET-mutant subgroup for PFS and the RET M918T-positive subgroup for overall survival)[6-8]. The naïve ITC, also included two studies, LIBRETTO-001[4] (using RET-fusion positive subgroup data) and SELECT[9, 10]. For all comparisons, the reported outcomes were PFS and overall survival. The results of these MAICs were used to inform the economic base case for RET-mutant MTC patients, and the results of the naïve ITC were used to inform the economic base case for RET-fusion-positive thyroid cancer patients. The submitting company concluded that, while the data from the LIBRETTO-001 trial were immature and not from a head-to-head study versus the relevant comparators, the results of the MAIC and naïve ITC indicated that selpercatinib was associated with significant improvements in PFS and overall survival compared with BSC in both the RET-mutant MTC and the previously-treated RET fusion-positive thyroid cancer populations. Selpercatinib was also associated with PFS and overall survival improvements versus cabozantinib in RET-mutant MTC. The company noted that a comparison against vandetanib was not possible.

*Other data were also assessed but remain confidential.**

Summary of evidence on comparative safety

No comparative safety data are available. According to the European Medicines Agency (EMA), selpercatinib presents substantial toxicity; however, its safety profile was considered consistent with that seen for other tyrosine kinase inhibitors, with significant gastrointestinal toxicities, hypertension, increased transaminases and QT interval prolongation. Overall, the EMA considered that the safety profile of selpercatinib in adult patients was manageable. Uncertainties remain and will be addressed by the specific obligations being imposed in the context of the conditional marketing authorisation.[3]

Safety was assessed in the overall safety analysis set, which included all patients who were enrolled in LIBRETTO-001 (regardless of tumour type or treatment history) and received one or more doses of selpercatinib at the 30 March 2020 data cut-off date. At this data cut-off, the median duration of treatment with selpercatinib was 11.1 months (12.0 months in RET- mutant MTC patients and 12.9 months in RET-fusion positive patients). Any treatment-emergent adverse event (AE) was reported by 99% (740/746) of all patients (99% [313/315] in RET-mutant MTC patients and 100% [42/42] in RET-fusion positive patients) and these were considered treatment-related in 92% (93% in RET-mutant MTC patients and 98% in RET-fusion positive patients). Patients reporting a grade 3 or higher AE were 60% (60% in RET-mutant MTC patients and in RET-fusion positive patients), patients with a reported serious AE were 35% (31% in RET-mutant MTC patients and 33% in RET-fusion positive patients), patients permanently discontinuing therapy due to an AE was 6.0% (4.8% in RET-mutant MTC patients and in RET-fusion positive patients). [3]

The most frequently reported treatment-related AEs of any grade with an incidence >10% were: dry mouth (36%), hypertension (26%), aspartate transaminase (AST) increased (26%), alanine transaminase (ALT) increased (26%), diarrhoea (22%), fatigue (19%), oedema peripheral (14%), electrocardiogram (ECG) QT prolonged (14%), constipation (13%), blood creatinine increased (12%), rash (12%), and nausea (10%).[3]

At data cut-off 30 March 2020, 14% (104/746) of patients had died, including 28 with RET-mutant MTC, 6 with RET-fusion positive thyroid cancer, 56 patients with RET fusion-positive non-small-cell lung cancer (NSCLC), and eight with other tumour RET alteration. The main reported reason for death were disease progression (67%) and AE (24%). The EMA noted that, although the population was too small to draw any precise conclusions, the number of deaths is higher in NSCLC patients than in the MTC population. [3]

Summary of clinical effectiveness issues

The clinical course of thyroid cancer is heterogeneous, varying from indolent and stable tumours, cured by surgical resection, to aggressive cancers associated with metastases and high mortality. Oncogenic mutations in the RET gene have been identified in MTC. MTC is not sensitive to radioactive iodine and is only curable in approximately 50% of patients through surgical resection. Locally recurrent disease is treated with reoperation and/or external beam radiation therapy; however, these treatments are associated with significant morbidity and are often not curative. Metastatic MTC is currently incurable and is treated with resection, radiation or systemic therapies. Two multikinase inhibitors (MKIs), cabozantinib and vandetanib, have marketing authorisation for progressive, unresectable locally advanced or metastatic MTC. These MKIs are not recommended for use within NHSScotland. RET gene fusions (chromosomal rearrangements) have been identified mainly in patients with papillary thyroid cancer and less frequently in other subtypes. Patients with RET fusion-positive thyroid cancer receive standard of care for their cancer subtype, which includes surgery and radioactive iodine. Recurrent disease is treated with reoperation and/or radioactive iodine, however, these are associated with significant morbidity and are often not curative. Two MKIs, sorafenib and lenvatinib, have marketing authorisation for the treatment of unresectable, radioactive iodine-refractory differentiated thyroid cancer and are accepted for use within NHSScotland.[3] Clinical experts consulted by SMC considered that selpercatinib fills an unmet need in this therapeutic area due to the lack of current treatment options. They consider selpercatinib a therapeutic advancement due to the targeted mechanism of action and consider its place in therapy for all patients who have disease with the relevant mutation.

The introduction of selpercatinib may be associated with service implications, due to various monitoring requirements (including AST, ALT levels, blood pressure, ECG and serum electrolytes). A companion diagnostic, testing for RET alterations, is also required: contact local laboratory for information.

Key strengths

- In the RET-mutant MTC primary analysis set and IAS patients, who had previously received vandetanib and/or cabozantinib, the ORR were 69% and 68%, respectively (data cut-off 16 December 2019). In the RET-fusion positive patient population previously treated with a systemic therapy other than radioactive iodine, the ORR was 79% (data cut-off 16 December 2019). Results at a later March 2020 data cut-off were supportive. The observed effects were clinically relevant in patient populations with limited treatment options, and the EMA considered that major therapeutic advantage was demonstrated.
- Selpercatinib is the first medicine to be approved specifically for RET-altered thyroid cancers.

Key uncertainties

- Evidence is provided from one small phase I/II, single-arm, open-label study, LIBRETTO-001, which is prone to various biases. Interpretation of all outcomes was hampered by the lack of a control group, which makes the relative magnitude of any benefits highly uncertain. Assessment of subjective outcomes such as quality of life and safety was limited by the open-label design. Data for the subset of RET-fusion thyroid cancer patients who had previously received sorafenib and/or lenvatinib (68%) were not presented separately.
- Median duration of follow-up was limited; and the data for the supportive secondary outcomes of duration of response, PFS and overall survival were immature. Longer-term data are required to confirm treatment effects and determine their durability.
- There are uncertainties concerning safety due to the lack of control group and heterogeneity of patients. There are limited data available in paediatric patients, elderly (>75 years old) and patients with low bodyweight.
- There are no direct comparative data, thus the submitting company conducted MAICs and a naïve ITC to compare selpercatinib versus placebo as a proxy for BSC and cabozantinib (in RET-mutant MTC). However, there were a number of limitations, which affected the validity of the results and made the conclusions highly uncertain. These included the limited volume of evidence, the heterogeneity between the studies in terms of patient characteristics and methodology, and the simple methods used for the naïve comparison. In addition, the populations included in the MAICs and naïve ITC were broader than the licensed populations.

EMA specific obligations[3]

To confirm the efficacy and safety of selpercatinib in the treatment of patients with RET fusion - positive thyroid cancer and RET-mutant MTC, the marketing authorisation holder (MAH) is required to submit the final study report from the pivotal study LIBRETTO-001 (due by December 2023).

To confirm the efficacy and safety of selpercatinib in the treatment of patients with RET-mutant MTC, the MAH required to submit the clinical study report of the Phase 3 study J2G-MC-JZJB (LIBRETTO-531) comparing selpercatinib to physician's choice of cabozantinib or vandetanib in patients with progressive, advanced, kinase inhibitor-naïve, RET-mutant MTC (due by February 2025).

The EMA specific obligations may address the key uncertainties in the clinical evidence presented.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of selpercatinib, as an orphan equivalent and end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Advanced MTC and RET fusion positive thyroid cancer are rare cancer types that present with disabling symptoms such as breathlessness, cough, pain and for MTC fatigue and intractable and distressing diarrhoea. There is always a significant impact on the quality of life and often on the finances of patients and their family and carers (due to time off work because of symptom burden and repeated hospital visits).
- There is a high unmet need, as there are no other treatments options available in second line after MKI failure or intolerance.
- In responders, selpercatinib is expected to significantly reduce symptom burden, which would improve the patients' quality of life, help them be more independent and reduce hospital visits. It would offer hope for a better future and may allow a return to a relatively normal life. It may potentially also increase survival.
- Clinicians are well versed in the management of MKI side effects, which appear to be reduced with selpercatinib compared with other MKIs thanks to the RET specificity. Overall, selpercatinib appears to be well tolerated.
- Selpercatinib is administered orally and can conveniently be dispensed at an outpatient clinic. RET genotype testing across Scotland will be required.

Additional Patient and Carer Involvement

We received a patient group submission from the Association for Multiple Endocrine Neoplasia Disorders (AMEND), which is a registered charity. AMEND has received 10% pharmaceutical company funding in the past two years, with none from the submitting company. Representatives from AMEND participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of selpercatinib compared to BSC for the treatment of adolescent (aged ≥12 years) and adult patients with progressive, unresectable locally advanced RET-mutant MTC following prior treatment with cabozantinib and/or vandetanib, and adult patients with advanced RET fusion-positive thyroid cancer following prior treatment with sorafenib and/or lenvatinib. SMC clinical expert feedback confirmed BSC as the appropriate

comparator for these two sub-populations. However, as noted in the clinical effectiveness section, MTC population patients who receive cabozantinib or vandetanib may receive the alternative (cabozantinib or vandetanib) after failure on the initial treatment. The company therefore provided an analysis versus cabozantinib in this population.

The economic analysis used a standard partitioned survival model with three health states (progression free, progressed and death). The model had a weekly cycle and a lifetime horizon of 25 years. The clinical data for selpercatinib for patient characteristics, PFS, overall survival, time on treatment and AEs were from the LIBRETTO-001 study. The any line patients from LIBRETTO-001 (n=212 IAS and SAS1) were used for the RET-mutant MTC population, and the pre-treated sub-group (n=19) for the RET fusion-positive thyroid cancer population.

For the RET-mutant MTC analysis an unanchored MAIC was performed for PFS and overall survival, with proxy outcomes for BSC derived using aggregate summary data from the RET-mutant MTC sub-group placebo arm of the EXAM study (n=62), a phase III trial of cabozantinib in patients with radiographically progressive MTC.[8] For the RET fusion-positive thyroid cancer population a naïve indirect comparison was performed, with proxy outcomes for BSC derived from the placebo arm of the SELECT study (n=131) which compared lenvatinib versus placebo in radioactive iodine-refractory thyroid cancer.[10] Given similar statistical fits, extrapolation of PFS and overall survival in the RET-mutant MTC was based on visual fits to the data and clinical expert opinion, with the log logistic selected for PFS and stratified log-logistic for overall survival. For the RET fusion-positive thyroid cancer population, PFS extrapolation for selpercatinib and BSC was performed using a stratified Weibull function in the base case based on visual fit and clinical expert plausibility validation, and a piecewise exponential function was fitted to the end of the observed overall survival data for both arms following an approach used in NICE TA535 and the SMC submission for lenvatinib. Grade ≥3 AEs with at least 2% difference between selpercatinib and BSC were included in the economic analysis for costs and disutilities, based on the full safety analysis set of LIBRETTO-001, EXAM and SELECT studies.

Age-adjusted utility values were applied by health state using published SMC guidance sources[11] using advanced or metastatic differentiated thyroid cancer (DTC) estimates for the RET-mutant MTC population, and also applied for the RET fusion-positive thyroid cancer population (0.80 for progression free, 0.64 for progressed). AE disutilities were derived from published literature and health technology assessment (HTA) submission sources, and assumed to have a duration of one month applied in the first model cycle.

Costs included medicine acquisition and administration costs, monitoring costs, BSC costs, AE management and end of life palliative costs. Selpercatinib medicine costs were based on a weighted average of doses in the LIBRETTO-001 study and accounted for dose reductions over the course of treatment. Time on treatment was assumed to be equivalent to PFS but adjusted for RET-mutant MTC patients and RET fusion-positive thyroid cancer patients to allow for treatment beyond progression in the LIBRETTO-001 study. For medicines administered orally, wastage was assumed. BSC related monitoring and resource use costs, health state resource use outpatient visits, blood tests, computerised tomography (CT) scans, AE costs, and end of life palliative care costs were largely based on estimates and unit costs used in prior NICE appraisals in MTC and thyroid cancer incorporating expert clinical opinion and validation. No subsequent treatments

were assumed for both patient populations, as patients would otherwise be receiving BSC. A cost was also included for the RET-fusion or RET-mutant portion of a multi-gene testing next generation sequencing (NGS) panel, estimated to be £34 per test from NHS England and NHS Improvement applied as part of the ongoing NICE appraisal of selpercatinib. This cost was applied to the positive test rate for each population to derive costs in the advanced RET-mutant MTC and for RET fusion-positive thyroid cancer patients.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price of selpercatinib.

In the base case for selpercatinib versus BSC, the incremental cost-effectiveness ratio (ICER) is estimated with PAS at £48,965/quality-adjusted life-year (QALY) for the RET-mutant MTC population, and £58,499/QALY for the RET fusion-positive thyroid cancer population (Table 3). The main driver of incremental costs was additional medicine acquisition costs for selpercatinib compared to BSC. Disaggregated base case results also showed that the majority of incremental costs and QALYs for selpercatinib were incurred in the progression free health state, for both the MTC and TC patient populations.

Table 3: Base case results Selpercatinib versus BSC (with PAS)

Analysis	ICER (cost/ QALY)
RET-mutant MTC	
Selpercatinib versus BSC	£48,965
Selpercatinib versus cabozantinib	£37,277
RET fusion-positive thyroid cancer	
Selpercatinib versus BSC	£58,499

In one-way sensitivity analysis, the most sensitive variables for the RET-mutant MTC population were the health state costs for BSC and varying health state utility estimates. For the RET fusion-positive thyroid cancer population varying the progression free utility for selpercatinib, the progressed state utility and progression free costs had most impact on the ICER. For the comparison with cabozantinib in the RET-mutant MTC population, varying cabozantinib overall survival had a large impact on the ICER (Table 4). In scenario analysis for the RET-mutant MTC population, there was most ICER sensitivity to the choice of parametric function for extrapolation of overall survival (Table 4). For the RET fusion-positive thyroid cancer population the ICER had some sensitivity to choice of function for PFS extrapolation, and using alternative utility sources (Table 4).

Table 4: Key sensitivity and scenario analysis results

Sensitivity/scenario analysis		RET-mutant MTC		RET fusion-positive thyroid cancer
		ICER with PAS (cost/ QALY) versus cabozantinib	ICER with PAS (cost/ QALY) versus BSC	ICER with PAS (cost/ QALY) versus BSC
Base case		£37,277	£48,965	£58,499
One-way sensitivity analyses:				
1	Health state utility – progression free (Selpercatinib) [Range= 0.643 – 0.957]	£30,538 - £47,832	£42,341 - £58,046	£49,306 - £71,905
2	Health state utility – progressed [Range= 0.515 – 0.765]	NR	£45,798 - £52,603	£55,263 - £62,136
3	Treatment-effects for cabozantinib - OS	£26,115 - £88,409	N/A	N/A
Scenario analyses:				
4	PFS – gamma	£40,056	£47,491	NR
5	PFS – spline knot 1	£37,286	£44,825	NR
6	PFS – stratified spline knot 2	£39,838	£46,980	NR
7	PFS – stratified lognormal	£120,280*	£108,152*	£65,423*
8	OS - stratified weibull	£47,161	£65,448	£147,358*
9	OS - stratified gompertz	Dominated*	£639,963*	£204,291*
10	OS – stratified lognormal	NR	NR	£790,972*
11	Utilities for PD = 0.5 (based on Fordham et al)	NR	£53,076	£62,588
12	Utility value of 0.72 for PFS	NR	£52,352	£62,936
13	NGS testing costs (£400)	£37,557	£49,163	£60,285
14	No diagnostic testing costs	NR	£49,947	£58,333
15	10 year time horizon	£41,229	£59,997	£65,498
16	Alternative ToT (using upper limit of 95% CI for mean time between PFS and treatment discontinuation)	£39,549	£50,574	£71,329

Abbreviations: CI, confidence interval, ICER, incremental cost-effectiveness ratio; NGS, next generation sequencing; NR, not reported; N/A, not applicable; OS, overall survival; PAS, patient access scheme; PD,

progressive disease; PF, progression free survival; QALY, quality adjusted life year; BSC, best supportive care; ToT, time on treatment
* The submitting company did not consider these OS/PFS extrapolations as plausible but these results are presented to show uncertainty and sensitivity in these parameters.

The economic analysis was associated with a number of limitations and uncertainties:

- The clinical evidence for selpercatinib consists of a single arm trial and consequently there is an absence of head-to-head clinical data versus a relevant comparator (BSC). Hence, indirect treatment comparisons were conducted for each patient population (RET-mutant MTC, RET-fusion positive thyroid cancer) to allow the relative effectiveness of selpercatinib versus BSC to be estimated for overall survival and PFS. There is therefore inherent uncertainty due to clinical study design differences, particularly in the RET fusion-positive thyroid cancer population which has particularly small patient numbers.
- ITCs (MAIC and naïve indirect comparison) are both associated with limitations, as discussed in the clinical effectiveness section above, so the relative effectiveness assessments for selpercatinib versus BSC in both patient populations and versus cabozantinib in the RET mutant MTC population are uncertain.
- There is uncertainty in the selpercatinib PFS and overall survival data due to median duration of follow-up being limited and so the data are immature requiring long-term extrapolation over the time horizon. Alternative extrapolation methods were explored with some resulting in a wide range of ICERs around the base case, confirming uncertainty around these parameters, though the company considered many not to be plausible extrapolations.
- Time on treatment (ToT) has been set to PFS in the model with adjustments based on LIBRETTO-001 so (ToT) went beyond progression but there is uncertainty surrounding this assumption. Scenario analysis increasing ToT beyond progression resulted in increased ICERs, particularly in the RET-fusion positive thyroid cancer population.
- Quality of life data were collected in the LIBRETTO-001 trial but utilities elicited from this source were not included in the analysis due to “low face validity”. Utilities in the economic base case are sourced from previous HTA submissions in differentiated thyroid cancer (DECISION trial) and published literature. The post-progression utility was also taken from a previous HTA submission in DTC (SMC 1055/15) but the original source is unclear. The utility values appear to have reasonable face validity but there is uncertainty in these values and the ICER has some sensitivity to variation in utility values.
- Testing costs to identify RET fusion or mutation patients, using an NGS panel, are included in the base case analysis but the costs are expected to be lower than those in Scottish clinical practice. Increasing testing costs in scenario analysis did not have a significant impact on the ICER but there remains uncertainty around testing not being routinely available in Scotland.
- There is uncertainty around the relevance of cabozantinib as an additional comparator, with sensitivity analysis showing large uncertainty in the ICER (Table 4), particularly when varying treatment effect.

The Committee also considered the benefits of selpercatinib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for the absence of other treatments of proven benefit was satisfied. In addition, as selpercatinib is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted selpercatinib for use on an interim basis in NHSScotland, subject to ongoing evaluation and future reassessment.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

The European Society for Medical Oncology (ESMO) published in September 2019 'Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.' These guidelines indicate that the RET kinase and vascular endothelial growth factor receptor type 2 (VEGFR2) inhibitors, cabozantinib and vandetanib, are the first-line systemic treatments for progressive metastatic MTC. It is also noted that no other treatments have been approved for second line use in patients with advanced MTC who have received first line treatment with cabozantinib and vandetanib. However, it is mentioned that current progress is being made with MKIs (such as sorafenib, motesanib, pazopanib, sunitinib, lenvatinib) that have already undergone phase II testing in advanced MTC patients. It is also noted that more selective RET inhibitors (such as selpercatinib and pralsetinib) appear promising and are now under investigation. For patients with radioactive iodine refractory differentiated thyroid cancer, lenvatinib and sorafenib should be considered the standard first-line systemic therapy. For patients who have been treated with lenvatinib and/or sorafenib, these guidelines indicate that while previous MKI therapy is not a contraindication for subsequent use of these drugs, data on second-line efficacy are scarce. [12]

Additional information: comparators

Best supportive care for RET fusion-positive thyroid cancer.
Best supportive care, vandetanib* and cabozantinib* for RET-mutant MTC.
*Not accepted for use by SMC.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Selpercatinib	**120 or 160mg twice daily**	**85,176 to 113,568**

Costs from eMC Dictionary of Medicines and Devices Browser on 30/04/2021. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 7 patients eligible for treatment with selpercatinib in year 1 and 2 patients in year 5, to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

References

1. Electronic Medicines Compendium (EMC). Eli Lilly and Company Limited. Retsevmo 40 mg hard capsules. Summary of product characteristics. . 2021 Mar 09 [cited; Available from: https://www.medicines.org.uk/emc/product/12195/smpc.

2. Electronic Medicines Compendium (EMC). Eli Lilly and Company Limited. Retsevmo 80 mg hard capsules. Summary of product characteristics. 2021 Mar 09 [cited; Available from: https://www.medicines.org.uk/emc/product/12196/smpc.

3. European Medicines Agency (EMA): European Public Assessment Report (EPAR). Selpercatinib (Retsevmo®). EMEA/H/C/005375/0000. Available at: http://www.ema.europe.eu/ [10 December 2020].

4. Wirth LJ, Sherman E, Robinson B, Solomon B, Kang H, Lorch J*, et al.* Efficacy of Selpercatinib in RET-Altered Thyroid Cancers. New England Journal of Medicine. 2020;383(9):825-35.

5. Eli Lilly C. LIBRETTO-001 Data on File (16th December 2019 data cut-off). 2019.

6. Elisei R, Schlumberger MJ, Müller SP, Schöffski P, Brose MS, Shah MH*, et al.* Cabozantinib in progressive medullary thyroid cancer. Journal of clinical oncology. 2013;31(29):3639.

7. Schlumberger M, Elisei R, Müller S, Schöffski P, Brose M, Shah M*, et al.* Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma. Annals of Oncology. 2017;28(11):2813-9.

8. Sherman SI, Clary DO, Elisei R, Schlumberger MJ, Cohen EEW, Schöffski P*, et al.* Correlative analyses of RET and RAS mutations in a phase 3 trial of cabozantinib in patients with progressive, metastatic medullary thyroid cancer. Cancer. 2016;122(24):3856-64.

9. National Institute for H, Care E. TA535: Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine. Available at: https://www.nice.org.uk/guidance/ta535 [Last accessed: 26th June 2020]. [cited; Available from: https://www.nice.org.uk/guidance/ta535.

10. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R*, et al.* Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. New England Journal of Medicine. 2015;372(7):621-30.

11. Scottish Medicines Consortium. Sorafenib (Nexavar) for the treatment of patients with progressive, locally advanced or metastatic, differentiated thyroid carcinoma, refractory to radioactive iodine. Available at https://www.scottishmedicines.org.uk/medicines-advice/sorafenib-nexavar-fullsubmission-105515/.

12. Filetti S, Durante C, Hartl D, Leboulleux S, Locati LD, Newbold K*, et al.* Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2019;30(12):1856-83.

This assessment is based on data submitted by the applicant company up to and including 11 June 2021.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.