SMC2732

selpercatinib hard capsules (Retsevmo®)

Eli Lilly and Company Limited

09 May 2025

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, 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

selpercatinib (Retsevmo®) is accepted for restricted use within NHSScotland.

Indication under review: as monotherapy for the treatment of adults and adolescents 12 years and older with advanced rearranged during transfection (RET)-mutant medullary thyroid cancer (MTC).

SMC restriction: patients who require systemic therapy and have not previously received systemic therapy.

In a phase III study in patients with RET-mutant MTC, selpercatinib showed a statistically significant improvement in progression-free survival compared with the investigator's choice of treatment.

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.

SMC has previously issued advice (SMC2370) for selpercatinib 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. This advice remains valid.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Selpercatinib is an inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase. It 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 recommended dose of selpercatinib is 120 mg (< 50 kg body weight) or 160 mg (≥ 50 kg body weight) twice daily, administered orally. Treatment should be continued until disease progression or unacceptable toxicity. For more information please see the Summary of Product Characteristics.[1]

In September 2021, selpercatinib was accepted for use by SMC on an interim basis 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 (SMC2370). This submission represents an extension to this indication to include adults and adolescents 12 years and older with advanced RET-mutant MTC who have not previously received systemic therapy.

1.2. Disease background

Thyroid cancer is a rare type of cancer with various subtypes, representing about 1% of all malignancies. MTC is a subtype of thyroid cancer that originates from non-follicular cells and is estimated to account for approximately 4% of all thyroid cancers.[4, 5] In adults, MTC can occur as a sporadic entity (70% to 80% of cases) or as familial (approximately 25% of cases).[2] RET-mutations are present in most cases of MTC.[2, 6] Compared with thyroid cancer that is differentiated from follicular cells, patients with metastatic MTC have a poorer prognosis with an estimated 5-year survival of around 40%.[2, 7, 8] Patients with RET-mutant MTC may also have poorer outcomes compared to those without RET-mutations.[9]

1.3. Company proposed position

Adults and adolescents 12 years and older with advanced RET-mutant MTC who require systemic therapy who have not previously received systemic therapy.

1.4. Treatment pathway and relevant comparators

Advanced RET-mutant MTC is currently incurable and is managed with resection, radiation or systemic therapies.[10] Two multikinase inhibitors (MKIs), cabozantinib and vandetanib, have a UK marketing authorisation for progressive, unresectable locally advanced or metastatic MTC.[11, 12] These MKIs are not recommended for use within NHSScotland (SMC1022/15 and SMC797/12). However, clinical experts contacted by SMC noted that patients may receive treatment with cabozantinib or vandetanib in the first-line setting through individual patient treatment request. A smaller proportion of patients receive best supportive care (BSC).

1.5. Category for decision-making process

Eligibility for interim acceptance decision option

Selpercatinib has conditional marketing authorisation from the Medicines and Healthcare Products Regulatory Agency.

Eligibility for a PACE meeting

Selpercatinib meets SMC orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

The main evidence to support the use of selpercatinib for this submission comes from the LIBRETTO-531 study. Details are summarised in table 2.1.

Table 2.1. Overview of relevant study.

Criteria	LIBRETTO-531[13]
Study design	International, randomised, open-label, phase III study.
Eligible patients	• Patients aged ≥ 12 years of age (if permitted by local regulatory authorities and institutional review boards, otherwise ≥ 18 years of age) • Pathologically confirmed, unresectable, locally advanced and/or metastatic MTC • Radiologically progressive disease as per RECIST v1.1 • A prospectively identified pathogenic RET alteration (somatic or germline) determined by polymerase chain-reaction assay or next-generation sequencing performed in accredited local laboratories or in a central laboratory • ECOG PS of 0 to 2 • No prior treatment with kinase inhibitors
Treatments and Randomisation	Patients were randomised 2:1 to receive oral selpercatinib (160 mg twice daily) or the physician's choice (termed the control group hereafter) of oral cabozantinib (140 mg once daily) or oral vandetanib (300 mg once daily); alternative doses of each medicine were used for patients aged 12 to 18 years. Treatment continued until disease progression, unacceptable toxicity, or other reasons for treatment discontinuation. Patients were permitted to receive treatment with selpercatinib beyond disease progression if the clinician considered that the patient is continuing to benefit. Patients randomised to the control group were not allowed to switch from cabozantinib to vandetanib or from vandetanib to cabozantinib during the study. However, the control group could potentially be eligible for a crossover to selpercatinib treatment (dependent on eligibility criteria) if disease progression was confirmed during the study by BICR. Randomisation was stratified according to RET mutation (M918T versus other) and, if assigned to the control group, the intended treatment (cabozantinib versus vandetanib).
Primary outcome	PFS as assessed by BICR, defined as the time from randomisation to the occurrence of disease progression (according to RECIST, version 1.1) or death. This was assessed in the intention to treat (ITT) population which included all randomised patients regardless of whether they received treatment.
Selected Secondary outcomes	• TFFS is defined as the time from randomisation to disease progression, discontinuation of treatment due to treatment-related adverse events), or death due to any cause • Proportion of time with "high-side-effect bother" based on FACT-GP5
Statistical analysis	Efficacy analysis was performed on the ITT population using hierarchal ranking of primary and secondary outcomes in the following order: PFS by BICR, TFFS by BICR, and proportion of time with "high-side-effect bother" based on FACT-GP5. All other outcomes (such as ORR and OS) were not accounted for in the multiple testing strategy and are described descriptively.

Abbreviations: BICR = blinded independent central review; ECOG PS = Eastern Cooperative Oncology Group performance status; FACT-GP5 = Functional Assessment of Cancer Therapy-General Item GP5; ITT = intention-to-treat population; MTC = medullary thyroid cancer; PFS = progression-free survival; ORR = overall response rate; OS = overall survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours version 1.1; RET = rearranged during transfection; TFFS = treatment failure-free survival

At the pre-specified interim analysis (data cut-off May 2023), treatment with selpercatinib resulted in a statistically significant improvement in progression-free survival (PFS) and treatment failure-free survival (TFFS) when compared with the control group; both outcomes were assessed by blinded independent central review (BICR). Other relevant outcomes are also presented in table 2.2.

Table 2.2: Primary and selected secondary outcomes from LIBRETTO-531 study (data cut-off May 2023).[13, 14]

	Selpercatinib (n=193)	**Control group: Cabozantinib or vandetanib (n=98)**
Primary outcome: PFS (as per RECIST version 1.1 assessed by BICR)		
Median duration of follow-up	12.5 months	11.0 months
PFS events, n	26	33
Median PFS	NR	16.8 months
HR (95% CI), p-value	0.28 (0.16 to 0.48), p<0.001	
KM estimated PFS at 12 months	87%	66%
KM estimated PFS at 24 months	76%	37%
KM estimated PFS at 30 months	76%	25%
Secondary outcome: TFFS (as per RECIST version 1.1 assessed by BICR)		
Median duration of follow-up	12.5 months	11.1 months
Median TFFS	NR	13.9 months
HR (95% CI), p-value	0.25 (0.15 to 0.42), p<0.0001	
KM estimated TFFS at 12 months	86%	62%
KM estimated TFFS at 30 months	76%	25%
Secondary outcome: ORR (as per RECIST version 1.1 assessed by BICR)		
ORR, %	69%	39%
CR, %	12%	4.1%
PR, %	57%	35%

Abbreviations: BICR = blinded independent central review; CI = confidence interval; CR = complete response; HR = hazard ratio; KM = Kaplan-Meier; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours version 1.1; TFFS = treatment failure-free survival

Investigator assessed PFS (HR=0.19) was consistent with BIRC-assessed PFS (HR=0.28), though was more favourable to selpercatinib than median BIRC-assessed PFS.[14]

At the May 2023 data cut-off, median follow-up for overall survival was approximately 15 months and 18 deaths had occurred; the HR was 0.37 (95% confidence interval [CI]: 0.15 to 0.95). Kaplan-Meier estimated OS at 18 months was 96% in the selpercatinib group and 93% in the control group.[13] At a later OS analysis, with a data lock of 11 March 2024, 26 events were observed across the two arms and the HR was 0.28 (95% CI: 0.12 to 0.61). The PFS HR for this analysis was 0.20 (95% CI: 0.13 to 0.32) and the ORR for selpercatinib was 82% compared with 44% for the control arm.[14]

2.2. Evidence to support the positioning proposed by the submitting company

All patients in the LIBRETTO-531 study were naïve to systemic therapy and the study provides direct evidence against the two most relevant comparators (cabozantinib and vandetanib).

2.3. Health-related quality of life outcomes

In LIBRETTO-531, the EORTC-QLQ-C30 questionnaire was completed by patients at baseline and during scheduled follow-up visits. Overall, the post-baseline scores numerically favoured selpercatinib over the control group for the quality of life and functioning scores.[15]

Comparative tolerability between selpercatinib (n=161) and the control group (n=81), was assessed as the proportion of time on treatment, post-baseline, with "high side-effect bother" (defined as a Functional Assessment of Cancer Therapy-General Item GP5 [FACT-GP5] score of 3 ("Quite a bit") or 4 ("Very much"); this was a pre-specified secondary outcome assessed in the statistical testing hierarchy. The selpercatinib group had a statistically significantly lower proportion of time on treatment where patients reported "high side-effect bother" (8%) than the control arm (24%).[14, 15]

2.4. Supportive studies

LIBRETTO-001 is an ongoing, open-label, single-arm, multi-cohort, phase I/II study evaluating the efficacy and safety of selpercatinib in patients with RET-altered cancers, including 324 patients with RET-mutant MTC. The relevant patient population for the indication under review is treatment-naïve patients with RET-mutant MTC (n=116), which are a subset of the cabozantinib/vandetanib-naïve cohort (n=143). At the January 2023 data cut-off, there were minor and non-meaningful differences in outcomes (ORR by independent review committee, PFS, and OS) when comparing these cohorts; ORR in the cabozantinib/vandetanib-naïve cohort was 83%.[16]

LIBRETTO-121 is an ongoing, multi-cohort, phase I/II study which recruited patients aged 6 months to 21 years old with advanced, RET-altered solid tumours. The time on selpercatinib treatment ranged from 0.4 months to 40.8 months. At the January 2023 data cut-off, 14/27 patients with advanced RET-mutant MTC have been recruited. Among patients with measurable disease at baseline, the ORR in MTC patients was 83% (5/6).[17]

2.5. Indirect evidence to support clinical and cost-effectiveness comparisons

Due to imbalances in baseline characteristics (caused by the lack of randomisation within the control group) that could influence efficacy outcomes in the LIBRETTO-531 study, the submitting company conducted an unanchored matching adjusted indirect comparison (MAIC) to adjust patient baseline characteristics in all three treatment groups (selpercatinib, cabozantinib and vandetanib) to match the overall study population. The MAIC-adjusted population informed the PFS and OS inputs to the economic analysis.

As a proxy for BSC, the EXAM study[18] investigated cabozantinib versus placebo; the HRs for BSC versus cabozantinib (derived from the RET-mutant positive subgroup in the EXAM study) was applied to the OS and PFS data of patients in the cabozantinib comparison arm of the LIBRETTO-531 study.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Unanchored MAIC
Population	Patients aged ≥ 12 years with progressive, advanced, kinase inhibitor-naïve, RET-mutant MTC
Comparators	Cabozantinib or vandetanib
Studies included	LIBRETTO-531[13]
Outcomes	PFS, OS, TTD
Results	**Selpercatinib versus cabozantinib:** the results suggested that selpercatinib has superior efficacy against cabozantinib for PFS (unweighted and MAIC-weighted) and OS (unweighted only). **Selpercatinib versus vandetanib:** the results suggest that there no significant difference between these two treatments for PFS and OS, though they numerically favoured selpercatinib.

Abbreviations: BSC = best supportive care; MAIC = matching adjusted indirect comparison; PFS = progression-free survival; OS = overall survival; TTD = time-to-treatment discontinuation.

3. Summary of Safety Evidence

In the LIBRETTO-531 study at the May 2023 data cut-off, the median duration of treatment in the selpercatinib group was 65 weeks; in the control group this was 28 weeks for cabozantinib and 80 weeks for vandetanib. For selpercatinib (n=193) compared with cabozantinib (n=72) and vandetanib (n=25), there were fewer patients who had a dose reduction due to treatment-emergent adverse events (AEs) (39% versus 79% and 72%), and lower proportions of patients with AEs that led to dose interruptions (56% versus 82%, and 64%).[13]

At the May 2023 data cut-off, fewer patients discontinued therapy due to a treatment-related AE in the selpercatinib group (n=193) compared with the control group (n=97) combined (2.1% versus 23%); a much larger proportion of patients remained on study treatment in the selpercatinib group (91%) than the control group (41%). In the group of patients who crossed over from the control group to selpercatinib treatment (n=24), 19/24 patients remained on selpercatinib treatment.[13]

Any grade ≥ 3 treatment-emergent AE was reported by 53% (102/193) of patients in the selpercatinib group and 76% (74/97) in the control group, and these were considered treatment-related in 37% and 68% respectively. In the selpercatinib and control groups, patients reporting a serious treatment-related AE were 5.7% versus 18%. The most common grade ≥ 3 treatment-emergent AEs (occurring in ≥ 5% in either treatment group), in the selpercatinib and control groups, were: hypertension (19% versus 18%); ALT increased (10% versus 2.1%; fatigue (3.6% versus 5.2%); diarrhoea (3.1% versus 8.2%); nausea (1.0% versus 5.2%); decreased appetite (0.5% versus 5.2%); palmar–plantar erythrodysesthesia syndrome (0.0% versus 9.3%); hypocalcaemia (1.0% versus 7.2%); and mucosal inflammation (0.5% versus 13%).[13]

There are very limited data available in children or adolescents aged less than 18 years. The summary of product characteristics highlights that patients should be dosed according to body weight and open growth plates in adolescent patients should be monitored.[14]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Selpercatinib is the first medicine to be licensed specifically for RET-altered thyroid cancers.[1]
- In LIBRETTO-531, patients with RET-mutant MTC who received selpercatinib had statistically significant improvements in PFS and TFFS compared with a control group consisting of two relevant comparators for this indication.
- Patients treated with selpercatinib also showed a numerically favourable improvement in overall response rate compared with the control group.
- Selpercatinib appears to have more favourable tolerability than the control group; this is supported by the statistically significant improvement in the secondary outcome proportion of time with "high-side-effect bother" based on FACT-GP5. This is further supported by the lower rates of treatment discontinuation, dose reduction and dose interruptions seen with selpercatinib.

4.2. Key uncertainties

- In LIBRETTO-531, the physician's choice of treatment was limited to cabozantinib only at the halfway point of the study; this resulted in fewer patients receiving vandetanib in the control group. Pre-specified subgroup analysis comparing selpercatinib with vandetanib should be interpreted with caution given the limited number of patients.[13]
- Overall survival results from LIBRETTO-531 are immature. The OS assessment in the ITT population may be confounded by the crossover of patients (n=24) from the control group, the limited duration of follow-up (~15 months of OS follow-up), and the low number of OS events in both treatment groups; all leading to high censoring rates for OS in both treatment groups (≥ 90%).[13, 14]
- In LIBRETTO-531, there were some differences in baseline characteristics likely due to the lack of randomisation to cabozantinib or vandetanib in the control group. The time from diagnosis of metastatic disease to study enrolment was longer in the control group (61.6 months) than in the selpercatinib group (42.7 months). The submitting company highlighted that these differences may have influenced efficacy and safety outcomes and was the main rationale for conducting a MAIC to adjust patient baseline characteristics. The supportive studies (LIBRETTO-001 and LIBRETTO-121) are small, single-arm, open-label study prone to various biases and the lack of a control group hampers the interpretation of PFS and OS.[2] The relevant population for this submission is a small subset of patients who were naïve to cabozantinib/vandetanib.
- Clinical evidence in patients under 18 years of age is severely limited; only one patient in LIBRETTO-531 (aged 12 years old), and three patients in LIBRETTO-001 (aged 15, 16, and 17) were <18 years of age.[14]
- The method used to compare selpercatinib versus BSC was based on a cross-trial chain of evidence (relying on EXAM's comparator arm and applying it to a different study), these results must be interpreted with caution since they add a level of uncertainty that cannot be quantified.

4.3. MHRA conditional marketing authorisation specific obligations

Selpercatinib has a conditional marketing authorisation from the MHRA with specific obligations; however, none of these relate to RET-mutant MTC.[14] Therefore, it is unlikely that the specific obligations/ongoing studies will address the key uncertainties in the clinical evidence presented. Final analysis of the LIBRETTO-531 study is expected in 2026.[13]

4.4. Clinical expert input

Clinical experts consulted by SMC considered that selpercatinib fills an unmet need and is a therapeutic advancement due to being a more selective treatment in this therapeutic area.

4.5. Service implications

Selpercatinib is an oral treatment which is a convenient route of administration for both patients and the service. No service implications are anticipated with the introduction of this treatment.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from the Association for Multiple Endocrine Neoplasia Disorders (AMEND), which is a registered charity.
- AMEND has received 7% pharmaceutical company funding in the past two years, with none from the submitting company.
- Metastatic RET mutant MTC results in a range of serious symptoms that have a huge negative impact on quality of life including fatigue and diarrhoea, ultimately resulting in working and normal family life becoming virtually impossible.
- Multi-kinase inhibitors are not specifically targeted at RET and therefore often cause serious side effects that, unless well managed, may have a similar negative impact on quality of life. MTC patients are aware of selpercatinib and its reputation for fewer / less severe side effects and improved outcomes in those with RET mutation MTC.
- Patients feel that selpercatinib should be made the first line treatment in metastatic RET mutant medullary thyroid cancer, providing them with hope and more time to spend with their families, as well as to continue working and contributing to society.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company presented an economic case, summarised in table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	A lifetime horizon of 35 years with a weekly cycle length.
Population	Adults and adolescents 12 years and older with advanced RET-mutant MTC who require systematic therapy, who have not previously received systematic therapy.
Comparators	Cabozantinib, vandetanib, and BSC.

Model description	A three-state partitioned survival model was used, with health states of progression-free (PF), progressed disease (PD) and death. Patients enter the model in the progression-free health state. Patients may either remain progression-free, transition to post-progression, or transition directly to death. Patients in the post-progression state may subsequently transition to death.
Clinical data	The main source of clinical evidence for selpercatinib, cabozantinib and vandetanib was the LIBRETTO-531 study[13]. PFS, OS and time-to-treatment discontinuation (TTD) estimates were based on MAIC-adjusted data from this study due to the lack of randomisation in the comparator arm. For BSC, survival estimates were derived from an indirect treatment comparison, using hazard ratios (HRs) for cabozantinib vs placebo from the EXAM study.[19] AEs rates were taken directly from LIBRETTO-531.
Extrapolation	Parametric curves were fitted independently to each treatment arm for the MAIC-adjusted PFS, OS and TTD. The BSC arm was extrapolated by applying a HR, derived from the indirect treatment comparison (ITC) to the selected OS and PFS curves for cabozantinib. PFS for selpercatinib was extrapolated using the stratified Weibull model. For the comparators a Weibull model was selected to extrapolate PFS. OS for all treatments was extrapolated using the Weibull model. Selpercatinib TTD was set equivalent to PFS plus a certain number of weeks. The exact number of weeks was estimated based on the observed time between progression and treatment discontinuation for patients receiving selpercatinib in the LIBRETTO-531 study, however that value was classed as academic in confidence (AiC) by the submitting company and so cannot be reported here. TTD for cabozantinib and vandetanib were extrapolated using the stratified Weibull curve.
Quality of life	EQ-5D-5L data was collected from LIBRETTO-531 study and mapped to EQ-5D-3L using Hernandez Alava et al[20], and included an annual age adjustment factor derived from Ara and Brazier et al.[21] Utility values for the PF and PD states were classed as AiC by the submitting company. Grade ≥3 AEs were also included in the model and assumed to occur in the first cycle of the model, and the disutilities were sourced from NICE TA516 (cabozantinib).[22]
Costs and resource use	Medicine acquisition, administration, monitoring, AEs, end of life costs were included in the model, as well as health state and resource use costs including diagnostic testing. Patients receiving selpercatinib and vandetanib were eligible for two alternative doses. Within the first treatment cycle patients received doses between 160 mg to 80 mg twice daily for selpercatinib and between 300 mg and 100 mg for vandetanib. The distribution between alternative doses was on observed date from the LIBRETTO-531 study. In subsequent treatment cycles, to account for dose reductions, patients were assumed to receive doses between 160 mg to 40 mg twice daily for selpercatinib and between 300 mg and 100 mg for vandetanib, such that the mean dose intensity matched that observed in the LIBRETTO-531 study.
PAS	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.

6.2. Results

The base case analysis, inclusive of the PAS discount on selpercatinib, suggested that selpercatinib was dominant compared to vandetanib, meaning it was estimated as resulting in lower costs and better health outcomes for patients. The base case analysis, inclusive of the PAS discount on selpercatinib, suggested that selpercatinib generated higher costs than cabozantinib but also better health outcomes. The resulting incremental cost effectiveness ratio (ICER) was estimated as £15,553 per quality-adjusted life-year (QALY). The base case analysis, inclusive of the PAS discount on selpercatinib, suggested that selpercatinib generated higher costs than BSC, but also better health outcomes. The resulting ICER was estimated as £26,106 per QALY.

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

6.3. Sensitivity analyses

The company tested areas of uncertainty within the model through sensitivity and scenario analyses. A range of sensitivity and scenario analyses were considered, and descriptions of these key scenarios are provided in table 6.3 below. Results presented include the confidential PAS discount on selpercatinib.

Table 6.2: Scenario analysis results (selpercatinib PAS)

				ICER (£/QALY)		
	parameter	**Base case**	**scenario**	**vs cabozantinib**	**Vs vandetanib**	**Vs BSC**
	Base case	-	-	15,553	Dominant	26,106
1	Time horizon	35 years	5 years	17,889	Dominant	59,856
2	Crossover adjustment	No OS crossover adjustment	Adjustment for treatment switching and expert opinion	10,705	Dominant	17,409
3	PFS Extrapolation	Selpercatinib: stratified Weibull Cabozantinib: Weibull Vandetanib: Weibull	Selpercatinib: Stratified loglogistic	22,318	Dominant	31,866
4			Selpercatinib: exponential Cabozantinib: exponential Vandetanib: exponential	21,313	Dominant	31,016
5	OS extrapolation	Selpercatinib: Weibull Cabozantinib: Weibull Vandetanib: Weibull	Selpercatinib: Spline knot 1 Cabozantinib: Weibull Vandetanib: Weibull	21,855	Dominant	35,657
6			Selpercatinib: Weibull Cabozantinib: gamma Vandetanib: gamma	18,817	Dominant	n/a
7	TTD	Selpercatinib: PFS + additional weeks Cabozantinib: Stratified Weibull Vandetanib: stratified Weibull	Set all treatments to PFS curve	10,950	Dominant	25,676
8	Utilities	EQ-5D data from LIBRETTO-531	Fordham et al vignette study	15,323	Dominant	25,279
9	Combined extrapolations		4 and 5	27,664	Dominant	40,218

Abbreviations: BSC = best supportive care; Incr. = Incremental; ICER =incremental cost-effectiveness ratio; PFS = progression-free survival; TTD = Time-to-treatment discontinuation; QALY = quality-adjusted life year; RDI =Relative dose intensity

6.4. Key strengths

- The use of a partitioned survival model was appropriate for the decision problem.
- The comparators included in the analysis were relevant and aligned with SMC clinical expert feedback.

- EQ-5D data were collected in LIBRETTO-531 study and was used in the economic model. The company conducted a systematic literature review to identify any relevant supplementary utility data.

6.5. Key uncertainties

- The follow-up from LIBRETTO-531 comparing selpercatinib to cabozantinib and vandetanib was immature. Immature data introduced uncertainty into the long-term survival estimates. The submission also relied on MAIC-adjusted estimates due to lack of randomisation in the blended comparator arm. This introduced uncertainty into the model due to the immaturity of the data and the inherent limitations associated with MAICs.
- LIBRETTO-531 study did not provide direct evidence for selpercatinib versus BSC. The submitting company estimated BSC outcomes by applying HRs from the EXAM study (cabozantinib versus placebo) to cabozantinib's survival rate in the LIBETTO-531 study. While the absence of direct evidence for BSC introduced some uncertainty, this was partially mitigated by the fact that BSC was not the primary comparator for this submission and patient population.
- The company explored both stratified and unstratified parametric models, as well as spline knot models. Although the use of stratified models was considered unusual, the approach was ultimately considered reasonable. Scenario analyses were available for alternative plausible curves across the parameters of PFS, OS and TTD (see Scenarios 3 to 7, table 6.3), which demonstrated that the choice of curves had a relatively modest impact on economic results.
- The approach to TTD differed between treatment arms, with the comparator arm extrapolated using a stratified Weibull curve while selpercatinib is assumed to discontinue treatment at PFS plus a certain number of weeks. The company states that extrapolating TTD for selpercatinib led to clinically implausible results. No scenario analysis was provided by the submitting company to test the impact of the selpercatinib arm assumption, but the impacts on the economic results was expected to be small.
- The dose distributions for selpercatinib, cabozantinib and vandetanib were sourced from the LIBRETTO-531 study. However, from treatment cycle two onwards, the proportion of patients receiving the full dose of selpercatinib (160 mg twice daily) was noticeably reduced compared to cycle one, and the robustness of these assumptions was not tested for in the cost-effectiveness analysis. The submitting company declined to provide scenarios assuming no dose reductions for all treatments, but the impacts on the economic results was expected to be small.

7. Conclusion

After considering all the available evidence, the Committee accepted selpercatinib for restricted use in NHSScotland.

8. Guidelines and Protocols

The European Society for Medical Oncology (ESMO) published the guideline: ESMO Clinical Practice Guideline update on the use of systemic therapy in advanced thyroid cancer. This was first published in 2019 and last updated in 2022.[10]

The National Institute of Health and Care Excellence (NICE) published Thyroid cancer: assessment and management guidelines in 2022.[23]

9. Additional Information

9.1. Product availability date

February 2023.

Table 9.1 List price of medicine under review

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

Costs from BNF online on 05 March 2025. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

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.**

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This assessment is based on data submitted by the applicant company up to and including **10 April 2025.**

**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:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

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.