Selpercatinib (Retsevmo®) as monotherapy for the treatment of adults and adolescents 12 years and older with advanced RET mutant medullary thyroid cancer (MTC)

General information

Drug description [1]	Indication [2]
Selpercatinib (Retsevmo®, Retevmo®[1], formerly known as LOXO-292) is an ATP-competitive, highly selective, small-molecule RET kinase inhibitor.	Selpercatinib (Retsevmo®) as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET mutant MTC.

Current treatment [3]

- Currently NICE recommends the following treatment options for patients with differentiated thyroid and MTC:
  - Lenvatinib and sorafenib for treating progressive, locally advanced or metastatic differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine, only if
    - they have not had a tyrosine kinase inhibitor before or
    - they have had to stop taking a tyrosine kinase inhibitor within 3 months of starting it because of toxicity (specifically, toxicity that cannot be managed by dose delay or dose modification).
  - Cabozantinib for treating progressive MTC in adults with unresectable, locally advanced or metastatic disease.
- Treatment options for patients with advanced or metastatic MTC that have progressed following first-line systemic therapy are limited and consists of supportive or palliative care.

Regulatory status

EMA [2]	FDA [4]
Approval status for this indication: On 21 July 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Retsevmo®. The CHMP adopted an extension of indication: ❖ Retsevmo® as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET mutant MTC. UPDATE 02/2023: Indication approved **Other indications**: Retsevmo® as monotherapy is indicated for the treatment of adults with: ❖ advanced RET fusion positive non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor. ❖ advanced RET fusion positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib. ✓ **Medicine under additional monitoring** ✓ **Medicine received a conditional marketing authorisation[2]**	**Approval status for this indication**: not approved **Other indications**: Retevmo® is indicated for the treatment of: ❖ Adult patients with locally advanced or metastatic NSCLC with a RET gene fusion, as detected by an FDA-approved test. ❖ Adult and paediatric patients 12 years of age and older with advanced or metastatic MTC with a RET mutation, as detected by an FDA-approved test, who require systemic therapy (this indication is approved under accelerated approval based on ORR and DOR). ❖ Adult and paediatric patients 12 years of age and older with advanced or metastatic thyroid cancer with a RET gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate) (this indication is approved under accelerated approval based on ORR and DOR). ❖ Adult patients with locally advanced or metastatic solid tumours with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options (this indication is approved under accelerated approval based on ORR and DOR).

Costs

56 Retsevmo® hard capsules 40 mg = € 2,524.02 (ex-factory price) [5].

Special warnings and precautions for use [6]

- **Increased alanine aminotransferase (ALT)/ aspartate aminotransferase (AST)**

[1] Retevmo® is the brand name of selpercatinib in the U.S.

[2] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

- Grade ≥3 increased ALT and Grade ≥3 increased AST were reported in patients receiving selpercatinib.
- ALT and AST should be monitored prior to the start of selpercatinib therapy, every 2 weeks during the first 3 months of treatment, monthly for the next 3 months of treatment, and otherwise as clinically indicated.
- Based on the level of ALT or AST elevations, selpercatinib may require dose modification.

❖ **Hypertension**
- Hypertension was reported in patients receiving selpercatinib.
- Patient blood pressure should be controlled before starting selpercatinib treatment, monitored during selpercatinib treatment and treated as needed with standard anti-hypertensive therapy. Based on the level of increased blood pressure, selpercatinib may require dose modification. Selpercatinib should be discontinued permanently if medically significant hypertension cannot be controlled with antihypertensive therapy.

❖ **QT interval prolongation**
- QT interval prolongation was reported in patients receiving selpercatinib.
- Selpercatinib should be used with caution in patients with such conditions as congenital long QT syndrome or acquired long QT syndrome or other clinical conditions that predispose to arrhythmias.
- Patients should have a QTcF interval of ≤470 ms and serum electrolytes within normal range before starting selpercatinib treatment. Electrocardiograms and serum electrolytes should be monitored in all patients after 1 week of selpercatinib treatment, at least monthly for the first 6 months and otherwise, as clinically indicated, adjusting frequency based upon risk factors including diarrhoea, vomiting, and/or nausea.
- Hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiating selpercatinib and during treatment. Monitor the QT interval with ECGs more frequently in patients who require treatment with concomitant medications known to prolong the QT interval.
- Selpercatinib may require dose interruption or modification.

❖ **Strong CYP3A4 inducers**
- Concomitant use of strong CYP3A4 inducers should be avoided due to the risk of decreased efficacy of selpercatinib.

❖ **Women of childbearing potential/Contraception in females and males**
- Women of childbearing potential must use highly effective contraception during treatment and for at least one week after the last dose of selpercatinib. Men with female partners of childbearing potential should use effective contraception during treatment and for at least one week after the last dose of selpercatinib.

❖ **Fertility**
- Based on nonclinical safety findings, male and female fertility may be compromised by treatment with Retsevmo®. Both men and women should seek advice on fertility preservation before treatment.

❖ **Hypersensitivity**
- Hypersensitivity was reported in patients receiving selpercatinib with a majority of events observed in patients with NSCLC previously treated with anti-PD-1/PD-L1 immunotherapy.
- Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or elevated aminotransferases.
- Suspend selpercatinib if hypersensitivity occurs, and begin steroid treatment. Based on the grade of hypersensitivity reactions, selpercatinib may require dose modification.
- Steroids should be continued until patient reaches target dose and then tapered. Permanently discontinue selpercatinib for recurrent hypersensitivity.

❖ **Haemorrhages**
- Serious including fatal haemorrhagic events were reported in patients receiving selpercatinib.
- Permanently discontinue selpercatinib in patients with severe or life-threatening haemorrhage.

❖ **Tumour lysis syndrome (TLS)**
- Cases of TLS have been observed in patients treated with selpercatinib. Risk factors for TLS include high tumour burden, pre-existing chronic renal insufficiency, oliguria, dehydration, hypotension, and acidic urine.
- These patients should be monitored closely and treated as clinically indicated, and appropriate prophylaxis including hydration should be considered.

Study characteristics: Libretto-001 [1, 7-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)

LIBRETTO-001 NCT03157128	162[3]	**phase 1 dose-escalation portion**: Selpercatinib orally at doses ranging from 20 mg once daily to 240 mg twice daily **phase 2 portion:** Selpercatinib orally 160 mg twice daily	-	objective response (complete response or partial response)	**ongoing[4]**, open-label, multicenter, phase 1–2 trial	RET	Loxo Oncology and others	[1]

Efficacy (I vs. C)	**Safety** (I vs. C)
Currently, there is no final analysis data available; the primary analysis efficacy data of LIBRETTO-001was already presented in the Fact Sheet Nr. 36 available at https://eprints.aihta.at/1292/1/Oncology%20Fact%20Sheet%20Nr.36_Update.pdf. **<u>Patient-reported outcomes (interim results) [10]:</u>** ❖ Among the overall MTC population (n = 226), 88 (39%) and 124 (55%) patients comprised the V/C-naïve and previous V/C subgroups, respectively. ❖ Compliance was >85% for both instruments at each time point. ❖ Most patients maintained/improved in all HRQoL subscales throughout treatment. ❖ Improvements in diarrhoea were clinically meaningful in 43.5% of patients overall and in 36.8% and 51.3% of V/C-naïve and previous V/C subgroups, respectively. At baseline, 80.4% of all patients reported diarrhoea on mSTIDAT. ❖ The percentage of patients who reported diarrhoea was reduced to less than half of all patients (range: 33.3%–48.3%) after cycle 2. **UPDATE [6]:** **Vandetanib and cabozantinib naïve RET-mutant medullary thyroid cancer (IRC assessment, n=142, median duration of follow up: 20.3 months; data cutoff-date: 15 June 2021)** Objective response (CR + PR): 81.0% (95% CI, 73.6-87.1) Complete response: 15.5% Partial response: 65.5% Median duration of response: NE (95% CI, NE-NE)	Currently, there is no final analysis data available; the primary analysis safety data of LIBRETTO-001 was already presented in the Fact Sheet Nr. 36 available at https://eprints.aihta.at/1292/1/Oncology%20Fact%20Sheet%20Nr.36_Update.pdf

[3] There were three efficacy analysis cohorts (55 with RET-mutant medullary thyroid cancer previously treated with vandetanib, cabozantinib, or both; 88 with RET-mutant medullary thyroid cancer not previously treated with vandetanib or cabozantinib; and 19 with RET fusion–positive previously treated thyroid cancer).
[4] The LIBRETTO-001 trial is currently ongoing; estimated study completion date is 11/2023.

12 months DOR rate: 91.9% (95% CI, 85.0-95.7) 24 months DOR rate: 83.7% (95% CI, 73.0-90.4) **Previously treated RET-mutant medullary thyroid cancer (IRC assessment, n=151, median duration of follow-up: 22.93 months; data cut-off date: 15 June 2021** Objective response (CR + PR): 73.5% (95% CI, 65.7-80.4) Complete response: 9.3% Partial response: 64.2% Median duration of response: NE (95% CI, 27.2-NE) 12 months DOR rate: 82.8% (95% CI, 74.1-88.8) 24 months DOR rate: 64.5% (95% CI, 52.9-73.9)	

ESMO-MCBS version 1.1 [11]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	3	-	ORR: 73.5%	65.7-80.4	ORR (PR+CR) ≥ 60%	3	-	-	-	3

Due to the low level of evidence (single-arm study design) the adapted scale was not applied.

Risk of bias - study level (case series) [12]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	partial	yes	yes	yes	no
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	unclear	yes	yes	unclear	yes

Overall risk of bias: moderate

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Abbreviations: AE=adverse event, AJ=adjustment, ALT=alanine aminotransferase, AST=aspartate aminotransferase, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HR=hazard ratio, HRQoL=health-related quality of life, I=intervention, Int.=intention, MG=median gain, MTC=medullary thyroid cancer, mSTIDAT=modified Systemic Therapy–Induced Diarrhea Assessment Tool, n=number of patients, NE=not estimable, NICE=National Institute for Health and Care Excellence, NSCLC=non small cell lung cancer, ORR=objective response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, QoL=quality of life, RET=rearranged during transfection, SAE=serious adverse event, ST=standard treatment, TLS=tumour lysis syndrome, V/C=vandetanib and/or cabozantinib

References:

1. Wirth LJ, Sherman E, Robinson B, Solomon B, et al. Efficacy of Selpercatinib in RET-Altered Thyroid Cancers. N Engl J Med 2020;383:825-35. [Available from: https://www.nejm.org/doi/full/10.1056/nejmoa2005651].

2. European Medicines Agency (EMA). Medicines. Retsevmo. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/retsevmo-1].
3. National Institute for Health Research (NIHR). Selpercatinib for advanced thyroid cancer with RET alterations. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/26736-TSID_10277-Selpercatinib-for-Advanced-Thyroid-Cancer-V2.0-DEC2019-NON-CONF.pdf].
4. U.S. Food and Drug Administration (FDA). Retevmo. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213246s002lbl.pdf].
5. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
6. European Medicines Agency (EMA). Retsevmo: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/retsevmo-epar-product-information_en.pdf].
7. Supplement to: Wirth LJ, Sherman E, Robinson B, et al. Efficacy of selpercatinib in RET-altered thyroid cancers. N Engl J Med 2020;383:825-35.
8. Protocol for: Wirth LJ, Sherman E, Robinson B, et al. Efficacy of selpercatinib in RET-altered thyroid cancers. N Engl J Med 2020;383:825-35.
9. U.S. National Library of Medicine, ClinicalTrials.gov. A Study of Selpercatinib (LOXO-292) in Participants With Advanced Solid Tumors, RET Fusion-Positive Solid Tumors, and Medullary Thyroid Cancer (LIBRETTO-001). [Available from: https://www.clinicaltrials.gov/ct2/show/NCT03157128].
10. Wirth LJ, Robinson B, Bon V, et al. Patient-Reported Outcomes with Selpercatinib Treatment Among Patients with RET-Mutant Medullary Thyroid Cancer in the Phase I/II LIBRETTO-001 Trial. The Oncologist, 2022, 27, 13–21.
11. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28: 2340–2366, 2017.
12. Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics; 2014. [Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about].