Date: 6 April 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

RETSEVMO

International non-proprietary name: selpercatinib

Pharmaceutical form: hard capsules

Dosage strengths: 40 mg, 80 mg

Route(s) of administration: oral

Marketing Authorisation Holder: Eli Lilly (Suisse) SA

Marketing Authorisation No.: 67862

Decision and Decision date: approved on 8 February 2021 (temporary authorisation in accordance with Art. 9a TPA)

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BID	twice daily
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DOR	Duration of Response
DTC	Differentiated thyroid carcinoma
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
IAS	Integrated analysis set
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MKI	Multikinase inhibitor
MTC	Medullary thyroid carcinoma
MTD	maximum tolerated dose
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
NSCLC	Non-small cell lung cancer
ORR	Objective Response Rate
OS	Overall Survival
PAS	Primary analysis set
PD	Pharmacodynamics
PFS	Progression-Free Survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
PTC	Papillary thyroid carcinoma
RAI	Radioactive iodine
RR-DTC	radioactive iodine-refractory differentiated thyroid cancer
RMP	Risk Management Plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAEs	Treatment emergent adverse events
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance selpercatinib of the medicinal product mentioned above.

Temporary authorisation for human medical products
The applicant requested a temporary authorisation in accordance with Art. 9a TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication

Retsevmo as monotherapy is indicated for the treatment of adults with:
- advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy and who have progressed following prior treatment
- advanced RET fusion-positive thyroid cancer who require systemic therapy and who have progressed following prior treatment

Retsevmo 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 and who have progressed following prior treatment.

RET testing:
The presence of a RET gene fusion (NSCLC and non-medullary thyroid cancer) or mutation (MTC) should be confirmed prior to initiation of treatment with Retsevmo.

2.2.2 Approved Indication (temporary authorisation in accordance with Art. 9a TPA.)

Retsevmo as monotherapy is indicated for the treatment of adults with
- metastatic RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy and have progressed following prior treatment *(*see "Clinical efficacy").
- advanced RET fusion-positive thyroid cancer who require systemic therapy and, have progressed following prior treatment including radioactive iodine (see "Clinical efficacy").

Retsevmo 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 and have progressed following prior treatment with tyrosine kinase inhibitors (see "Clinical efficacy").
The efficacy and safety of Retsevmo in patients with additional oncogenic driver mutations have not been evaluated (see "Warning and precautions").

2.2.3 Requested Dosage

The recommended dose of selpercatinib is 160 mg orally, twice daily.

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	20 May 2020
Formal control completed	20 May 2020
List of Questions (LoQ)	24 July 2020
Answers to LoQ	1 October 2020
Predecision	19 November 2020
Answers to Predecision	14 January 2021
Final Decision	8 February 2021
Decision	Approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical Context

RET is a receptor tyrosine kinase (RTK) and contributes to the maintenance of neural, neuroendocrine, haematopoietic and male germ cell tissues. Aberrantly activated RET can act as an oncogene in multiple malignancies.
RET rearrangements involve the 3'sequence of RET and the 5'sequence other partner genes. Clinical data suggest that these rearrangements occur in up to 10%-20% of papillary thyroid cancers, 2% of NSCLCs and in other solid tumours (colon < 1%, pancreatic cancer < 1% and spitzoid melanoma < 1%).[1]

RET fusion-positive NSCLC:

NSCLC accounts for 80% of lung cancers, and adenocarcinoma is the most common histological subtype. The anticipated 5-year survival for patients with clinical stage IIIB NSCLC is approximately 26% and less than 5% for patients who present with clinical stage IV disease. RET gene fusions have been identified in 1-2% of non-small cell lung cancers (NSCLC).[1] Patients with RET-driven NSCLC are currently treated with the current standard of care for second-line NSCLC (chemotherapies, immune checkpoint inhibitors) regardless of RET mutation.

RET-mutant Medullary Thyroid Carcinoma (MTC)
MTC is a rare thyroid tumour, accounting for approximately 3%-5% of all thyroid cancers. Most cases are are diagnosed at an advanced stage. The prognosis is unfavourable, with a 5-year survival rate of approximately 86% and a 10-year survival rate of 50-65%.[2]
Activating mutations in the RET gene are the main driver mutation in medullary thyroid cancer. Approximately 50% of sporadic forms carry a somatic RET mutation, and familial cases have an identifiable germline mutation in at least 90% of cases.[3]
Complete surgical resection is recommended as initial treatment. In cases of aggressive local disease, external beam radiotherapy is possible. In case of metastatic lesions and disease progression after initial therapy, systemic therapy should be initiated. For patients with MTC and distant metastases who are symptomatic or have progressive disease, tyrosine kinase inhibitors are treatments of choice. However, these treatments are associated with relevant toxicity, which represents a major limitation of these therapies

RET fusion-positive thyroid cancer
Papillary thyroid carcinoma (PTC) is the most common (~80%) malignancy of the thyroid gland. RET fusion-positive thyroid cancer consists of two forms: differentiated thyroid carcinoma (DTC) and poorly differentiated thyroid cancer. Differentiated thyroid carcinoma (DTC) includes the histologic subtypes of papillary, follicular and Hurthle cell carcinoma and can occur in the paediatric population. DTC accounts for 1.4% of all paediatric malignancies, and the most common form is papillary thyroid carcinoma. Approximately 5 – 20% of papillary thyroid carcinomas have RET rearrangements, more commonly detected in children than in adults. RET fusions are uncommon in thyroid cancer subtypes other than PTC.
Standard of care in patients with DTC is thyroidectomy or lobectomy and postoperative treatment with radioactive iodine (RAI) therapy for patients at high risk of persistent disease or disease recurrence after total thyroidectomy. However, 30% of patients have recurrence of disease. For patients with radioactive iodine-refractory differentiated thyroid cancer (RR-DTC), treatment options are limited. Two tyrosine kinase inhibitors are authorised in Switzerland for RR-DTC. However, these therapies are associated with significant risks such as hypertension and hand-foot syndrome.

[1] Subbiah et al. State-of-the-Art Strategies of Targeting RET-Dependent Cancers. J Clin Oncol 2020 Apr 10;38(11):1209-1221.
[2] Viola et al. Management of Medullary Thyroid Cancer. Endocrinol Metab Clin N Am 48 (2019) 285–301
[3] Thomas et al. Diagnosis and pathologic characteristics of medullary thyroid carcinoma—review of current guidelines. Current Oncology, Vol. 26, No. 5, October 2019

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4 Quality Aspects

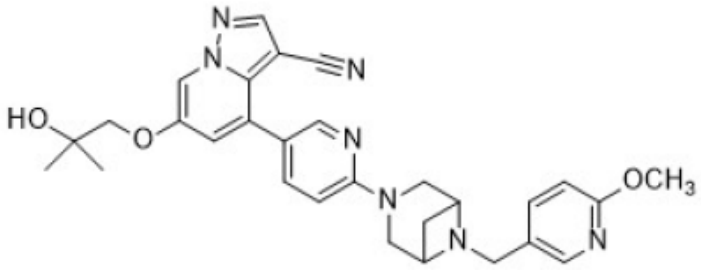
4.1 Drug Substance

Selpercatinib capsules contain the drug substance selpercatinib.

Chemical name: The IUPAC name for selpercatinib is 6-(2-hydroxy-2-methylpropoxy)-4-(6-(6-((6-methoxypyridin-3-yl)methyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile.

Molecular formula / molecular mass: The molecular formula of selpercatinib is $C_{29}H_{31}N_7O_3$ and the relative molecular mass is 525.61 g/mol.

Molecular structure: The chemical structure of selpercatinib is as follows:



Selpercatinib is a white to light yellow powder. It is manufactured as an anhydrous, crystalline form. Selpercatinib has a pH-dependent solubility profile. Solubility is greatest in acidic media and decreases as pH increases.

Selpercatinib is manufactured by a multi-step chemical synthesis. The synthesis has been adequately described, and the process is controlled with appropriate in-process controls and tests for isolated intermediates.

The specifications are in line with the recommendations of the relevant ICH guidelines and are considered appropriate in order to ensure a consistent quality of selpercatinib.

Appropriate stability data have been presented and justify the established retest period.

4.2 Drug Product

Selpercatinib capsules are available in 40 and 80 mg strengths, consisting of drug substance and excipients in hard gelatin capsules. The 40 mg is a size 2 gray opaque capsule with black “Lilly”, “3977” and “40 mg” script. The 80 mg product is a size 0 blue opaque capsule with black “Lilly”, “2980” and “80 mg” script. The product strengths are expressed in terms of the active component, selpercatinib.

Selpercatinib capsules, 40 mg and 80 mg, are composed of a blend of selpercatinib and standard excipients (microcrystalline cellulose and silicon dioxide) for solid dosage forms. Both capsules are produced from the same blend formulation.

For the control of selpercatinib capsules, adequate tests and acceptance criteria for release and at shelf-life are established. The specifications include relevant physicochemical characteristics, identification of the drug substance, as well as assay and purity tests.

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Selpercatinib capsules are packaged into white HDPE (high density polyethylene) bottles. These bottles are sealed with plastic closures containing an aluminium foil induction heat seal liner.

Drug product stability studies were conducted with primary stability batches of the 40 and 80 mg strengths (three batches of each strength). Based on these studies, an appropriate shelf-life was established for the capsules. The storage recommendation is “Do not store above 30°C”.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

Regarding the marketing authorisation application for Retsevmo, Swissmedic conducted an abridged evaluation, which was based on the FDA assessment report (May 8th 2020) provided by the applicant.
Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Retsevmo in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. Since the MTC indication includes patients who can have a prolonged life expectancy, carcinogenicity studies with selpercatinib will be conducted, and the reports were requested as a post-marketing commitment. The lack of safety margins is acceptable considering the proposed indication. The adverse effects in animals generally correlate with the findings in the clinical trials. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on a previous regulatory decision by FDA. The available assessment reports and respective product information from FDA were used as a basis for the clinical pharmacology evaluation

6.2 Dose Finding and Dose Recommendation

The requested dose of selpercatinib 160 mg BID for phase II was evaluated in the phase 1 dose escalation part of study LIBRETTO-001.

Selpercatinib causes concentration-dependent QTc prolongation. Therefore, the selpercatinib dosage is reduced to 120 mg BID in patients weighing <50 kg and to 80 mg BID in patients with severe hepatic impairment. In addition, selpercatinib dose reductions are necessary when co-administration with strong and moderate CYP3A4 inhibitors cannot be avoided. The reduction in dose in patients weighing < 50 kg is implemented to keep the maximum exposure below threshold levels likely to result in substantial QTc prolongation.

6.3 Efficacy

The applicant submitted one pivotal study, LIBRETTO-001 (LOXO-RET-17001). LIBRETTO-001 is a multicentre, open-label, Phase 1/2 study in patients with advanced solid tumours.
This study is ongoing and includes two parts: Phase 1 (dose escalation) and Phase 2 (dose expansion); the study is currently in Phase 2.

Phase 1 was a dose escalation part that included patients with advanced solid tumours with RET alteration/activation. The primary endpoint of phase I was to evaluate the maximum tolerated dose (MTD) and recommend a phase II dose (RP2D).

Phase 2 consisted of five cohorts including patients with three primary tumour types, which form the basis of this application: patients with RET fusion-positive NSCLC, patients with RET-mutant MTC, and patients with RET fusion-positive thyroid cancer.

For patients enrolled in phase II, evidence of RET gene alteration in tumour was required. Identification of a RET gene alteration was prospectively determined in local laboratories using next generation sequencing (NGS), polymerase chain reaction (PCR), or fluorescence in situ hybridisation (FISH). Patients with an oncogenic driver that could cause resistance to selpercatinib treatment were excluded (for details see information for healthcare professionals, “Warnings and precautions” section).

The major efficacy outcome for phase II was Objective Response Rate (ORR) as determined by a blinded independent review committee (IRC) according to RECIST v1.1 or RANO as appropriate for the tumour type. Relevant secondary endpoints were Duration of Response (DOR, IRC-assessed), Progression-Free Survival (PFS), and Overall Survival (OS).

No multiplicity control was foreseen for potential multiple interim analyses in these single-arm cohorts without a randomised control arm, and the statistical methodology in the statistical analysis plan (SAP) was designed for the different cohorts of phase 1 and 2, but not separately for the analysis sets (Primary analysis set: PAS, Integrated analysis set: IAS). Therefore, all analyses in this trial for PAS and IAS are of an exploratory nature.

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Overall, 746 patients were included. Of these, 653 patients (87.5%) received a starting dose of 160 mg selpercatinib BID and 712 patients (95.4%) at least one dose of 160 mg selpercatinib BID. Data for patients with previously treated NSCLC presented comparable demographics and baseline characteristics for the IAS of 160 mg BID and the IAS for all doses. Therefore, efficacy analyses were accepted irrespective of applied dose.

RET fusion-positive non-small cell lung cancer (NSCLC) – previously treated (cut-off March 2020)

Overall, 239 patients with RET fusion-positive NSCLC who were previously treated with platinum-based chemotherapy were included in LIBRETTO-001. Of these, 218 patients were followed for at least 6 months from the first dose of selpercatinib and were considered efficacy eligible. The primary data set (PAS) includes the first 105 patients (Phase I and Phase II patients), and the integrated analysis set (IAS) includes all patients previously treated with platinum-based chemotherapy.
The included patient population was representative for RET fusion-positive NSCLC. For the primary analysis population (PAS), the median age was 61 years, 41.0% of patients were male, and 71.4% were never smokers. Most common fusion partners were KIF5B and CCDC6. Most patients (98%) had metastatic disease at enrolment and 80% were diagnosed as stage 4. All patients had received prior systemic therapy with a median of 3 prior systemic regimens including anti PD1/PD-L1 therapy (55.2%). Further details of the included patient population are summarised in the information for healthcare professionals.

In the PAS population, the median duration of follow-up was 15.7 months. Overall, the 105 patients in the PAS were eligible for efficacy. The ORR was 63.5% and the median DOR was 17.5 months. In the IAS population, the median duration of follow-up was 12 months. Of the 239 patients included in the IAS set, 218 were eligible for efficacy. The ORR was 56.9% and the median DOR was 17.5 months.

RET-mutant medullary thyroid cancer (MTC) - previously treated (cut-off March 2020)

Overall, 153 patients who were previously treated with cabozantinib and/or vandetanib were enrolled in LIBRETTO-001. Of these, 143 patients were followed for at least 6 months from the first dose of selpercatinib and were considered efficacy eligible. The primary data set (PAS) includes the first 55 of 143 consecutively enrolled patients, while the IAS includes all patients previously treated with cabozantinib or vandetanib.

For the primary analysis population, the median age was 57 years, 1 patient was <18 years of age, 98.2% of patients had metastatic disease. The most common mutation was M918T, followed by extracellular cysteine mutations. All included patients had received prior systemic therapy with a median of 2 prior systemic regimens, and all patients had previous MKI therapy. Further details of the included patient population are summarised in the information for healthcare professionals.

In the PAS population, the median duration of follow-up was 17.5 months. The ORR was 69.1% and the median DOR was 17.5 months. In the IAS population, the median duration of follow-up was 10 months. The ORR was 69.2% and the median DOR was not estimable.

Efficacy in RET fusion-positive thyroid cancer (cut-off March 2020)

Of the RET fusion-positive thyroid cancer patients previously treated with systemic therapy and enrolled in LIBRETTO-001, 22 patients had the opportunity to be followed for at least 6 months from the first dose of selpercatinib and were considered efficacy eligible. The primary assessment of efficacy was based on the first 19 of the 22 consecutively enrolled patients. For the primary analysis population, the median age was 54 years, and 47.4% of patients were male. All included patients had metastatic disease. Patients had received a median of 4 prior systemic therapies (range: 1-7). All 22

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patients had received prior systemic treatment including therapy with MKI (78.9%), and 18 patients had also received radioactive iodine. The different histologies represented in the 19 patients included: papillary (n = 13), poorly differentiated (n = 3), anaplastic (n = 2), and Hurthle cell (n = 1). The most common fusion partner was CCDC6 (47.4%) followed by NCOA4 (31.6%).

In the PAS population, the median duration of follow-up was 20.3 months. The ORR was 78.9% and the median DOR was 18.4 months. In the population with all efficacy evaluable patients, the ORR was 77.3% and the median DOR was 18.4 months after a median duration of follow-up of 20.3 months.

6.4 Safety

Safety (cut-off March 2020)

The safety review included data from 746 patients who received at least one dose of selpercatinib, including 345 patients with RET fusion-positive NSCLC, 315 patients with RET-mutant MTC, 42 patients with RET fusion-positive thyroid cancer, 28 patients with RET fusion-positive cancers other than thyroid or lung, and 16 patients with other cancers.

The most common treatment emergent adverse events (TEAEs, ≥15%) were dry mouth, diarrhoea, hypertension, AST increased, ALT increased, fatigue, constipation, oedema peripheral, headache, nausea, blood creatinine increased, abdominal pain, rash, ECG QT prolonged, cough, vomiting and dyspnoea. TEAEs ≥ grade 3 occurred in 63%, most common events (≥5%) were hypertension, ALT increased and AST increased. Overall, 35.1% had treatment emergent serious adverse events; the most common SAE was pneumonia. Overall, 25 patients died due to a grade 5 TEAE. Grade 5 TEAEs were pneumonia (2), bronchitis (1), haemoptysis (1), hypoxia (1), sepsis (3), general health deterioration (1), respiratory failure (2), cerebrovascular accident (1), cardiac arrest (3), cardiac failure (1), cardio-respiratory arrest (2), cerebral haemorrhage (1), septic shock (1), brain herniation (1), multiple organ dysfunction syndrome (1), neoplasm progression (1), obstruction gastric (1), procedural haemorrhage (1).

There were some differences in the most common TEAEs reported for the different tumour types. However, the primary safety risks of selpercatinib, such as hepatotoxicity, hypertension, QT interval prolongation, haemorrhagic events and hypersensitivity, were observed throughout the safety pool regardless of treated tumour type.

Paediatric Patients

Limited data are available on the clinical experience with selpercatinib in paediatric patients. As of 16 December 2019, 3 patients <18 years old were enrolled in the LIBRETTO-001 study, all of whom had RET-mutant MTC. They were aged 15, 16, and 17 years at the time of study entry, two received a starting dose of 160 mg selpercatinib BID, and one patient received a starting dose of 80 mg BID. Further data are available from LIBRETTO-121 (5 patients, only safety data) and from single patient protocols. However, these additional data were limited because these patients had divergent dose levels, and the evaluated indications deviated from the current application.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

There are no approved therapies in Switzerland specifically for patients with RET-driven cancers such as RET fusion-positive NSCLC, RET fusion-positive thyroid cancer or RET-mutant MTC. Patients with RET-driven cancers are currently treated with the standard of care corresponding to their tumour type, regardless of RET mutation.

The efficacy provided with this submission demonstrated compelling ORR rates for RET fusion-positive NSCLC, RET-mutant MTC and RET fusion-positive thyroid cancer in second-line treatment.

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Due to the limited size of the efficacy database, including uncertainties due to the single-arm nature of the submitted study and the presently available efficacy data (including immature data for OS), a temporary authorisation was granted for selpercatinib.

Given the unmet medical need in paediatric patients with advanced or metastatic RET-mutant MTC, the biological similarity to adult patients, and preliminary evidence of safety and efficacy, a temporary authorisation was accepted for second-line treatment of patients with RET-mutant MTC aged 12 years and older.

Selpercatinib is associated with severe toxicities. Relevant risks are hepatotoxicity, hypertension, QT interval prolongation, haemorrhagic events, hypersensitivity, and impaired wound healing. These risks are adequately described in the information for healthcare professionals. However, further long-term safety data are needed. In particular, additional data are required to characterise the effect of selpercatinib on growth and development in paediatric patients.

In the context of the temporary authorisation in accordance with Art. 9a TPA, conditions to be fulfilled for an ordinary authorisation were defined. In order to confirm currently available results, updated efficacy and safety results of LIBRETTO-001 have to be submitted. Furthermore, additional efficacy and safety data of paediatric patients are expected from LIBRETTO-001, LIBRETTO-531, LIBRETTO-121 (NCT03899792). In addition, the phase III studies LIBRETTO-431 (RET Fusion-Positive NSCLC, NCT04194944) and LIBRETTO-531 (RET mutant MTC, NCT04211337) are currently running, and results are expected in October 2023 and February 2025.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Retsevmo was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.
Retsevmo is temporarily authorised – see "Properties/Effects" section.

RETSEVMO™

Composition

Active substances

Selpercatinib

Excipients

Microcrystalline cellulose, colloidal Silica

Retsevmo
40 mg Capsule Shell Composition
Gelatin, titanium dioxide (E171), black Iron Oxide (E172)

Retsevmo 80 mg Capsule Shell Composition
Gelatin, titanium dioxide (E171), Brilliant Blue FCF (E133)

Retsevmo Capsules Black Ink Composition
Shellac, propylene glycol, potassium hydroxide, *black* iron oxide *(E172)*

Pharmaceutical form and active substance quantity per unit

Hard capsule.

Retsevmo 40 mg hard capsules:
Each hard capsule contains 40 mg selpercatinib.
Gray opaque capsule, size 2, with ”Lilly”, “3977” and “40 mg” black printing on body of capsule.

Retsevmo 80 mg hard capsules:
Each hard capsule contains 80 mg selpercatinib.
Light blue opaque capsule, size 0, with ”Lilly” “2980” and “80 mg” black printing on body of capsule.

Indications/Uses

Retsevmo as monotherapy is indicated for the treatment of adults with

- metastatic RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy and have progressed following prior treatment *(see «clinical efficacy»)*.

- advanced RET fusion-positive thyroid cancer who require systemic therapy and, have progressed following prior treatment including radioactive iodine *(see «clinical efficacy»).*

Retsevmo 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 and have progressed following prior treatment with tyrosine kinase inhibitors (see “clinical efficacy”).

The efficacy and safety of Retsevmo in patients with additional oncogenic driver mutations have not been evaluated (see «Warning and precautions»).

Dosage/Administration

Initiation of treatment

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

The presence of a *RET* gene fusion (NSCLC and non-medullary thyroid cancer) or mutation (MTC) should be confirmed with a validated assay for RET-fusions and RET-mutations, prior to initiation of treatment with Retsevmo.

Usual dosage

The recommended dosage of Retsevmo based on body weight is:

- Less than 50 kg: 120 mg
- 50 kg or greater: 160 mg

Take Retsevmo orally twice daily (approximately every 12 hours) until disease progression or unacceptable toxicity.

Dose adjustment following undesirable effects/interactions

Management of some adverse reactions may require dose interruption and/or dose reduction. Retsevmo dose modifications are summarised in Table 1.

Table 1 Recommended Dose Modifications for Retsevmo for Adverse Reactions

Dose Reduction	Patients Weighing Less Than 50 kg	Patients Weighing 50 kg or Greater
First	80 mg orally twice daily	120 mg orally twice daily
Second	40 mg orally twice daily	80 mg orally twice daily
Third	40 mg orally once daily	40 mg orally twice daily

Permanently discontinue Retsevmo in patients unable to tolerate three dose reductions.

The recommended dosage modifications for adverse reactions are provided in Table 2.

Table 2. Recommended dosage in patients Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Hepatotoxicity *(see Warnings and Precautions)*	Grade 3 or Grade 4	• Withhold selpercatinib and monitor AST/ALT once weekly until resolution to Grade 1 or baseline. • Resume at reduced dose by 2 dose levels and monitor AST and ALT once weekly until 4 weeks after reaching dose taken prior to the onset of Grade 3 or 4 increased AST or ALT. • Increase dose by 1 dose level after a minimum of 2 weeks without recurrent increased ALT or AST and then increase to dose taken prior to the onset of Grade 3 or 4 increased AST or ALT after a minimum of 4 weeks without recurrence. • Permanently discontinue selpercatinib if Grade 3 or 4 ALT or AST increases recur despite dose modifications.
Hypertension *(see Warnings and Precautions)]*	Grade 3	• Withhold selpercatinib for Grade 3 hypertension that persists despite optimal antihypertensive therapy. • Resume at a reduced dose when hypertension is controlled.
	Grade 4	• Discontinue selpercatinib.
QT Interval (Prolongation *see Warnings and Precautions)*	Grade 3	• Withhold selpercatinib until recovery to baseline or Grade 0 or 1. • Resume at a reduced dose.
	Grade 4	• Discontinue selpercatinib.
Hemorrhagic Events *(see Warnings and Precautions)*	Grade 3 or Grade 4	• Withhold selpercatinib until recovery to baseline or Grade 0 or 1. • Discontinue selpercatinib for severe or life-threatening hemorrhagic events.
Hypersensitivity Reactions *(see Warnings and Precautions)*	All Grades	• Withhold selpercatinib until resolution of the event. Initiate corticosteroids. • Resume at a reduced dose by 3 dose levels while continuing corticosteroids. • Increase dose by 1 dose level each week until the dose taken prior to the onset of hypersensitivity is reached, then taper corticosteroids.
Other Adverse Reactions (*see*	Grade 3 or Grade 4	• Withhold selpercatinib until recovery to baseline or Grade 0 or 1. • Resume at a reduced dose.

Adverse Reaction	Severity	Dosage Modification
Adverse Reactions)		

Hypertension

Selpercatinib should be discontinued permanently if medically significant hypertension cannot be controlled with antihypertensive therapy (see “Warnings and precautions”).

CYP inhibitors

Avoid concomitant use of strong and moderate CYP3A inhibitors with selpercatinib. If concomitant use of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the selpercatinib dose as recommended in Table 3. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume selpercatinib at the dose taken prior to initiating the CYP3A inhibitor (see chapter *Interactions*).

Table 3. Recommended Dosage for Concomitant Use of Strong and Moderate CYP3A Inhibitors

	Recommended Retsevmo Dosage	
Current Retsevmo Dosage	**Moderate CYP3A Inhibitor**	**Strong CYP3A Inhibitor**
120 mg orally twice daily	80 mg orally twice daily	40 mg orally twice daily
160 mg orally twice daily	120 mg orally twice daily	80 mg orally twice daily

CYP inducers

Concomitant use of strong and moderate CYP inducers should be avoided (see “Interactions”).

Medicinal products with impact on gastric pH

Concomitant use of selpercatinib with proton pump inhibitors, H2 receptor antagaonists or antacids with local effect should be avoided. If however the concomitant use cannot be avoided, the following recommendations for administration have to be considered.

Proton pump inhibitors

Concomitant use of a proton pump inhibitor must be accompanied by a meal (see “Interactions”).

H_2 receptor antagonists

Retsevmo should be administered 2 hours before concomitant H_2 receptor antagonists (see “Interactions”).

Antacids with local effect

Selpercatinib must be taken 2 hours before or 2 hours after administraton of an antacid with local effect (see «Interactions»)

Patients with impaired hepatic function

In patients with mild to moderate hepatic impairment (total bilirubin ≤ ULN (upper limit of normal) with AST > ULN or total bilirubin > 1 to 3 x ULN, regardless of AST) a dose adjustment is not required. In patients with severe hepatic impairment [total bilirubin > 3 to 10 x ULN, regardless of AST) should receive a reduced dose of 80 mg twice daily (see «Pharmacokinetics»)

Reduce the recommended dosage of Retsevmo for patients with severe hepatic impairment as recommended in Table 4.

Table 4 Recommended Retsevmo Dosage for Severe Hepatic Impairment

Current Retsevmo Dosage	**Recommended Retsevmo Dosage**
120 mg orally twice daily	80 mg orally twice daily
160 mg orally twice daily	80 mg orally twice daily

Patients with impaired renal functionIn patients with mild, (estimated Glomerular Filtration Rate (eGFR) calculated based on Modification of Diet in Renal Disease (MDRD) equation ≥60 and <90 mL/min/1.73 m2), moderate (eGFR ≥30 and <60 mL/min/1.73 m2), or severe (eGFR ≥15 and <30 mL/min/1.73 m2) renal impairment (a dose adjustment is not required. There are no data in patients with end stage renal disease, or in patients on dialysis. (see «Pharmacokinetics»).

Elderly patients

No dose adjustment is required based on age (see “Pharmacokinetics”).

Children and adolescents

Retsevmo should not be used in children aged less than 12 years.

There is no data in children or adolescents with RET fusion-positive NSCLC or thyroid cancer.

In RET-mutant MTC, there are very limited data available in children or adolescents aged less than 18 years (see under “ Pharmacodynamic”, “Undesirable effects” and “Clinical efficacy”). Patients should be dosed according to body weight (see “Doseage Administration”).

Mode of administration

For oral use.
The capsule should be swallowed whole (patients should not open, crush, or chew the capsule before swallowing), and can be taken with or without food.
Patients should take the doses at approximately the same times every day. Do not take a missed dose unless it is more than 6 hours until next scheduled dose.
If a patient vomits or misses a dose of Retsevmo, the patient should be instructed to take the next dose at its scheduled time; an additional dose should not be taken.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in “Composition”.

Warnings and precautions

Increased ALT/AST
Grade ≥3 increased ALT and Grade ≥3 increased AST were reported in patients receiving selpercatinib (see "Undesirable effects").

Monitor ALT and AST prior to initiating selpercatinib , every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue Retsevmo based on the severity (see “Dosage/Administration”).

Hypertension
Hypertension was reported in patients receiving selpercatinib in clinical trials (see "Undesirable effects"). Patient blood pressure is to be controlled before starting selpercatinib treatment. Do not initiate selpercatinib in patients with uncontrolled blood pressure. Optimize blood pressure prior to initiating selpercatinib treatment. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust anti-hypertension therapy as appropriate. Withhold, reduce dose, or permanently discontinue Retsevmo based on the severity (see “posology and admistration”).

QT Interval Prolongation
QT interval prolongation was reported in patients receiving selpercatinib in clinical trials (see “Properties/Effects”). 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.

Selpercatinib has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction.

Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure.
Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating selpercatinib and during treatment.
Monitor the QT interval more frequently when selpercatinib is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withold and dose reduce or permanently discontinue selpercatinib based on severity (see “posology and admistration”).

Hemorrhagic Events
Serious including fatal hemorrhagic events can occur with selpercatinib. Permanently discontinue selpercatinib in patients with severe or life-threatening hemorrhage (see “posology and administration”).

Hypersensitivity
Hypersensitivity occurred in patients receiving selpercatinib. Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminitis.

If hypersensitivity occurs, withhold Retsevmo and begin corticosteroids at a dose of 1 mg/kg. Upon resolution of the event, resume selpercatinib at a reduced dose and increase the dose of selpercatinib by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity (see “posology and admistration”). Continue steroids until patient reaches target dose and then tamper. Permanently discontinue selpercatinib for recurrent hypersensitivity.

Risk of Impaired Wound Healing
Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, selpercatinib has the potential to adversely affect wound healing.

Withhold selpercatinib for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of selpercatinib after resolution of wound healing complications has not been established.

Fertility

Based on nonclinical safety findings, male and female fertility may be compromised by treatment with Retsevmo (see "*Preclinical data"*). Both men and women should seek advice on fertility preservation before treatment.

Concomitant oncogenic driver mutations

The efficacy and safety of selpercatinib in patients with known oncogenic driver alterations has not been established. The following driver mutations have been excluded from Libretto-001 study:

• NSCLC: EGFR or MET mutations, ALK or ROS rearrangements, activating mutation KRAS
• MTC: ALK or RAS rearrangements
• Thyroid carcinoma (except MTC): BRAF mutation or activating RAS mutation.

Interactions

Effect of selpercatinib on other medicinal products

Sensitive CYP2C8 substrates

Coadministration of selpercatinib with sensitive CYP2C8 substrates may increase plasma concentrations of the CYP2C8 substrates, this can result in an increase in adverse drug reactions, when already small increases in CYP2C8 substrate concentrations can result in an increase in adverse drug reactions. If the concomitant use cannot be avoided, the medicinal product information of the concomitantly administered medicinal product should be considered for possible dose adjustments.

Selpercatinib increased the C_{max} and AUC of repaglinide (a substrate of CYP2C8) by approximately 188% and 91% respectively. Therefore, coadministration with sensitive CYP2C8 substrates (e.g., enzalutamide, paclitaxel, repaglinide, torasemide, sorafenib, , buprenorphine, selexipag, dasabuvir and monteukast), should be avoided.

Sensitive CYP3A4 substrates

Coadministration of selpercatinib with sensitive CYP3A4 substrates may increase plasma concentrations of the CYP3A4 substrates, this can result in an increase in adverse drug reactions., when already small increases in CYP3A4 substrate concentrations can result in an increase in adverse drug reactions. If the concomitant use cannot be avoided, the medicinal product information of the concomitantly administered medicinal product should be considered for possible dose adjustments.

Selpercatinib increased C_{max} and AUC of midazolam (a CYP3A4 substrate) by approximately 39% and 54%, respectively. Therefore, concomitant use with sensitive CYP3A4 substrates, (e.g.,

alfentanil, avanafil, darifenacin, darunavir, midazolam, naloxegol, simvastatin, tipranavir, triazolam, vardenafil), should be avoided.

Effect of other medicinal products on selpercatinib

Sepercatinib metabolism is through CYP3A4. Therefore, medicinal products that can influence CYP3A4 enzyme activity may alter the pharmacokinetics of selpercatinib.

Strong CYP3A4 inhibitors
Agents that may increase selpercatinib plasma concentrations
Selpercatinib is metabolized predominantly by CYP3A4. Coadministration of selpercatinib with a strong CYP3A4 inhibitor may increase selpercatinib plasma concentrations (see "Dosage/Administration").
Itraconazole increased the C_{max} and AUC of selpercatinib by 30% and 130%, respectively, compared to selpercatinib given alone. If strong CYP3A and/or P-gp inhibitors, including, but not limited to, ketoconazole itraconazole, voriconazole, ritonavir, saquinavir, and posaconazole , have to be coadministered, the dose of selpercatinib should be reduced (see «Dosage/Administration»).

Strong CYP3A4 inducers

Agents that may decrease selpercatinib plasma concentrations

Coadministration of selpercatinib with a strong CYP3A4 inducer may decrease selpercatinib plasma concentrations (see «Dosage/Administration»).
Coadministration of rifampicin, a strong CYP3A4 inducer resulted in a decrease of approximately etwa 87% and 70% in selpercatinib C_{max} and AUC respectively, compared to selpercatinib alone, therefore the concomitant use of strong CYP3A4 inducers including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St. John's Wort (Hypericum perforatum), should be avoided.

Other interactions

Coadministration with medicinal products that affect gastric pH
Selpercatinib has pH-dependent solubility, with decreased solubility at higher pH that can result in a loss of efficacy.(see "Dosage/Administration").

No clinically significant differences in selpercatinib pharmacokinetics were observed when coadministered with multiple daily doses of ranitidine (H_2 receptor antagonist) given 2 hours after the selpercatinib dose.

Coadministration with medicinal products that are proton pump inhibitors
Coadministration with multiple daily doses of omeprazole (a proton pump inhibitor) decreased selpercatinib $AUC_{0\text{-}INF}$ and C_{max} when selpercatinib was administered fasting. Coadministration with multiple daily doses of omeprazole did not significantly change the selpercatinib $AUC_{0\text{-}INF}$ and C_{max} when Retsevmo was administered with food.
Under fasting conditions, coadministration of omeprazole led to a 69% to 88% lower overall and peak exposure to selpercatinib compared to selpercatinib administered alone.

Coadministration with medicinal products that are substrates of transporters
Selpercatinib inhibits the renal transporter multidrug and toxin extrusion protein 1 (MATE1). In vivo interactions of selpercatinib with clinically relevant substrates of MATE1, such as creatinine, may occur.
Selpercatinib is an in vitro inhibitor of P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP).

Selpercatinib is an in vitro substrate for P-gp and BCRP.
Selpercatinib is a substrate for P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) *in vitro*, however these transporters do not appear to limit the oral absorption of selpercatinib, as its oral bioavailability is 73% and its exposure was increased minimally by co-administration of the P-gp inhibitor rifampicin (increase of approximately 6.5% and 19% in selpercatinib $AUC_{0\text{-}24}$ and C_{max}, respectively).

Paediatric population
Interaction studies have only been performed in adults .

In vitro Data
CYP enzymes: Selpercatinib is not an inhibitor or inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant selpercatinib concentrations.

Transporter systems: Selpercatinib is an inhibitor of MATE1, P-gp, and BCRP, but not of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BSEP, and MATE2-K at clinically relevant Selpercatinib concentrations. Selpercatinib is a substrate of P-gp and BCRP, but not of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K.

Pregnancy, lactation

Contraception

Women of childbearing potential have to use a reliable contraception during treatment and for at least 2 weeks after the last dose of selpercatinib. Men with female partners of childbearing potential should use a reliable contraception during treatment and for at least 2 weeks after the last dose of selpercatinib.

Pregnancy

There are no available data from the use of selpercatinib in pregnant women. Studies in animals have shown reproductive toxicity (see “Preclinical data”). It should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus. Pregnant women should be informed about the risk to the foetus.

Lactation

It is unknown whether selpercatinib is excreted in human milk. A risk to newborns/infants cannot be excluded. Due to the potential risk for the breastfed child, breastfeeding should be discontinued during treatment with Retsevmo and for at least 2 weeks after the last dose.

Fertilität

The effect of Selpercatinib on human fertility is unknown. Based on results from nonclinical safety studies, Retsevmo may compromise male and female fertility (see «Preclinical data».

Effects on ability to drive and use machines

No studies have been conducted to determine the effects of selpercatinib on the ability to drive or use machines. In the absence of studies to determine the ability to drive and use machines while receiving selpercatinib patients should be advised to be cautious when driving or using machines in case they experience fatigue or dizziness during treatment with Retsevmo (see "Undesirable effects").

Undesirable effects

Summary of the safety profile

The most common adverse reactions (>20%) observed in selpercatinib-treated patients are dry mouth, diarrhoea, hypertension, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, fatigue and constipation.

The most common serious adverse drug reactions (ADRs) are hypertension (0.9%), increased aspartate aminotransferase (AST) (1.6%) and increased alanine aminotransferase (ALT) (1.6%).
Permanent discontinuation of Retsevmo for treatment emergent adverse events, regardless of attribution occurred in 6% of patients.
ADRs resulting in permanent discontinuation (2 or more patients) included increased ALT (0.4%), increased AST (0.3%), hypersensitivity (0.4%), and thrombocytopenia (0.3%).

The adverse drug reactions [b] reported in the 746 patients treated with Retsevmo are described below.

The adverse drug reactions are classified according to the MedRASystem Organ Class.
Frequency groups are defined by the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), and not known (cannot be estimated from available data).

Immune system disorders[a]
Common: Hypersensitivity[c] (4.3%, Grade 3: 1.7%)

Metabolism and nutrition disorders
Very Common: Decreased appetite (14.1%, Grade 3: 0.1%) Magnesium decreased [b] (25.6%, Grade 3 and 4: 0.5%)

Nervous system disorders
Very common: Headache[c] (24%, Grade 3: 1.5%,), Dizziness[c] (14.6%, Grade 3: 0.1%)

Cardiac disorders
Very common: Electrocardiogram QT prolonged (18.1%, Grade 3 and 4: 4%,)

Vascular disorders
Very common: Hypertension[c] (37.4 %, Grade 3 and 4: 19.4%)

Gastrointestinal disorders
Very common: Dry Mouth[c] (40.3%, Grade 3 and 4: 0%), Diarrhoea[c] (39%, Grade 3: 3.5%), Constipation (27.1%, Grade 3: 0.5%,), Nausea (23.5%, Grade 3: 0.7%), Abdominal pain[c] (25.5%, Grade 3: 1.9%,), Vomiting (16.2%, Grade 3: 0.9%)

Skin and subcutaneous tissue disorders

Very common: Rash[c] (28.7%, Grade 3: 0.7%)

General disorders and administration site conditions

Very common: Pyrexia (14.3%, Grade 3: 0.1%), Fatigue[c] (38.2%, Grade 3: 2.3%), Oedema[c] (38.7%, Grade 3: 0.5%),

Hepatobiliary disorders[b]

Very common: ALT Increased (49.5%, Grade 3 and 4: 10.6%), AST Increased (55%, Grade 3 and 4: 9%)

Renal disorders [b]

Very common: Creatinine Increased (39.1 %, Grade 3 and 4: 1.2%)

Blood and Lymphatic disorders [b]

Very common: lymphocyte count decreased (46.2%, Grade 3 and 4: 16.1%), and platelets decreased (34.5%, Grade 3 and 4: 3.0%)

[a] Hypersensitivity reactions were characterized by a maculopapular rash often preceded by a fever with associated arthralgias/myalgias during the patient's first cycle of treatment (typically between Days 7-21).
[b] Only patients with baseline and at least one post-baseline result are included.
[c] Consolidated terms:
-Diarrhea includes diarrhea, defecation urgency, frequent bowel movements, and anal incontinence
-Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain
- Fatigue includes fatigue, asthenia, malaise.
- Edema includes edema, edema peripheral, face edema, eye edema, eyelid edema, generalized edema, localized edema, lymph edema, scrotal edema, peripheral swelling, scrotal swelling, swelling, swelling face, eye swelling, peripheral swelling
- Includes rash, rash erythematous, rash macular, rash maculopapular, rash morbilliform, rash pruritic
- Headache includes headache, sinus eadache, tension headache
- Cough includes cough, productive cough
- Dyspnea includes dyspnea, dyspnea exertional, dyspnea at rest
- Hemorrhage includes epistaxis, hematuria, hemoptysis, contusion, rectal hemorrhage, vaginal hemorrhage, ecchymosis, hematochezia, petechiae, traumatic hematoma, anal hemorrhage, blood blister, blood urine present, cerebral hemorrhage, gastric hemorrhage, hemorrhage intracranial, spontaneous hematoma, abdominal wall hematoma, angina bullosa hemorrhagica, diverticulum intestinal hemorrhagic, eye hemorrhage, gastrointestinal hemorrhage, gingival bleeding, hematemesis, hemorrhagic anemia, intraabdominal hemorrhage, lower gastrointestinal hemorrhage, melena, mouth hemorrhage, occult blood positive, pelvic hematoma, periorbital hematoma, pharyngeal hemorrhage, pulmonary contusion, purpura, retroperitoneal hematoma, subarachnoid hemorrhage, subdural hemorrhage, upper gastrointestinal hemorrhage, vessel puncture site hematoma.

Description of selected undesirable effects

Transaminase elevations (AST / ALT increased)

Based on laboratory assessment, ALT and AST elevations were reported in 49.5% and 55% patients, respectively. Grade 3 or 4 ALT or AST elevations were reported in 10.6% and 9.1% patients respectively and serious undesirable effects in 2.6%.
The median time to first onset was: AST increase 4.1 weeks (range: 0.7, 104.6), ALT increase 4.1 weeks (range: 0.9, 79.3).
Dose modification is recommended for patients who develop Grade 3 or 4 ALT or AST increase (see "Dosage/Administration").

QT interval prolongation
Review of ECG data showed 6.2% of patients had >500 msec maximum post-baseline QTcF value, and 17.5% of patients had a >60 msec maximun increase from baseline in QTcF intervals.

There were no reports of Torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation, or ventricular flutter. No patient discontinued treatment due to QT prolongation.
Retsevmo may require dose interruption or modification (see "Dosage/Administration" and "Warnings and precautions").

Hypertension
Hypertension has been reported in 37.4% of patients, grade 3 in 19.3% and grade 4 in 0.1% of patients.In patients receiving selpercatinib, the median maximum increase from baseline systolic pressure was 29 mm Hg (range: -11, +96). Only 13% of patients retained their baseline grade during treatment, 45% had an increasing shift of 1 grade, 32.7% of 2 grades, and 8.3% of 3 grades. Overall, a total of 19.4% displayed treatment-emergent Grade 3 hypertension (defined as maximum systolic greater than 160 mm Hg)..
Only 1 patient permanently discontinued due to hypertension. Dose modification is recommended in patients who develop hypertension (see "Dosage/Administration"). Selpercatinib should be suspended temporarily for medically significant hypertension until controlled with antihypertensive therapy. Dosing should be resumed at the next lower dose if clinically indicated.
Increased Creatinine

In healthy subjects administered selpercatinib 160 mg orally twice daily, serum creatinine increased 18% after 10 days. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed *(see Properties/Effects).*

Additional information on special populations
Paediatric patients
There were 3 patients < 18 years (range 15-17) of age in LIBRETTO001. The safety of selpercatinib in children aged less than 18 years has not been established.

Animal Toxicity Data In 4-week general toxicology studies in rats: animals showed signs of physeal hypertrophy and tooth dysplasia at doses resulting in exposures ≥ approximately 3 times the human exposure at the 160 mg twice daily clinical dose. Minipigs also showed signs of minimal to marked increases in physeal thickness at the 15 mg/kg high dose level (approximately 0.3 times the human exposure at the 160 mg twice daily clinical dose). Rats in both the 4- and 13-week toxicology studies had malocclusion and tooth discoloration at the high dose levels (≥ 1.5 times the human exposure at the 160 mg twice daily clinical dose) that persisted during the recovery period.

Elderly

In patients receiving selpercatinib, 24.5% were ≥65-74 years of age, 8.2% were 75-84 years of age, and 1.07% ≥ 85 years of age. The safety profile in elderly patients (≥ 65 years) is consistent with that seen in younger patients (< 65 years).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Symptoms of overdose have not been established. In the event of suspected overdose, supportive care should be provided.

Properties/Effects

ATC code

not yet assigned

Mechanism of action

Selpercatinib is a small molecule inhibitor of the rearranged during transfection (*RET*) receptor tyrosine kinase. Selpercatinib inhibited wild type RET and multiple mutated RET isoforms as well as VEGFR1 and VEGFR3 with IC50 values ranging from 0.92 nM to 67.8 nM. In other enzyme assays, selpercatinib also inhibited FGFR 1, 2, and 3 at higher concentrations that were still clinically achievable. Selpercatinib was 250 times more selective for RET than for 98% of ~300 kinases, including VEGFR2, tested in preclinical studies. In cellular assays, selpercatinib inhibited RET at

approximately 60 fold lower concentrations than FGFR1 and 2 and approximately 8 fold lower concentration than VEGFR3.
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 tumor cell lines. In in vitro and in vivo tumor models, selpercatinib demonstrated anti tumor activity in cells harboring constitutive activation of RET protein resulting from gene fusions and mutations, including CCDC6 RET, KIF5B RET, RET V804M, and RET M918T. In addition, selpercatinib showed anti-tumor activity in mice intracranially implanted with a patient-derived RET fusion positive tumor.

Pharmacodynamics

Cardiac Electrophysiology
In a thorough QT study with positive control in 32 healthy subjects an exposure-response analysis indicated that supra therapeutic concentrations, could lead to an increase in QTc > 20 ms.
In patients receiving selpercatinib, QT interval prolongation was reported. Therefore, dose interruption or modification may be required in patients (*see "posology and warning and precations").*

Clinical efficacy

The efficacy of Retsevmo was evaluated in adult patients with advanced RET fusion-positive NSCLC, RET-mutant MTC and RET fusion-positive thyroid cancer patients enrolled in a phase 1/2, multicenter, open-label, single-arm clinical trial: Study LIBRETTO-001. Patients in both the phase 1 and phase 2 portions of the study had progressed on or were intolerant to standard therapy, or no standard therapy existed.
Patients in the phase 2 portion of the study received Retsevmo 160 mg orally twice daily until unacceptable toxicity or disease progression. Identification of a RET gene alteration was prospectively determined in local laboratories using next generation sequencing (NGS), polymerase chain reaction (PCR), or fluorescence in situ hybridization (FISH). The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as determined by a blinded independent review committee (BIRC) according to RECIST v1.1.

RET fusion-positive Non-Small Cell Lung Cancer – Previously treated

Of the *RET* fusion--positive NSCLC patients previously treated with platinum-based chemotherapy and enrolled in LIBRETTO-001, 218 patients had the opportunity to be followed for at least 6 months

and were considered efficacy eligible. The primary assessment of efficacy for *RET* fusion-positive NSCLC was based on the first 105 of the 218 consecutively enrolled patients. Patients enrolled into LIBRETTO-001 had advanced NSCLC with a *RET* gene fusion. The majority of the patients had nonsquamous NSCLC, and one patient had squamous NSCLC. For the primary analysis population the median age was 61 years (range 23 years to 81 years) 41.0% of patients were male. 52.4% of patients were white while 38.1% were Asian, 4.8% were Black and 3.8% Hispanic/Latino. ECOG performance status was reported as 0-1 (98.1%) or 2 (1.9%). 98.1% of patients had metastatic disease. 100% (n=105) of patients received prior systemic therapy with a median of 3 prior systemic regimens and 56.2% (n = 59) received 3 or more prior systemic regimens. Prior treatments included anti PD1/PDL1 therapy (55.2%), multikinase inhibitor (MKI) (47.6%) and taxanes (35.2%). 49.2% had other systemic therapy. The most common fusion partner was KIF5B (56.2%), followed by CCDC6 (22.9%) and then NCOA4 (1.9%).
In the primary analysis set with 105 previously treated RET fusion-positive NSCLC patients, the objective response rate (ORR) was 63.8% (95% CI: 53.9-73) and the median duration of response was 17.5 months (95% CI: 12-not estimable(NE)) with a median follow-up of 15.67 months. In the efficacy eligible patient population (n=218), the ORR was 56.9% (95% CI:50.0-63.6) and the median duration of response was 17.5 months (95% CI:12.5-NE) with a median follow-up of 11.9 months.

RET fusion-positive thyroid cancer-Previously treated

Of the *RET* fusion-positive thyroid cancer patients, enrolled in LIBRETTO-001, 22 patients had the opportunity to be followed for at least 6 months and were considered efficacy eligible. All 22 patients received prior systemic treatment and 18 patients also received radioactive iodine treatment.

The primary assessment of efficacy was based on the first 19 of the 22 consecutively enrolled patients. Within then included 19 pretreated patients of the primary analysis set, the following histologies where observed: papillary (n = 13), poorly differentiated (n = 3), anaplastic (n = 2), and Hurthle cell (n = 1). The median age was 54 years (range 20 to 88 years). 51.9% of patients were male. 74.1% of patients were white while 7.4% were Asian, 3.7% were Black and 11.1% were Hispanic/Latino. ECOG performance status was reported as 0-1 (88.9%) or 2 (11%). 100% of patients had metastatic disease. Of the 27 patients with RET fusion-positive thyroid cancer, 19 patient of primary analysis set were previously treated with systemic therapy.
Patients had received a median of 4 prior systemic therapies (range: 1-7). Prior therapies included radioactive iodine (84.2%), MKI (78.9%) and 42.1% had other systemic therapy.

In the primary analysis set with 19 previously treated RET fusion-positive thyroid cancer patients, the objective response rate was 78.9% (95% CI: 54.4, 93.9) and the median duration of response was

18.4 months (95% CI: 7.6-NE) with a median follow-up of 20.27 months. In the efficacy eligible patient population (n=22), the ORR was 77.3% and the median duration of response was 18.4 months (95% CI:10.1-NE) with a median follow-up of 20.27 months.

RET-mutant Medullary Thyroid Cancer-Previously treated

Of the RET-mutant MTC patients previously treated with cabozantinib and/or vandetanib and enrolled in LIBRETTO-001, 143 patients had the opportunity to be followed for at least 6 months and were considered efficacy eligible. The primary assessment of efficacy for *RET*-mutant MTC was based on the first 55 of 143 consecutively enrolled patients. For the primary analysis population, the median age was 57 years (range 17 years to 84 years); 1 patient (1.3%) was <18 years of age. 65.6% of patients were male. 89.1% of patients were white while 0% were Asian, 1.8% were Black and 7.3% were Hispanic/Latino. ECOG performance status was reported as 0-1 (95.0%) or 2 (5%). 98.2% of patients had metastatic disease. 100% (n = 55) of patients received prior systemic therapy with a median of 2 prior systemic regimens and 32.7% (n = 18) received 3 or more prior systemic regimens. The most common mutation was M918T (60%), followed by extracellular cysteine mutations (12.7%).

In the primary analysis set with 55 previously treated RET mutant MTC patients, the objective response rate was 69.1% (95% CI: 55.2-80.9) and the median duration of response was not estimable (95% CI: 19.1-NE) with a median follow-up of 17.45 months. In the efficacy eligible patient population (n=143), the ORR was 69.2% (95% CI:61.0-76.7) and the median duration of response was not estimable (95% CI:19.1-NE) with a median follow-up of 10.05 months.
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Temporary authorisation

The medicinal product Retsevmo has been granted temporary authorisation as the clinical data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be transformed into an ordinary authorisation.

Pharmacokinetics

The pharmacokinetics of selpercatinib were evaluated in patients with locally advanced or metastatic solid tumors administered 160 mg twice daily unless otherwise specified. Steady-state selpercatinib AUC and Cmax increased in a dose proportional manner over the dose range of 20 mg once daily to 240 mg twice daily.

Steady-state was reached by approximately 7 days and the median accumulation ratio after administration of 160 mg twice daily was 3.4-fold. Mean steady-state selpercatinib [coefficient of variation (CV%)] Cmax was 2,980 (53%) ng/mL and AUC0 24h was 51,600 (58%) ng*h/mL.

In vitro studies indicate that selpercatinib does not inhibit or induce CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations.

In vitro studies indicate that selpercatinib inhibits MATE1, P-gp, and BCRP, but does not inhibit OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BSEP, and MATE2 K at clinically relevant concentrations. Selpercatinib may increase serum creatinine by decreasing renal tubular secretion of creatinine via inhibition of MATE1.

Absorption

After an oral dose of 160 mg, Retsevmo was rapidly absorbed, with T_{max} of approximately 2 hours. Geometric mean absolute oral bioavailability was 73% (range: 60-82%).

Effect of food

Compared to selpercatinib AUC and C_{max} in the fasted state, selpercatinib AUC was increased by 9% and C_{max} was reduced by 14% after oral administration of a single 160 mg dose to healthy subjects taken with a high-fat meal.
These changes were not considered to be clinically relevant. Therefore, selpercatinib can be taken with or without food.

Distribution

Selpercatinib mean (CV%) volume of distribution (V_{ss}/F) is 191 (69%) L following oral administration of selpercatinib in adult patients. Selpercatinib is 96% bound to human plasma proteins in vitro and it’s binding is independent of concentration. The blood-to-plasma concentration ratio is 0.7.

Metabolism

Selpercatinib is metabolized predominantly by CYP3A4. Following oral administration of a single [^{14}C] radiolabeled 160 mg dose of selpercatinib to healthy subjects, unchanged selpercatinib constituted 86% of the measured radioactive components in plasma.

Elimination

The mean (CV%) clearance (CL/F) of selpercatinib is 6.0 (49%) L/h and the half-life is 22 hours following oral administration of selpercatinib in adult patients. Following oral administration of a single [^{14}C] radiolabeled 160 mg dose of selpercatinib to healthy subjects, 69% (14% unchanged) of the administered radioactivity was recovered in faeces and 24% (11.5% unchanged) was recovered in urine.

Kinetics in specific patient groups

Age, gender and body weight

Age (range: 15 years to 90 years) and gender had no clinically meaningful effect on the pharmacokinetics of Retsevmo.

Hepatic impairment

The selpercatinib AUC0-INF increased by 7%, 32%, and 77% in subjects with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST), moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST), and severe (total bilirubin greater than 3 to 10 times ULN and any AST) hepatic impairment, respectively, compared to subjects with normal hepatic function.
There is limited clinical data on the safety of selpercatinib in patients with severe hepatic impairment. Therefore dose modification is recommended for patients with severe hepatic impairment (see "section *Posology and method of administration"*).

Renal impairment

In a clinical pharmacology study using single dose selpercatinib 160 mg, exposure (AUC) was unchanged in subjects with mild, moderate, or severe renal impairment. End stage renal disease and dialysis patients have not been studied.

Paediatric population
Based on limited pharmacokinetic data, the Cmax and AUC was similar in adolescent patients, 12-18 years of age, and in adults.

Preclinical data

Safety pharmacology / toxcicity after repeated dose

Repeat-dose studies were conducted in rats and minipigs to characterize toxicity. Target organs of toxicity common to the rat and minipig were hematopoietic system, lymphoid tissues, tongue, pancreas, epiphyseal growth plate, and male reproductive tissues. In general, toxicities in these

organs were reversible; the exception was testicular toxicity. Reversible toxicity was observed in the ovaries and gastrointestinal tract in minipigs only; at high doses, gastrointestinal toxicity caused morbidity at exposures in minipigs that were generally lower than exposures determined in humans at the recommended dose. In one minipig study, females exhibited a slight, reversible increase in QTc prolongation of approximately 12% compared to controls and 7 % compared to pre-dose values. Target organs of toxicity observed only in rats were incisor tooth, liver, vagina, lungs, Brunner's gland, and multi-tissue mineralization associated with hyperphosphatemia. These toxicities were reversible. These toxicities only occurring in these organs in rats were reversible.

Genotoxicity

Selpercatinib was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay, with or without metabolic activation, or clastogenic in the in vitro micronucleus assay in human peripheral lymphocytes, with or without metabolic activiation. Selpercatinib was positive at high doses in the in vivo micronucleus assay in rat at approximately 11-fold above the human Cmax at the recommended dose of 160 mg twice daily.
In an in vivo micronucleus assay in rats, selpercatinib was positive at concentrations >7 times the Cmax at the human dose of 160 mg twice daily. In an in vitro micronucleus assay in human peripheral blood lymphocytes, an equivocal response was observed at a concentration approximately 485 times the Cmax at the human dose.

Carcinogenicity

Long-term studies to assess the carcinogenic potential of selpercatinib have not been performed.

Reproductive toxicity

In an embryo-foetal development study, daily oral administration of selpercatinib at doses greater than or equal to 100 mg/kg [approximately 3.6 times the human geometric mean exposure based on the area under the curve (AUC) at the clinical dose of 160 mg twice daily] to pregnant rats during organogenesis resulted in 100% post-implantation loss. At the dose of 50 mg/kg [approximately 1.5 times the human geometric mean exposure based on the AUC at the clinical dose of 160 mg twice daily], 6 of 8 females had 100% early resorptions; the remaining 2 females had primarily early resorptions and only 3 viable foetuses across the 2 litters. The 3 viable foetuses had lower foetal body weight and 2 foetuses in 1 litter had a short tail and the single foetus in the other litter had a small snout and localized foetal edema of the neck and thorax.

Results of studies conducted in rats and minipigs suggest that selpercatinib can impair fertility in males and females.

In a fertility study in male rats, there were no effects of selpercatinib on mating or fertility. However, at all doses, germ cell depletion and spermatid retention in the testes and increased cellular debris in the epididymis were observed dose-dependently. These effects were associated with reduced organ weights, reduced sperm motility, and an increase in the number of abnormal sperm at the highest dose, at which AUC-based exposure was approximately 2.3 times the clinical exposure at the recommended human dose. Microscopic findings in the fertility study in male rats were consistent with effects in repeat dose studies in rats and minipigs, in which dose-dependent, non-reversible testicular degeneration was associated with reduced luminal sperm in the epididymis at AUC-based exposure levels 0.1 to 0.4 times the clinical exposure at the recommended human dose.

In a fertility and early embryonic study in female rats, there were no effects of selpercatinib on mating or fertility. However, at the high dose only, a reduction in the number of estrous cycles with an increase in the pre-coital interval was observed, and there was an increase in the number of dead embryos, increased postimplantation loss, and a reduction in the number of live embryos. These effects were observed at AUC-based exposure levels approximately equal to clinical exposure at the recommended human dose. In repeat-dose studies in female rats, reversible vaginal mucification with individual cell cornification and altered estrous cycles was noted at clinically relevant AUC-based exposure levels. In female minipigs, decreased corpora lutea and/or corpora luteal cysts were observed at AUC-based exposure levels 0.07 to 0.3 times the clinical exposure at the recommended human dose.

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

Do not store above 30°C.
Keep the container in the outer carton in order to protect the contents from moisture.Keep out of the reach of children.

Authorisation number

67’862 (Swissmedic).

Packs

Retsevmo 40 mg: 60 hard capsules (A)

Retsevmo 80 mg: 60 and 120 hard capsules (A)

Not all pack sizes may be marketed.

Marketing authorisation holder

Eli Lilly (Suisse) SA, 1214 Vernier/GE.

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