

レットヴィモカプセル 40mg

レットヴィモカプセル 80mg

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1.5 起原又は発見の経緯及び開発の経緯

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目次

1.5 起原又は発見の経緯及び開発の経緯.....	1
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1.5 起原又は発見の経緯及び開発の経緯

セルペルカチニブは、RETのATP結合部位を競合的に阻害するよう設計された低分子であり、RETに対して選択性の高い阻害剤である。RET融合遺伝子陽性の固形がん、RET遺伝子変異陽性の甲状腺髄様癌、及びその他のRET活性化腫瘍を含む進行性の固形がんを対象とした国際共同第I/II相試験であるLOXO-RET-17001試験（LBRETTO-001、J2G-OX-JZJA、以下17001試験）のデータに基づき、本邦では「RET融合遺伝子陽性の切除不能な進行・再発の非小細胞肺癌」「RET融合遺伝子陽性の根治切除不能な甲状腺癌」「RET遺伝子変異陽性の根治切除不能な甲状腺髄様癌」を適応として承認を取得している。

RET融合遺伝子陽性の非小細胞肺癌及び甲状腺癌を除く固形がんに対するセルペルカチニブの開発の経緯は、主に本申請資料第2.5項に記載した。表1.5-1に第2.5項での当該内容等の記載場所を示す。また、開発の経緯図を図1.5-1に示す。

表 1.5-1 第 1.5 項の内容の第 2.5 項での記載箇所

第 1.5 項に記載する内容	第 2 部での記載場所	
起原又は発見の経緯、臨床開発の経緯、規制当局からの助言の経緯、臨床データパッケージ	2.5.1	製品開発の根拠
臨床試験の概略	2.5.3	臨床薬理に関する概括評価
	2.5.4	有効性の概括評価
	2.5.5	安全性の概括評価
本剤の有効性及び安全性に基づく有用性に関する記載	2.5.6	ベネフィットとリスクに関する結論

今般、17001試験の新たに得られたデータを踏まえ、セルペルカチニブがRET融合遺伝子陽性の非小細胞肺癌及び甲状腺癌を除く固形がんに対して良好なベネフィット・リスクプロファイルを示したこと、及びRET融合遺伝子が発癌性の遺伝子異常としての役割を果たしていると考えられることから、セルペルカチニブはがん種横断的なRET融合遺伝子陽性の固形がん患者に対する有効な治療選択肢になり得ると考え、製造販売承認事項一部変更承認申請を行うこととした。

試験項目		2017	2018	2019	2020	2021	2022	2023
臨床試験	第 I/II 相試験							



図 1.5-1 セルペルカチニブの開発の経緯図

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1.6 外国における使用状況等に関する資料

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目次

1.6	外国における使用状況等に関する資料	1
1.6.1	外国における申請・承認状況	1
1.6.2	外国における添付文書	2

1.6 外国における使用状況等に関する資料

1.6.1 外国における申請・承認状況

セルペルカチニブは、2019年12月に米国及び欧州で承認申請を行い、米国では2020年5月に、欧州では2021年2月に、*RET*融合遺伝子陽性の非小細胞肺癌、*RET*融合遺伝子陽性の甲状腺癌、及び*RET*遺伝子変異陽性の甲状腺髄様癌に対して承認を取得した。2024年4月時点で、セルペルカチニブは40以上の国又は地域で承認されている。

*RET*融合遺伝子陽性の固形がんに対しては、米国では2022年9月、欧州では2024年4月に承認されており、2024年4月時点で米国、欧州含め30以上の国又は地域で承認されている。

1.6.2 外国における添付文書

セルペルカチニブの米国の添付文書（USPI）、EUの製品概要（SmPC）及び企業中核データシート（CDS）を添付する。

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RETEVMO safely and effectively. See full prescribing information for RETEVMO.

RETEVMO® (selpercatinib) capsules, for oral use
RETEVMO® (selpercatinib) tablets, for oral use

Initial U.S. Approval: 2020

RECENT MAJOR CHANGES

Dosage and Administration (2.3) 04/2024

INDICATIONS AND USAGE

RETEVMO® is a kinase inhibitor indicated for the treatment of:

- Adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a *rearranged during transfection (RET)* gene fusion, as detected by an FDA-approved test (1.1)
- Adult and pediatric patients 12 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) with a *RET* mutation, as detected by an FDA-approved test, who require systemic therapy¹ (1.2)
- Adult and pediatric 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)¹ (1.3)
- Adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options¹ (1.4)

¹ This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

DOSAGE AND ADMINISTRATION

- Select patients for treatment with RETEVMO based on the presence of a *RET* gene fusion (NSCLC, thyroid, or other solid tumors) or specific *RET* gene mutation (MTC). (2.1, 14)
- Recommended dosage in adults and pediatric patients 12 years of age or older is based on weight (2.3):
 - Less than 50 kg: 120 mg orally twice daily
 - 50 kg or greater: 160 mg orally twice daily
- Reduce RETEVMO dose in patients with severe hepatic impairment. (2.7, 8.7)

DOSAGE FORMS AND STRENGTHS

- Capsules: 40 mg, 80 mg. (3)
- Tablets: 40 mg, 80 mg, 120 mg, 160 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Hepatotoxicity:** Monitor ALT and AST prior to initiating RETEVMO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose, or permanently discontinue RETEVMO based on severity. (2.5, 5.1)
- Interstitial Lung Disease (ILD)/Pneumonitis:** Monitor for new or worsening pulmonary symptoms. Withhold, reduce the dose or permanently discontinue RETEVMO based on severity. (2.5, 5.2)
- Hypertension:** Do not initiate RETEVMO in patients with uncontrolled hypertension. Optimize blood pressure (BP) prior to initiating RETEVMO. Monitor BP after 1 week, at least monthly thereafter and as clinically indicated. Withhold, reduce dose, or permanently discontinue RETEVMO based on severity. (2.5, 5.3)

- QT Interval Prolongation:** Monitor patients who are at significant risk of developing QTc prolongation. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment. Monitor QT interval more frequently when RETEVMO is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue RETEVMO based on severity. (2.5, 5.4)
- Hemorrhagic Events:** Permanently discontinue RETEVMO in patients with severe or life-threatening hemorrhage. (2.5, 5.5)
- Hypersensitivity:** Withhold RETEVMO and initiate corticosteroids. Upon resolution, resume at a reduced dose and increase dose by 1 dose level each week until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. (2.5, 5.6)
- Tumor Lysis Syndrome:** Closely monitor patients at risk and treat as clinically indicated. (5.7)
- Risk of Impaired Wound Healing:** Withhold RETEVMO 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 RETEVMO after resolution of wound healing complications has not been established. (5.8)
- Hypothyroidism:** Monitor thyroid function before treatment with RETEVMO and periodically during treatment. Withhold until clinically stable or permanently discontinue based on severity. (5.9)
- Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the possible risk to a fetus and to use effective contraception. (5.10, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (≥25%) were edema, diarrhea, fatigue, dry mouth, hypertension, abdominal pain, constipation, rash, nausea, and headache. (6)

The most common Grade 3 or 4 laboratory abnormalities (≥5%) were decreased lymphocytes, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), decreased sodium, and decreased calcium. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Acid-Reducing Agents:** Avoid coadministration. If coadministration cannot be avoided, take RETEVMO with food (with PPI) or modify its administration time (with H2 receptor antagonist or locally-acting antacid). (2.4, 7.1)
- Strong and Moderate CYP3A Inhibitors:** Avoid coadministration. If coadministration cannot be avoided, reduce the RETEVMO dose. (2.6, 7.1)
- Strong and Moderate CYP3A Inducers:** Avoid coadministration. (7.1)
- CYP2C8 and CYP3A Substrates:** Avoid coadministration. If coadministration cannot be avoided, modify the substrate dosage as recommended in its product labeling. (7.2)
- Certain P-gp Substrates:** Avoid coadministration. If coadministration cannot be avoided, modify the substrate dosage as recommended in its product labeling. (7.2)

USE IN SPECIFIC POPULATIONS

- Lactation:** Advise not to breastfeed. (8.2)
- Pediatric Use:** Monitor open growth plates in adolescent patients. Consider interrupting or discontinuing RETEVMO if abnormalities occur. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 *RET* Fusion-Positive Non-Small Cell Lung Cancer
- 1.2 *RET*-Mutant Medullary Thyroid Cancer

- 1.3 *RET* Fusion-Positive Thyroid Cancer
- 1.4 Other *RET* Fusion-Positive Solid Tumors
- 2 DOSAGE AND ADMINISTRATION**
 - 2.1 Patient Selection
 - 2.2 Important Administration Instructions
 - 2.3 Recommended Dosage
 - 2.4 Dosage Modifications for Concomitant Use of Acid-Reducing Agents
 - 2.5 Dosage Modifications for Adverse Reactions
 - 2.6 Dosage Modifications for Concomitant Use of Strong and Moderate CYP3A Inhibitors
 - 2.7 Dosage Modification for Severe Hepatic Impairment
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
 - 5.1 Hepatotoxicity
 - 5.2 Interstitial Lung Disease/Pneumonitis
 - 5.3 Hypertension
 - 5.4 QT Interval Prolongation
 - 5.5 Hemorrhagic Events
 - 5.6 Hypersensitivity
 - 5.7 Tumor Lysis Syndrome
 - 5.8 Risk of Impaired Wound Healing
 - 5.9 Hypothyroidism
 - 5.10 Embryo-Fetal Toxicity
- 6 ADVERSE REACTIONS**
 - 6.1 Clinical Trials Experience
- 7 DRUG INTERACTIONS**

- 7.1 Effects of Other Drugs on RETEVMO
- 7.2 Effects of RETEVMO on Other Drugs
- 7.3 Drugs that Prolong QT Interval
- 8 USE IN SPECIFIC POPULATIONS**
 - 8.1 Pregnancy
 - 8.2 Lactation
 - 8.3 Females and Males of Reproductive Potential
 - 8.4 Pediatric Use
 - 8.5 Geriatric Use
 - 8.6 Renal Impairment
 - 8.7 Hepatic Impairment
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
 - 12.1 Mechanism of Action
 - 12.2 Pharmacodynamics
 - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY**
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 14 CLINICAL STUDIES**
 - 14.1 *RET* Fusion-Positive Non-Small Cell Lung Cancer
 - 14.2 *RET*-Mutant Medullary Thyroid Cancer
 - 14.3 *RET* Fusion-Positive Thyroid Cancer
 - 14.4 Other *RET* Fusion-Positive Solid Tumors
- 16 HOW SUPPLIED/STORAGE AND HANDLING**
- 17 PATIENT COUNSELING INFORMATION**

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 *RET* Fusion-Positive Non-Small Cell Lung Cancer

RETEVMO® is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a *rearranged during transfection (RET)* gene fusion, as detected by an FDA-approved test.

1.2 *RET*-Mutant Medullary Thyroid Cancer

RETEVMO is indicated for the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic medullary thyroid cancer (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 overall response rate and duration of response [see *Clinical Studies (14.2)*]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

1.3 *RET* Fusion-Positive Thyroid Cancer

RETEVMO is indicated for the treatment of adult and pediatric 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 overall response rate and duration of response [see *Clinical Studies (14.3)*]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

1.4 Other *RET* Fusion-Positive Solid Tumors

RETEVMO is indicated for the treatment of adult patients with locally advanced or metastatic solid tumors 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 overall response rate and duration of response [see *Clinical Studies (14.4)*]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for treatment with RETEVMO based on the presence of a *RET* gene fusion (NSCLC, thyroid cancer, or other solid tumors) or specific *RET* gene mutation (MTC) in tumor specimens [see *Clinical Studies (14)*]. Information on FDA-approved test(s) for the detection of *RET* gene fusions and *RET* gene mutations is available at: <http://www.fda.gov/CompanionDiagnostics>. An FDA-approved companion diagnostic test for the detection of *RET* gene fusions and *RET* gene mutations in plasma or in tumors other than NSCLC and thyroid cancer is not currently available.

2.2 Important Administration Instructions

RETEVMO may be taken with or without food unless coadministered with a proton pump inhibitor (PPI) [see *Dosage and Administration (2.4)*, *Clinical Pharmacology (12.3)*].

2.3 Recommended Dosage

The recommended dosage of RETEVMO, based on body weight, is:

- Less than 50 kg: RETEVMO 120 mg taken orally twice daily with or without food
- 50 kg or greater: RETEVMO 160 mg taken orally twice daily with or without food

Continue treatment with RETEVMO until disease progression or unacceptable toxicity.

Swallow the capsules whole. Do not crush or chew the capsules.

Swallow the tablets whole. Do not crush or chew the tablets.

Do not take a missed dose unless it is more than 6 hours until next scheduled dose.

If vomiting occurs after RETEVMO administration, do not take an additional dose and continue to the next scheduled time for the next dose.

2.4 Dosage Modifications for Concomitant Use of Acid-Reducing Agents

Avoid concomitant use of a PPI, a histamine-2 (H₂) receptor antagonist, or a locally-acting antacid with RETEVMO [see *Drug Interactions (7.1)*]. If concomitant use cannot be avoided:

- Take RETEVMO with food when coadministered with a PPI.
- Take RETEVMO 2 hours before or 10 hours after administration of an H₂ receptor antagonist.
- Take RETEVMO 2 hours before or 2 hours after administration of a locally-acting antacid.

2.5 Dosage Modifications for Adverse Reactions

The recommended dose reductions for adverse reactions are provided in Table 1.

Table 1: Recommended RETEVMO Dose Reductions 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 RETEVMO in patients unable to tolerate three dose reductions.

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

Table 2: Recommended RETEVMO Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Hepatotoxicity [see Warnings and Precautions (5.1)]	Grade 3 or Grade 4	- Withhold RETEVMO 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 recurrence 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.
Interstitial Lung Disease/ Pneumonitis [see Warnings and Precautions (5.2)]	Grade 2	- Withhold RETEVMO until resolution. - Resume at a reduced dose. - Discontinue RETEVMO for recurrent ILD/pneumonitis.
	Grade 3 or Grade 4	Discontinue RETEVMO for confirmed ILD/pneumonitis.
Hypertension [see Warnings and Precautions (5.3)]	Grade 3	Withhold RETEVMO for Grade 3 hypertension that persists despite optimal antihypertensive therapy. Resume at a reduced dose when hypertension is controlled.
	Grade 4	Discontinue RETEVMO.
QT Interval Prolongation [see Warnings and Precautions (5.4)]	Grade 3	- Withhold RETEVMO until recovery to baseline or Grade 0 or 1. - Resume at a reduced dose.
	Grade 4	Discontinue RETEVMO.
Hemorrhagic Events [see Warnings and Precautions (5.5)]	Grade 3 or Grade 4	- Withhold RETEVMO until recovery to baseline or Grade 0 or 1. - Discontinue RETEVMO for severe or life-threatening hemorrhagic events.
Hypersensitivity Reactions [see Warnings and Precautions (5.6)]	All Grades	- Withhold RETEVMO 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.
Hypothyroidism [see Warnings and Precautions (5.9)]	Grade 3 or Grade 4	- Withhold RETEVMO until resolution to Grade 1 or baseline. - Discontinue RETEVMO based on severity.
Other Adverse Reactions [see Adverse Reactions (6.1)]	Grade 3 or Grade 4	- Withhold RETEVMO until recovery to baseline or Grade 0 or 1. - Resume at a reduced dose.

2.6 Dosage Modifications for Concomitant Use of Strong and Moderate CYP3A Inhibitors

Avoid concomitant use of strong and moderate CYP3A inhibitors with RETEVMO. If concomitant use of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the RETEVMO dose as recommended in Table 3. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume RETEVMO at the dose taken prior to initiating the CYP3A inhibitor [see Drug Interactions (7.1)].

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

Current RETEVMO Dosage	Recommended RETEVMO 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

2.7 Dosage Modification for Severe Hepatic Impairment

Reduce the recommended dosage of RETEVMO for patients with severe hepatic impairment as recommended in Table 4 [see *Use in Specific Populations* (8.7)].

Table 4: Recommended RETEVMO Dosage for Severe Hepatic Impairment

Current RETEVMO Dosage	Recommended RETEVMO Dosage
120 mg orally twice daily	80 mg orally twice daily
160 mg orally twice daily	80 mg orally twice daily

3 DOSAGE FORMS AND STRENGTHS

Capsules:

- 40 mg: gray opaque capsule imprinted with “Lilly”, “3977” and “40 mg” in black ink.
- 80 mg: blue opaque capsule imprinted with “Lilly”, “2980” and “80 mg” in black ink.

Tablets:

- 40 mg: light gray, film coated, round tablet debossed with “Ret 40” on one side and “5340” on the other side.
- 80 mg: dark red-purple, film coated, round tablet debossed with “Ret 80” on one side and “6082” on the other side.
- 120 mg: light purple, film coated, round tablet debossed with “Ret 120” on one side and “6120” on the other side.
- 160 mg: light pink, film coated, round tablet debossed with “Ret 160” on one side and “5562” on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Serious hepatic adverse reactions occurred in 3% of patients treated with RETEVMO. Increased AST occurred in 59% of patients, including Grade 3 or 4 events in 11% and increased ALT occurred in 55% of patients, including Grade 3 or 4 events in 12% [see *Adverse Reactions* (6.1)]. The median time to first onset for increased AST was 6 weeks (range: 1 day to 3.4 years) and increased ALT was 5.8 weeks (range: 1 day to 2.5 years).

Monitor ALT and AST prior to initiating RETEVMO, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue RETEVMO based on the severity [see *Dosage and Administration* (2.5)].

5.2 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, and fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with RETEVMO. ILD/pneumonitis occurred in 1.8% of patients who received RETEVMO, including 0.3% with Grade 3 or 4 events, and 0.3% with fatal reactions.

Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold RETEVMO and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Withhold, reduce dose or permanently discontinue RETEVMO based on severity of confirmed ILD [see *Dosage and Administration* (2.5)].

5.3 Hypertension

Hypertension occurred in 41% of patients, including Grade 3 hypertension in 20% and Grade 4 in one (0.1%) patient [see *Adverse Reactions* (6.1)]. Overall, 6.3% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications.

Do not initiate RETEVMO in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating RETEVMO. Monitor blood pressure after 1 week, at least monthly thereafter and as clinically indicated. Initiate or adjust

anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue RETEVMO based on the severity [see *Dosage and Administration* (2.5)].

5.4 QT Interval Prolongation

RETEVMO can cause concentration-dependent QT interval prolongation [see *Clinical Pharmacology* (12.2)]. An increase in QTcF interval to >500 ms was measured in 7% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 20% of patients [see *Adverse Reactions* (6.1)]. RETEVMO 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 RETEVMO and during treatment.

Monitor the QT interval more frequently when RETEVMO is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue RETEVMO based on the severity [see *Dosage and Administration* (2.5)].

5.5 Hemorrhagic Events

Serious including fatal hemorrhagic events can occur with RETEVMO. Grade ≥ 3 hemorrhagic events occurred in 3.1% of patients treated with RETEVMO, including 4 (0.5%) patients with fatal hemorrhagic events, including cerebral hemorrhage (n = 2), tracheostomy site hemorrhage (n = 1), and hemoptysis (n=1).

Permanently discontinue RETEVMO in patients with severe or life-threatening hemorrhage [see *Dosage and Administration* (2.5)].

5.6 Hypersensitivity

Hypersensitivity occurred in 6% of patients receiving RETEVMO, including Grade 3 hypersensitivity in 1.9%. The median time to onset was 1.9 weeks (range: 5 days to 2 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminitis.

If hypersensitivity occurs, withhold RETEVMO and begin corticosteroids at a dose of 1 mg/kg prednisone (or equivalent). Upon resolution of the event, resume RETEVMO at a reduced dose and increase the dose of RETEVMO by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity [see *Dosage and Administration* (2.5)]. Continue steroids until patient reaches target dose and then taper. Permanently discontinue RETEVMO for recurrent hypersensitivity.

5.7 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) occurred in 0.6% of patients with medullary thyroid carcinoma receiving RETEVMO [see *Adverse Reactions* (6.1)]. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

5.8 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, RETEVMO has the potential to adversely affect wound healing.

Withhold RETEVMO 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 RETEVMO after resolution of wound healing complications has not been established.

5.9 Hypothyroidism

RETEVMO can cause hypothyroidism. Hypothyroidism occurred in 13% of patients treated with RETEVMO; all reactions were Grade 1 or 2. Hypothyroidism occurred in 13% of patients (50/373) with thyroid cancer and 13% of patients (53/423) with other solid tumors including NSCLC [see *Adverse Reactions* (6.1)].

Monitor thyroid function before treatment with RETEVMO and periodically during treatment. Treat with thyroid hormone replacement as clinically indicated. Withhold RETEVMO until clinically stable or permanently discontinue RETEVMO based on severity [see *Dosage and Administration* (2.5)].

5.10 Embryo-Fetal Toxicity

Based on data from animal reproduction studies and its mechanism of action, RETEVMO can cause fetal harm when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryo lethality and malformations.

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the last dose [see *Use in Specific Populations* (8.1, 8.3)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hepatotoxicity [see *Warnings and Precautions* (5.1)]
- Interstitial Lung Disease / Pneumonitis [see *Warnings and Precautions* (5.2)]
- Hypertension [see *Warnings and Precautions* (5.3)]
- QT Interval Prolongation [see *Warnings and Precautions* (5.4)]
- Hemorrhagic Events [see *Warnings and Precautions* (5.5)]
- Hypersensitivity [see *Warnings and Precautions* (5.6)]
- Tumor Lysis Syndrome [see *Warnings and Precautions* (5.7)]
- Risk of Impaired Wound Healing [see *Warnings and Precautions* (5.8)]
- Hypothyroidism [see *Warnings and Precautions* (5.9)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

RET Gene Fusion or Gene Mutation Positive Solid Tumors

The pooled safety population described in the WARNINGS and PRECAUTIONS and below reflects exposure to RETEVMO as a single agent at 160 mg orally twice daily evaluated in 796 patients with advanced solid tumors in LIBRETTO-001 [see *Clinical Studies* (14)]. Among the 796 patients who received RETEVMO, 84% were exposed for 6 months or longer and 73% were exposed for greater than one year. Among these patients, 96% received at least one dose of RETEVMO at the recommended dosage of 160 mg orally twice daily.

The median age was 59 years (range: 15 to 92 years); 0.3% were pediatric patients 12 to 16 years of age; 51% were male; and 69% were White, 23% were Asian, 5% were Hispanic/Latino, and 3% were Black. The most common tumors were NSCLC (45%), MTC (40%), and non-medullary thyroid carcinoma (7%).

Serious adverse reactions occurred in 44% of patients who received RETEVMO. The most frequent serious adverse reactions ($\geq 2\%$ of patients) were pneumonia, pleural effusion, abdominal pain, hemorrhage, hypersensitivity, dyspnea, and hyponatremia. Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions included sepsis (n = 6), respiratory failure (n = 5), hemorrhage (n = 4), pneumonia (n = 3), pneumonitis (n = 2), cardiac arrest (n = 2), sudden death (n = 1), and cardiac failure (n = 1).

Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received RETEVMO. Adverse reactions resulting in permanent discontinuation in $\geq 0.5\%$ of patients included increased ALT (0.6%), fatigue (0.6%), sepsis (0.5%), and increased AST (0.5%).

Dosage interruptions due to an adverse reaction occurred in 64% of patients who received RETEVMO. Adverse reactions requiring dosage interruption in $\geq 5\%$ of patients included increased ALT, increased AST, diarrhea, and hypertension.

Dose reductions due to an adverse reaction occurred in 41% of patients who received RETEVMO. Adverse reactions requiring dosage reductions in $\geq 2\%$ of patients included increased ALT, increased AST, QT prolongation, fatigue, diarrhea, drug hypersensitivity, and edema.

The most common adverse reactions ($\geq 25\%$) were edema, diarrhea, fatigue, dry mouth, hypertension, abdominal pain, constipation, rash, nausea, and headache.

The most common Grade 3 or 4 laboratory abnormalities ($\geq 5\%$) were decreased lymphocytes, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), decreased sodium, and decreased calcium.

Table 5 summarizes the adverse reactions in LIBRETTO-001.

Table 5: Adverse Reactions (≥20%) in Patients Who Received RETEVMO in LIBRETTO-001

Adverse Reaction	RETEVMO (n = 796)	
	Grades 1-4 [#] (%)	Grades 3-4 (%)
Gastrointestinal		
Diarrhea ¹	47	5*
Dry Mouth	43	0
Abdominal pain ²	34	2.5*
Constipation	33	0.8*
Nausea	31	1.1*
Vomiting	22	1.8*
Vascular		
Hypertension	41	20
General		
Edema ³	49	0.8*
Fatigue ⁴	46	3.1*
Arthralgia	21	0.3*
Skin		
Rash ⁵	33	0.6*
Nervous System		
Headache ⁶	28	1.4*
Respiratory		
Cough ⁷	24	0
Dyspnea ⁸	22	3.1
Investigations		
Prolonged QT interval	21	4.8*
Blood and Lymphatic System		
Hemorrhage ⁹	22	2.6

¹ Diarrhea includes diarrhea, defecation urgency, frequent bowel movements, gastrointestinal hypermotility, anal incontinence.

² Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness, epigastric discomfort, gastrointestinal pain.

³ Edema includes edema, edema peripheral, face edema, periorbital edema, eye edema, eyelid edema, orbital edema, localized edema, lymphedema, scrotal edema, peripheral swelling, scrotal swelling, swelling, swelling face, eye swelling, generalized edema, genital edema.

⁴ Fatigue includes fatigue, asthenia, malaise.

⁵ Rash includes rash, rash erythematous, rash macular, rash maculopapular, rash morbilliform, rash papular, rash pruritic, butterfly rash, exfoliative rash, rash follicular, rash generalized, rash vesicular.

⁶ Headache includes headache, sinus headache, tension headache.

⁷ Includes cough, productive cough, upper airway cough syndrome.

⁸ Includes dyspnea, dyspnea exertional, dyspnea at rest.

⁹ Hemorrhage includes hemorrhage, 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, hemorrhage subcutaneous, spontaneous hematoma, abdominal wall hematoma, angina bullosa hemorrhagica, conjunctival hemorrhage, disseminated intravascular coagulation, diverticulum intestinal hemorrhagic, eye hemorrhage, gastrointestinal hemorrhage, gingival bleeding, hematemeses, hemorrhagic stroke,

hemorrhoidal hemorrhage, hepatic hemorrhage, hepatic hematoma, intraabdominal hemorrhage, laryngeal hemorrhage, lower gastrointestinal hemorrhage, melena, mouth hemorrhage, occult blood positive, post procedural hemorrhage, postmenopausal hemorrhage, pelvic hematoma, periorbital hematoma, periorbital hemorrhage, pharyngeal hemorrhage, pulmonary contusion, purpura, retinal hemorrhage, retroperitoneal hematoma, scleral hemorrhage, skin hemorrhage, subarachnoid hemorrhage, subdural hemorrhage, upper gastrointestinal hemorrhage, uterine hemorrhage, vessel puncture site hematoma.

* Only includes a grade 3 adverse reaction.

Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03

Clinically relevant adverse reactions in $\leq 15\%$ of patients who received RETEVMO include hypothyroidism (13%); hypersensitivity (6%); interstitial lung disease/pneumonitis, chylothorax, chylous ascites or tumor lysis syndrome (all < 2%).

Table 6 summarizes the laboratory abnormalities in LIBRETTO-001.

Table 6: Select Laboratory Abnormalities ($\geq 20\%$) Worsening from Baseline in Patients Who Received RETEVMO in LIBRETTO-001

Laboratory Abnormality	RETEVMO ¹	
	Grades 1-4 [#] (%)	Grades 3-4 (%)
Chemistry		
Increased AST	59	11
Decreased calcium	59	5.7
Increased ALT	56	12
Decreased albumin	56	2.3
Increased glucose	53	2.8
Increased creatinine	47	2.4
Decreased sodium	42	11
Increased alkaline phosphatase	40	3.4
Increased total cholesterol	35	1.7
Increased potassium	34	2.7
Decreased glucose	34	1.0
Decreased magnesium	33	0.6
Increased bilirubin	30	2.8
Hematology		
Decreased lymphocytes	52	20
Decreased platelets	37	3.2
Decreased hemoglobin	28	3.5
Decreased neutrophils	25	3.2

¹ Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 765 to 791 patients.

Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03

Increased Creatinine

In healthy subjects administered RETEVMO 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 *Clinical Pharmacology* (12.3)].

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on RETEVMO

Acid-Reducing Agents

Concomitant use of RETEVMO with acid-reducing agents decreases selpercatinib plasma concentrations [see *Clinical Pharmacology* (12.3)], which may reduce RETEVMO anti-tumor activity.

Avoid concomitant use of PPIs, H2 receptor antagonists, and locally-acting antacids with RETEVMO. If coadministration cannot be avoided, take RETEVMO with food (with a PPI) or modify its administration time (with a H2 receptor antagonist or a locally-acting antacid) [see *Dosage and Administration* (2.4)].

Strong and Moderate CYP3A Inhibitors

Concomitant use of RETEVMO with a strong or moderate CYP3A inhibitor increases selpercatinib plasma concentrations [see *Clinical Pharmacology* (12.3)], which may increase the risk of RETEVMO adverse reactions, including QTc interval prolongation.

Avoid concomitant use of strong and moderate CYP3A inhibitors with RETEVMO. If concomitant use of strong and moderate CYP3A inhibitors cannot be avoided, reduce the RETEVMO dosage and monitor the QT interval with ECGs more frequently [see *Dosage and Administration* (2.6), *Warning and Precautions* (5.4)].

Strong and Moderate CYP3A Inducers

Concomitant use of RETEVMO with a strong or moderate CYP3A inducer decreases selpercatinib plasma concentrations [see *Clinical Pharmacology* (12.3)], which may reduce RETEVMO anti-tumor activity.

Avoid coadministration of strong or moderate CYP3A inducers with RETEVMO.

7.2 Effects of RETEVMO on Other Drugs

CYP2C8 and CYP3A Substrates

RETEVMO is a moderate CYP2C8 inhibitor and a weak CYP3A inhibitor. Concomitant use of RETEVMO with CYP2C8 and CYP3A substrates increases their plasma concentrations [see *Clinical Pharmacology* (12.3)], which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of RETEVMO with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

Certain P-gp Substrates

RETEVMO is a P-gp inhibitor. Concomitant use of RETEVMO with P-gp substrates increases their plasma concentrations [see *Clinical Pharmacology* (12.3)], which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of RETEVMO with P-gp substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for P-gp substrates provided in their approved product labeling.

7.3 Drugs that Prolong QT Interval

RETEVMO is associated with QTc interval prolongation [see *Warnings and Precautions* (5.4), *Clinical Pharmacology* (12.2)]. Monitor the QT interval with ECGs more frequently in patients who require treatment with concomitant medications known to prolong the QT interval.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies, and its mechanism of action [see *Clinical Pharmacology* (12.1)], RETEVMO can cause fetal harm when administered to a pregnant woman. There are no available data on RETEVMO use in pregnant women to inform drug-associated risk. Administration of selpercatinib to pregnant rats during the period of organogenesis resulted in embryoletality and malformations at maternal exposures that were approximately equal to the human exposure at the clinical dose of 160 mg twice daily. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Selpercatinib administration to pregnant rats during the period of organogenesis at oral doses ≥ 100 mg/kg [approximately 3.6 times the human exposure based on the area under the curve (AUC) at the clinical dose of 160 mg twice daily] resulted in 100% post-implantation loss. At the dose of 50 mg/kg [approximately equal to the human exposure (AUC) at the clinical dose of 160 mg twice daily], 6 of 8 females had 100% early resorptions; the remaining 2 females had high levels of early resorptions with only 3 viable fetuses across the 2 litters. All viable fetuses had decreased fetal body weight and malformations (2 with short tail and one with small snout and localized edema of the neck and thorax).

8.2 Lactation

Risk Summary

There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with RETEVMO and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

Based on animal data, RETEVMO can cause embryoletality and malformations at doses resulting in exposures less than or equal to the human exposure at the clinical dose of 160 mg twice daily [see *Use in Specific Populations* (8.1)].

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating RETEVMO [see *Use in Specific Populations* (8.1)].

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the last dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the last dose.

Infertility

RETEVMO may impair fertility in females and males of reproductive potential [see *Use in Specific Populations* (8.4), *Nonclinical Toxicology* (13.1)].

8.4 Pediatric Use

The safety and effectiveness of RETEVMO have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced *RET* fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of RETEVMO for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older [see *Adverse Reactions* (6.1), *Clinical Pharmacology* (12.3), *Clinical Studies* (14.2, 14.3)]. The safety and effectiveness of RETEVMO have not been established in these indications in patients less than 12 years of age.

The safety and effectiveness of RETEVMO have not been established in pediatric patients for other indications [see *Indications and Usage* (1)].

Juvenile Animal Toxicity Data

In a juvenile rat toxicity study, animals were dosed daily with selpercatinib from post-natal day 21 to day 70 (approximately equivalent to a human child to late adolescent). Selpercatinib increased physeal thickness of multiple bones, extending into the metaphysis and associated with decreased trabecular bone, which was not reversible at doses approximately equivalent to or greater than the adult human exposure at the clinical dose of 160 mg twice daily. Growth plate changes were associated with impairment of bone modeling, resulting in decreased femur length and with reduction in bone mineral density. Selpercatinib also induced reversible hypocellularity of bone marrow in males at ≥ 30 mg/kg (approximately equivalent to or greater than the adult human exposure at the clinical dose of 160 mg twice daily), and reversible alterations of dentin composition at ≥ 50 mg/kg (approximately 3 times the adult human exposure at the clinical dose of 160 mg twice daily). Irreversible, dose-dependent degeneration of testicular germinal epithelium, with vacuolation of Sertoli cells and corresponding depletion of spermatozoa in the epididymides, was also observed at ≥ 30 mg/kg.

(approximately equivalent to or greater than the adult human exposure at the clinical dose of 160 mg twice daily) and affected male reproductive performance at 50 mg/kg (approximately 3 times the adult human exposure at the clinical dose of 160 mg twice daily). Females exhibited delay in attainment of vaginal patency, a marker of sexual maturity, at 125 mg/kg (approximately 4 times the adult human exposure at the clinical dose of 160 mg twice daily); this affect was associated with lower mean body weight. Similar effects in irregular thickening of growth plates in adult rats and minipigs, and tooth dysplasia and malocclusion, resulting in tooth loss in adult rats were observed in repeat dose studies of up to 13-week duration with selpercatinib.

Monitor growth plates in adolescent patients with open growth plates. Consider interrupting or discontinuing therapy based on the severity of any growth plate abnormalities and based on an individual risk-benefit assessment.

8.5 Geriatric Use

Of 796 patients who received RETEVMO, 34% (268 patients) were ≥ 65 years of age and 9% (74 patients) were ≥ 75 years of age. No overall differences were observed in the safety or effectiveness of RETEVMO between patients who were ≥ 65 years of age and younger patients.

8.6 Renal Impairment

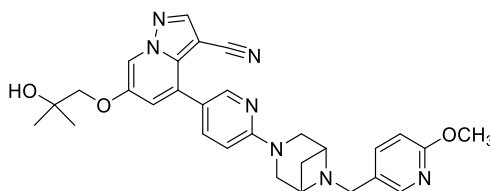
No dosage modification is recommended for patients with mild to severe renal impairment [estimated Glomerular Filtration Rate (eGFR) ≥ 15 to 89 mL/min, estimated by Modification of Diet in Renal Disease (MDRD) equation]. The recommended dosage has not been established for patients with end-stage renal disease (ESRD) [see *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

Reduce the dose when administering RETEVMO to patients with severe [total bilirubin greater than 3 to 10 times upper limit of normal (ULN) and any AST] hepatic impairment [see *Dosage and Administration* (2.7)]. No dosage modification is recommended for patients 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) or moderate (total bilirubin greater than 1.5 to 3 times ULN and any AST) hepatic impairment. Monitor for RETEVMO-related adverse reactions in patients with hepatic impairment [see *Clinical Pharmacology* (12.3)].

11 DESCRIPTION

RETEVMO contains selpercatinib, a kinase inhibitor. The molecular formula for selpercatinib is $C_{29}H_{31}N_7O_3$ and the molecular weight is 525.61 g/mol. The chemical name 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. Selpercatinib has the following chemical structure:



Selpercatinib is a white to light yellow powder that is slightly hygroscopic. The aqueous solubility of selpercatinib is pH dependent, from sparingly soluble at low pH to practically insoluble at neutral pH.

RETEVMO capsules contain either 40 mg or 80 mg of selpercatinib in hard gelatin capsules for oral use. Each capsule contains inactive ingredients of colloidal silicon dioxide and microcrystalline cellulose. The 40 mg capsule shell is composed of gelatin, titanium dioxide, ferric oxide black and black ink. The 80 mg capsule shell is composed of gelatin, titanium dioxide, FD&C blue #1 and black ink. The black ink is composed of shellac, potassium hydroxide and ferric oxide black.

RETEVMO tablets contain 40 mg, 80 mg, 120 mg or 160 mg of selpercatinib as film coated, debossed tablets for oral use. Each tablet contains inactive ingredients of croscarmellose sodium, hydroxypropyl cellulose, mannitol, microcrystalline cellulose, and sodium stearyl fumarate. The tablet film coating material contains polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc. Additionally, the film coating of the 40 mg, 80 mg, and 120 mg tablets contains ferrousferrous oxide and the film coating of the 80 mg, 120 mg, and 160 mg tablets contain ferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Selpercatinib is a kinase inhibitor. 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. 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 proteins 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.

12.2 Pharmacodynamics

Exposure-Response Relationship

Selpercatinib exposure-response relationships and the time course of pharmacodynamic response have not been fully characterized.

Cardiac Electrophysiology

The effect of RETEVMO on the QTc interval was evaluated in a thorough QT study in healthy subjects. The largest mean increase in QTc is predicted to be 10.6 msec (upper 90% confidence interval: 12.1 msec) at the mean steady-state maximum concentration (C_{max}) observed in patients after administration of 160 mg twice daily. The increase in QTc was concentration-dependent.

12.3 Pharmacokinetics

The pharmacokinetics of selpercatinib capsules were evaluated in patients with locally advanced or metastatic solid tumors administered 160 mg twice daily unless otherwise specified. The capsule and tablet dosage forms of selpercatinib are bioequivalent. Steady state selpercatinib AUC and C_{max} increased in a slightly greater than dose proportional manner over the dose range of 20 mg once daily to 240 mg twice daily [0.06 to 1.5 times the maximum recommended total daily dosage].

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%)] C_{max} was 2,980 (53%) ng/mL and AUC_{0-24h} was 51,600 (58%) ng*h/mL.

Absorption

The median t_{max} of selpercatinib is 2 hours. The mean absolute bioavailability of RETEVMO capsules is 73% (60% to 82%) in healthy subjects.

Effect of Food

For both the capsule and tablet dosage forms no clinically significant differences in selpercatinib AUC or C_{max} were observed following administration of a high-fat meal (approximately 900 calories, 58 grams carbohydrate, 56 grams fat and 43 grams protein) in healthy subjects.

Distribution

The apparent volume of distribution (V_{ss}/F) of selpercatinib is 191 L.

Protein binding of selpercatinib is 96% in vitro and is independent of concentration. The blood-to-plasma concentration ratio is 0.7.

Elimination

The apparent clearance (CL/F) of selpercatinib is 6 L/h in patients and the half-life is 32 hours following oral administration of RETEVMO in healthy subjects.

Metabolism

Selpercatinib is metabolized predominantly by CYP3A4. Following oral administration of a single radiolabeled 160 mg dose of selpercatinib to healthy subjects, unchanged selpercatinib constituted 86% of the radioactive drug components in plasma.

Excretion

Following oral administration of a single radiolabeled 160 mg dose of selpercatinib to healthy subjects, 69% of the administered dose was recovered in feces (14% unchanged) and 24% in urine (12% unchanged).

Specific Populations

The apparent volume of distribution and clearance of selpercatinib increase with increasing body weight (27 kg to 179 kg).

No clinically significant differences in the pharmacokinetics of selpercatinib were observed based on age (15 years to 92 years), sex, or mild, moderate, or severe renal impairment (eGFR ≥ 15 to 89 mL/min). The effect of ESRD on selpercatinib pharmacokinetics has not been studied.

Patients with Hepatic Impairment

The selpercatinib AUC_{0-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.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Proton-Pump Inhibitors (PPI): Coadministration with multiple daily doses of omeprazole (PPI) decreased selpercatinib AUC_{0-INF} and C_{max} when RETEVMO was administered fasting. Coadministration with multiple daily doses of omeprazole did not significantly change the selpercatinib AUC_{0-INF} and C_{max} when RETEVMO was administered with food (Table 7).

Table 7: Change in Selpercatinib Exposure After Coadministration with PPI

	Selpercatinib AUC_{0-INF}	Selpercatinib C_{max}
RETEVMO fasting	Reference	Reference
RETEVMO fasting + PPI	↓ 69%	↓ 88%
RETEVMO with a high-fat meal ¹ + PPI	↑ 2%	↓ 49%
RETEVMO with a low-fat meal ² + PPI	No change	↓ 22%

¹ High-fat meal: approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively; approximately 800 to 1,000 calories total.

² Low-fat meal: approximately 390 calories and 10 g of fat.

H2 Receptor Antagonists: No clinically significant differences in selpercatinib pharmacokinetics were observed when coadministered with multiple daily doses of ranitidine (H2 receptor antagonist) given 10 hours prior to and 2 hours after the RETEVMO dose (administered fasting).

Strong CYP3A Inhibitors: Coadministration of multiple doses of itraconazole (strong CYP3A inhibitor) increased the selpercatinib AUC_{0-INF} by 133% and C_{max} by 30%.

Moderate CYP3A Inhibitors: Coadministration of multiple doses of diltiazem, fluconazole, or verapamil (moderate CYP3A inhibitors) is predicted to increase the selpercatinib AUC by 60-99% and C_{max} by 46-76%.

Strong CYP3A Inducers: Coadministration of multiple doses of rifampin (strong CYP3A inducer) decreased the selpercatinib AUC_{0-INF} by 87% and C_{max} by 70%.

Moderate CYP3A Inducers: Coadministration of multiple doses of bosentan or efavirenz (moderate CYP3A inducers) is predicted to decrease the selpercatinib AUC by 40-70% and C_{max} by 34-57%.

Weak CYP3A Inducers: Coadministration of multiple doses of modafinil (weak CYP3A inducer) is predicted to decrease the selpercatinib AUC by 33% and C_{max} by 26%.

CYP2C8 Substrates: Coadministration of RETEVMO with repaglinide (sensitive CYP2C8 substrate) increased the repaglinide AUC_{0-INF} by 188% and C_{max} by 91%.

CYP3A Substrates: Coadministration of RETEVMO with midazolam (sensitive CYP3A substrate) increased the midazolam AUC_{0-INF} by 54% and C_{max} by 39%.

P-glycoprotein (P-gp) Substrates: Coadministration of RETEVMO with dabigatran (P-gp substrate) increased the dabigatran AUC_{0-INF} by 38% and C_{max} by 43%.

P-gp Inhibitors: No clinically significant differences in selpercatinib pharmacokinetics were observed when coadministered with a single dose of rifampin (P-gp inhibitor).

MATE1 Substrates: No clinically significant differences in glucose levels were observed when metformin (MATE1 substrate) was coadministered with selpercatinib.

In Vitro Studies

CYP Enzymes: Selpercatinib does not inhibit or induce CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations.

Transporter Systems: Selpercatinib inhibits MATE1 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 [see *Adverse Effects (6.1)*]. Selpercatinib is a substrate for P-gp and BCRP, but not for OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with selpercatinib. Selpercatinib was not mutagenic in the in vitro bacterial reverse mutation (Ames) assays, with or without metabolic activation, or clastogenic in the in vitro micronucleus assay in human peripheral lymphocytes, with or without metabolic activation. Selpercatinib was positive in the in vivo micronucleus assay in rats at concentrations >7 times the C_{max} at the human dose of 160 mg twice daily.

In general toxicology studies, male rats and minipigs exhibited testicular degeneration which was associated with luminal cell debris and/or reduced luminal sperm in the epididymis at selpercatinib exposures approximately 0.4 (rat) and 0.1 (minipig) times the clinical exposure by AUC at the recommended human dose. In a dedicated fertility study in male rats, administration of selpercatinib at doses up to 30 mg/kg/day (approximately twice the clinical exposure by AUC at the 160 mg twice daily dose) for 28 days prior to cohabitation with untreated females did not affect mating or have clear effects on fertility. Males did, however, display a dose-dependent increase in testicular germ cell depletion and spermatid retention at doses ≥ 3 mg/kg (~0.2 times the clinical exposure by AUC at the 160 mg twice daily dose) accompanied by altered sperm morphology at 30 mg/kg.

In a dedicated fertility study in female rats treated with selpercatinib for 15 days before mating to Gestational Day 7, there were decreases in the number of estrous cycles at a dose of 75 mg/kg (approximately equal to the human exposure by AUC at the 160 mg twice daily clinical dose). While selpercatinib did not have clear effects on mating performance or ability to become pregnant at any dose level, half of females at the 75 mg/kg dose level had 100% nonviable embryos. At the same dose level in females with some viable embryos there were increases in post-implantation loss. In a 3-month general toxicology study in minipigs, there were findings of decreased or absent corpora lutea at a selpercatinib dose of 15 mg/kg (approximately 0.3 times to the human exposure by AUC at the 160 mg twice daily clinical dose). Corpora luteal cysts were present in the minipig at selpercatinib doses ≥ 2 mg/kg (approximately 0.07 times the human exposure by AUC at the 160 mg twice daily clinical dose).

14 CLINICAL STUDIES

14.1 RET Fusion-Positive Non-Small Cell Lung Cancer

The efficacy of RETVMO was evaluated in patients with advanced *RET* fusion-positive NSCLC enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001, NCT03157128). The study enrolled patients with advanced or metastatic *RET* fusion-positive NSCLC who had progressed on platinum-based chemotherapy and patients with locally advanced (stage III who were not candidates for surgical resection or definitive chemoradiation) or metastatic NSCLC without prior systemic therapy in separate cohorts. Identification of a *RET* gene alteration was prospectively determined in local laboratories using next generation sequencing (NGS), polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH) or other local testing methods. Adult patients received RETVMO 160 mg orally twice daily until unacceptable toxicity or disease progression; patients enrolled in the dose escalation phase were permitted to adjust their dose to 160 mg twice daily. The major efficacy outcome measures were confirmed 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 NSCLC Previously Treated with Platinum Chemotherapy

Efficacy was evaluated in 247 patients with *RET* fusion-positive NSCLC previously treated with platinum chemotherapy enrolled into a cohort of LIBRETTO-001.

The median age was 61 years (range: 23 to 81); 57% were female; 44% were White, 48% were Asian, 4.9% were Black, and 2.8% were Hispanic/Latino. ECOG performance status was 0-1 (97%) or 2 (3%) and 97% of patients had metastatic disease. Patients received a median of 2 prior systemic therapies (range 1–15); 58% had prior anti-PD-1/PD-L1 therapy. *RET* fusions were detected in 94% of patients using NGS (84.6% tumor samples; 9.3% blood or plasma samples), 4.0% using FISH, 1.6% using PCR and 0.4% by other local testing methods.

Efficacy results for previously treated *RET* fusion-positive NSCLC are summarized in Table 8.

Table 8: Efficacy Results in LIBRETTO-001 (*RET* Fusion-Positive NSCLC Previously Treated with Platinum Chemotherapy)

	RETEVMO (n = 247)
Overall Response Rate¹ (95% CI)	61% (55%, 67%)
Complete response	7.3%
Partial response	54%
Duration of Response	
Median in months (95% CI)	28.6 (20, NE)
% with ≥ 12 months ²	63%

¹ Confirmed overall response rate assessed by BIRC.

² Based on observed duration of response.

NE = not estimable

For the 144 patients who received an anti-PD-1 or anti-PD-L1 therapy, either sequentially or concurrently with platinum-based chemotherapy, an exploratory subgroup analysis of ORR was 63% (95% CI: 54%, 70%) and the median DOR was 28.6 months (95% CI: 14.8, NE).

Among the 247 patients with previously treated *RET* fusion-positive NSCLC, 16 had measurable CNS metastases at baseline as assessed by BIRC. One patient received radiation therapy (RT) to the brain within 2 months prior to study entry. Responses in intracranial lesions were observed in 14 of these 16 patients; 39% of responders had an intracranial DOR of ≥ 12 months.

Treatment-naïve *RET* Fusion-Positive NSCLC

Efficacy was evaluated in 69 patients with treatment-naïve *RET* fusion-positive NSCLC enrolled into a cohort of LIBRETTO-001.

The median age was 63 years (range 23 to 92); 62% were female; 70% were White, 19% were Asian, and 6% were Black. ECOG performance status was 0-1 (94%) or 2 (6%) and 99% of patients had metastatic disease. *RET* fusions were detected in 91% of patients using NGS (60.9% tumor samples; 30.4% in blood), 7.2% using FISH and 1.4% using PCR.

Efficacy results for treatment naïve *RET* fusion-positive NSCLC are summarized in Table 9.

Table 9: Efficacy Results in LIBRETTO-001 (Treatment-Naïve *RET* Fusion-Positive NSCLC)

	RETEVMO (n = 69)
Overall Response Rate¹ (95% CI)	84% (73%, 92%)
Complete response	5.8%
Partial response	78%
Duration of Response	
Median in months (95% CI)	20.2 (13, NE)
% with ≥ 12 months ²	50%

¹ Confirmed overall response rate assessed by BIRC.

² Based on observed duration of response.

NE = not estimable

Among the 69 patients with treatment-naïve *RET* fusion-positive NSCLC, 5 had measurable CNS metastases at baseline as assessed by BIRC. Two patients received RT to the brain within 2 months prior to study entry. Responses in intracranial lesions were observed in 4 of these 5 patients; 38% of responders had an intracranial DOR of ≥ 12 months.

14.2 *RET*-Mutant Medullary Thyroid Cancer

The efficacy of RETEVMO was evaluated in patients with *RET*-mutant MTC enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001, NCT03157128). The study enrolled patients with advanced or metastatic *RET*-mutant MTC who had been previously treated with cabozantinib or vandetanib (or both) and patients with advanced or metastatic *RET*-mutant MTC who were naïve to cabozantinib and vandetanib in separate cohorts.

RET-Mutant MTC Previously Treated with Cabozantinib or Vandetanib

Efficacy was evaluated in 55 patients with *RET*-mutant advanced MTC who had previously treated with cabozantinib or vandetanib enrolled into a cohort of LIBRETTO-001.

The median age was 57 years (range: 17 to 84); 66% were male; 89% were White, 7% were Hispanic/Latino, and 1.8% were Black. ECOG performance status was 0-1 (95%) or 2 (5%) and 98% of patients had metastatic disease. Patients received a median of 2 prior systemic therapies (range 1 – 8). *RET* mutation status was detected in 82% of patients using NGS (78% tumor samples; 4% blood or plasma), 16% using PCR, and 2% using an unknown test. The protocol excluded patients with synonymous, frameshift or nonsense *RET* mutations; the specific mutations used to identify and enroll patients are described in Table 10.

Table 10: Mutations used to Identify and Enroll Patients with *RET*-Mutant MTC in LIBRETTO-001

RET Mutation Type¹	Previously Treated (n = 55)	Cabozantinib/Vandetanib Naïve (n = 88)	Total (n = 143)
M918T	33	49	82
Extracellular cysteine mutation ²	7	20	27
V804M or V804L	5 ⁴	6	11
Other ³	10	13	23

¹ Somatic or germline mutations; protein change.

² Extracellular cysteine mutations involving cysteine residues 609, 611, 618, 620, 630, and 634.

³ Other included: K666N (1), D631_L633delinsV (2), D631_L633delinsE (5), D378_G385delinsE (1), D898_E901del (2), A883F (4), E632_L633del (4), L790F (2), T636_V637insCRT(1), D898_E901del + D903_S904delinsEP (1).

⁴ One patient also had a M918T mutation.

Efficacy results for *RET*-mutant MTC are summarized in Table 11.

Table 11: Efficacy Results in LIBRETTO-001 (*RET*-Mutant MTC Previously Treated with Cabozantinib or Vandetanib)

	RETEVMO (n = 55)
Overall Response Rate¹ (95% CI)	69% (55%, 81%)
Complete response	9%
Partial response	60%
Duration of Response	
Median in months (95% CI)	NE (19.1, NE)
% with ≥ 6 months ²	76

¹ Confirmed overall response rate assessed by BIRC.

² Based on observed duration of response.

NE = not estimable

Cabozantinib and Vandetanib-naïve *RET*-Mutant MTC

Efficacy was evaluated in 88 patients with *RET*-mutant MTC who were cabozantinib and vandetanib treatment-naïve enrolled into a cohort of LIBRETTO-001.

The median age was 58 years (range: 15 to 82) with two patients (2.3%) aged 12 to 16 years; 66% were male; and 86% were White, 4.5% were Asian, and 2.3% were Hispanic/Latino. ECOG performance status was 0-1 (97%) or 2 (3.4%). All patients (100%) had metastatic disease and 18% had received 1 or 2 prior systemic therapies (including 8% kinase inhibitors, 4.5% chemotherapy, 2.3% anti-PD1/PD-L1 therapy, and 1.1% radioactive iodine). *RET* mutation status was detected in 77.3% of patients using NGS (75.0% tumor samples; 2.3% blood samples), 18.2% using PCR, and 4.5% using an unknown test. The mutations used to identify and enroll patients are described in Table 10.

Efficacy results for cabozantinib and vandetanib-naïve *RET*-mutant MTC are summarized in Table 12.

Table 12: Efficacy Results in LIBRETTO-001 (Cabozantinib and Vandetanib-naïve *RET*-Mutant MTC)

	RETEVMO (n = 88)
Overall Response Rate¹ (95% CI)	73% (62%, 82%)
Complete response	11%
Partial response	61%
Duration of Response	
Median in months (95% CI)	22.0 (NE, NE)
% with ≥6 months ²	61

¹ Confirmed overall response rate assessed by BIRC.

² Based on observed duration of response.

NE = not estimable

14.3 *RET* Fusion-Positive Thyroid Cancer

The efficacy of RETEVMO was evaluated in patients with advanced *RET* fusion-positive thyroid cancer enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001, NCT03157128). Efficacy was evaluated in 27 patients with *RET* fusion-positive thyroid cancer who were radioactive iodine (RAI)-refractory (if RAI was an appropriate treatment option) and were systemic therapy naïve and patients with *RET* fusion-positive thyroid cancer who were RAI-refractory and had received sorafenib, lenvatinib, or both, in separate cohorts.

The median age was 54 years (range 20 to 88); 52% were male; 74% were White, 11% were Hispanic/Latino, 7.4% were Asian, and 3.7% were Black. ECOG performance status was 0-1 (89%) or 2 (11%). All (100%) patients had metastatic disease with primary tumor histologies including papillary thyroid cancer (78%), poorly differentiated thyroid cancer (11%), anaplastic thyroid cancer (7%) and Hurthle cell thyroid cancer (4%). Patients had received a median of 3 prior therapies (range 1–7). *RET* fusion-positive status was detected in 93% of patients using NGS tumor samples and in 7% using blood samples.

Efficacy results for *RET* fusion-positive thyroid cancer are summarized in Table 13.

Table 13: Efficacy Results in LIBRETTO-001 (*RET* Fusion-Positive Thyroid Cancer)

	RETEVMO Previously Treated (n = 19)	RETEVMO Systemic Therapy Naïve (n = 8)
Overall Response Rate¹ (95% CI)	79% (54%, 94%)	100% (63%, 100%)
Complete response	5.3%	12.5%
Partial response	74%	88%
Duration of Response		
Median in months (95% CI)	18.4 (7.6, NE)	NE (NE, NE)
% with ≥6 months ²	87	75

¹ Confirmed overall response rate assessed by BIRC.

² Based on observed duration of response.

NE = not estimable

14.4 Other *RET* Fusion-Positive Solid Tumors

The efficacy of RETEVMO was evaluated in patients with locally advanced or metastatic *RET* fusion-positive solid tumors enrolled in a multicenter, open-label, multi-cohort clinical trial (LIBRETTO-001, NCT03157128). Efficacy was evaluated in 41 patients with *RET* fusion-positive tumors other than NSCLC and thyroid cancer with disease progression on or following prior systemic treatment or who had no satisfactory alternative treatment options.

The median age was 50 years (range 21 to 85), 54% were female, 68% were White, 24% were Asian, and 4.9% were Black; 7% were Hispanic/Latino. ECOG performance status was 0-1 (95%) or 2 (5%) and 95% of patients had metastatic disease. Thirty-seven patients (90%) received prior systemic therapy (median 2 [range 0 – 9]; 32% received 3 or more). The most common cancers were pancreatic adenocarcinoma (27%), colorectal (24%), salivary (10%) and unknown primary (7%). *RET* fusion-positive status was detected in 97.6% of patients using NGS and 2.4% using FISH.

Efficacy results for *RET* fusion-positive solid tumors other than NSCLC and thyroid cancer are summarized in Table 14 and Table 15.

Table 14: Efficacy Results in LIBRETTO-001 (Other *RET* Fusion-Positive Solid Tumors)

	RETEVMO (n = 41)
Overall Response Rate¹ (95% CI)	44% (28, 60)
Complete response	4.9%
Partial response	39%
Duration of Response	
Median in months (95% CI)	24.5 (9.2, NE)
% with ≥6 months ²	67%

¹ Confirmed overall response rate assessed by BIRC.

² Based on observed duration of response.

NE = not estimable

Table 15: Efficacy Results by Tumor Type in LIBRETTO-001 (Other *RET* Fusion-Positive Solid Tumors)

Tumor Type	Patients (n = 41)	ORR ^{1,2}		DOR Range (months)
		n (%)	95% CI	
Pancreatic adenocarcinoma	11	6 (55%)	(23, 83)	2.5, 38.3+
Colorectal	10	2 (20%)	(2.5, 56)	5.6, 13.3
Salivary	4	2 (50%)	(7, 93)	5.7, 28.8+
Unknown primary	3	1 (33%)	(0.8, 91)	9.2
Breast	2	PR, CR	NA	2.3+, 17.3
Sarcoma (soft tissue)	2	PR, SD	NA	14.9+
Xanthogranuloma	2	NE, NE	NA	NA
Carcinoid (bronchial)	1	PR	NA	24.1+
Carcinoma of the skin	1	NE	NA	NA
Cholangiocarcinoma	1	PR	NA	5.6+
Ovarian	1	PR	NA	14.5+
Pulmonary carcinosarcoma	1	NE	NA	NA

Rectal neuroendocrine	1	NE	NA	NA
Small intestine	1	CR	NA	24.5

+ denotes ongoing response.

¹ Confirmed overall response rate assessed by BIRC.

² Best overall response for each patient is presented for tumor types with ≤ 2 patients.

CI = confidence interval, CR = complete response, DOR = duration of response, NA = not applicable, NE = not evaluable, ORR = overall response rate, PR = partial response, SD = stable disease.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

RETEVMO capsules are supplied as follows:

Capsule Strength	Description	Package Configuration	NDC Number
40 mg	Gray opaque, imprinted with "Lilly", "3977" and "40 mg" in black ink	60 count bottle	NDC 0002-3977-60
80 mg	Blue opaque, imprinted with "Lilly", "2980" and "80 mg" in black ink	60 count bottle	NDC 0002-2980-60
		120 count bottle	NDC 0002-2980-26

RETEVMO tablets are supplied in bottles with desiccant in the following configurations:

Tablet Strength	Description	Package Configuration	NDC Number
40 mg	Light gray, film coated, round tablets debossed with "Ret 40" on one side and "5340" on the other side	60 count bottle	NDC 0002-5340-60
80 mg	Dark red-purple, film coated, round tablets debossed with "Ret 80" on one side and "6082" on the other side	60 count bottle	NDC 0002-6082-60
120 mg	Light purple, film coated, round tablets debossed with "Ret 120" on one side and "6120" on the other side	60 count bottle	NDC 0002-6120-60
160 mg	Light pink, film coated, round tablets debossed with Ret "160" on one side and "5562" on the other side	60 count bottle	NDC 0002-5562-60

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions between 15°C and 30°C (59°F to 86°F) are permitted [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hepatotoxicity

Advise patients that hepatotoxicity can occur and to immediately contact their healthcare provider for signs or symptoms of hepatotoxicity [see *Warnings and Precautions* (5.1)].

Interstitial Lung Disease (ILD)/Pneumonitis

Advise patients that ILD/ pneumonitis can occur and to contact their healthcare provider immediately for signs or symptoms of ILD including new or worsening cough or shortness of breath [see *Warnings and Precautions* (5.2)].

Hypertension

Advise patients that they will require regular blood pressure monitoring and to contact their healthcare provider if they experience symptoms of increased blood pressure or elevated readings [see *Warnings and Precautions* (5.3)].

QT Prolongation

Advise patients that RETEVMO can cause QTc interval prolongation and to inform their healthcare provider if they have any QTc interval prolongation symptoms, such as syncope [see *Warnings and Precautions* (5.4)].

Hemorrhagic Events

Advise patients that RETEVMO may increase the risk for bleeding and to contact their healthcare provider if they experience any signs or symptoms of bleeding [see *Warnings and Precautions* (5.5)].

Hypersensitivity Reactions

Advise patients to monitor for signs and symptoms of hypersensitivity reactions, particularly during the first month of treatment [see *Warnings and Precautions* (5.6)].

Tumor Lysis Syndrome

Advise patients to contact their healthcare provider promptly to report any signs and symptoms of TLS [see *Warnings and Precautions* (5.7)].

Risk of Impaired Wound Healing

Advise patients that RETEVMO may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure [see *Warnings and Precautions* (5.8)].

Hypothyroidism

Advise patients that RETEVMO can cause hypothyroidism and to immediately contact their healthcare provider for signs or symptoms of hypothyroidism [see *Warnings and Precautions* (5.9)].

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the possible risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions* (5.10), *Use in Specific Populations* (8.1)].

Advise females of reproductive potential to use effective contraception during the treatment with RETEVMO and for 1 week after the last dose [see *Use in Specific Populations* (8.3)].

Advise males with female partners of reproductive potential to use effective contraception during treatment with RETEVMO and for 1 week after the last dose [see *Use in Specific Populations* (8.3)].

Lactation

Advise women not to breastfeed during treatment with RETEVMO and for 1 week after the last dose [see *Use in Specific Populations* (8.2)].

Infertility

Advise males and females of reproductive potential that RETEVMO may impair fertility [see *Use in Specific Populations* (8.4), *Nonclinical Toxicology* (13.1)].

Drug Interactions

Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid St. John's wort, proton pump inhibitors, H2 receptor antagonists, and antacids while taking RETEVMO.

If PPIs are required, instruct patients to take RETEVMO with food. If H2 receptor antagonists are required, instruct patients to take RETEVMO 2 hours before or 10 hours after the H2 receptor antagonist. If locally-acting antacids are required, instruct patients to take RETEVMO 2 hours before or 2 hours after the locally-acting antacid [see *Drug Interactions* (7.1, 7.2)].

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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ 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 adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 40 mg hard capsules

Retsevmo 80 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Retsevmo 40 mg hard capsules

Each hard capsule contains 40 mg selpercatinib.

Retsevmo 80 mg hard capsules

Each hard capsule contains 80 mg selpercatinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

Retsevmo 40 mg hard capsules

Grey opaque capsule, 6 x 18 mm (size 2), imprinted with “Lilly”, “3977” and “40 mg” in black ink.

Retsevmo 80 mg hard capsules

Blue opaque capsule, 8 x 22 mm (size 0), imprinted with “Lilly”, “2980” and “80 mg” in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted (see sections 4.4 and 5.1)

Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with:

- advanced *RET* fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate)
- advanced *RET*-mutant medullary thyroid cancer (MTC)

4.2 Posology and method of administration

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

RET testing

The presence of a *RET* gene mutation (MTC) or fusion (all other tumour types) should be confirmed by a validated test prior to initiation of treatment with Retsevmo.

Posology

The recommended dose of Retsevmo based on body weight is:

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

If a patient vomits or misses a dose, the patient should be instructed to take the next dose at its scheduled time; an additional dose should not be taken.

Treatment should be continued until disease progression or unacceptable toxicity.

The current selpercatinib dose should be reduced by 50% if co-administering with a strong CYP3A inhibitor. If the CYP3A inhibitor is discontinued, the selpercatinib dose should be increased (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor.

Dose adjustments

Management of some adverse reactions may require dose interruption and/or dose reduction. Retsevmo dose modifications are summarised in Table 1 and Table 2.

Table 1 Recommended dose modifications for Retsevmo for adverse reactions based on body weight

Dose modification	Adults and adolescents ≥50 Kg	Adults and adolescents <50 Kg
Starting dose	160 mg orally twice daily	120 mg orally twice daily
First dose reduction	120 mg orally twice daily	80 mg orally twice daily
Second dose reduction	80 mg orally twice daily	40 mg orally twice daily
Third dose reduction	40 mg orally twice daily	Not applicable

Table 2 Recommended dose modifications for adverse reactions

Adverse drug reaction (ADR)		Dose modification
Increased ALT or AST	Grade 3 or Grade 4	• Suspend dose until toxicity resolves to baseline (see sections 4.4 and 4.8). Resume at a dose reduced by 2 levels. • If after at least 2 weeks selpercatinib is tolerated without recurrent increased ALT or AST, increase dosing by 1 dose level. • If selpercatinib is tolerated without recurrence for at least 4 weeks, increase to dose taken prior to the onset of Grade 3 or 4 increased AST or ALT. • Permanently discontinue selpercatinib if Grade 3 or 4 ALT or AST increases recur despite dose modifications.
Hypersensitivity	All Grades	• Suspend dose until toxicity resolves and begin corticosteroids at a dose of 1 mg/kg (see sections 4.4 and 4.8). Resume selpercatinib at 40 mg twice daily while continuing steroid treatment. Discontinue selpercatinib for recurrent hypersensitivity. • If after at least 7 days, selpercatinib is tolerated without recurrent hypersensitivity, incrementally increase the selpercatinib dose by 1 dose level each week, until the dose taken prior to the onset of hypersensitivity is reached. Taper steroid dose after selpercatinib has been tolerated for at least 7 days at the final dose.
QT interval prolongation	Grade 3	• Suspend dose for QTcF intervals >500 ms until the QTcF returns to <470 ms or baseline (see section 4.4). • Resume selpercatinib treatment at the next lower dose level.
	Grade 4	• Permanently discontinue selpercatinib if QT prolongation remains uncontrolled after two dose reductions or if the patient has signs or symptoms of serious arrhythmia.

Hypertension	Grade 3	• Patient blood pressure should be controlled before starting treatment. • 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 (see sections 4.4 and 4.8).
	Grade 4	• Selpercatinib should be discontinued permanently if medically significant hypertension cannot be controlled.
Haemorrhagic events	Grade 3	• Selpercatinib should be suspended until recovery to baseline. Resume at a reduced dose. If Grade 3 events reoccur following dose modification, permanently discontinue selpercatinib.
	Grade 4	• Permanently discontinue selpercatinib.
Interstitial lung disease (ILD)/Pneumonitis	Grade 2	• Withhold selpercatinib until resolution. • Resume at a reduced dose. • Discontinue selpercatinib for recurrent ILD/pneumonitis
	Grade 3 or Grade 4	• Discontinue selpercatinib.
Other adverse reactions	Grade 3 or Grade 4	• Selpercatinib should be suspended until recovery to baseline. Resume at a reduced dose. • If Grade 4 events reoccur following dose modification, permanently discontinue selpercatinib.

Special populations

Elderly

No dose adjustment is required based on age (see section 5.2).

No overall differences were observed in the treatment emergent adverse events or effectiveness of selpercatinib between patients who were ≥ 65 years of age and younger patients. Limited data are available in patients ≥ 75 years.

Renal impairment

Dose adjustment is not necessary in patients with mild, moderate or severe renal impairment. There are no data in patients with end stage renal disease, or in patients on dialysis (section 5.2).

Hepatic impairment

Close monitoring of patients with impaired hepatic function is important. No dose adjustment is required for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. Patients with severe (Child-Pugh class C) hepatic impairment should be dosed with 80 mg selpercatinib twice daily (section 5.2).

Paediatric population

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

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

Retsevmo is intended to be used from the age of 12 years for the treatment of patients with RET-mutant MTC and RET fusion-positive thyroid cancer (see section 5.1). In RET-mutant MTC and RET fusion-positive thyroid cancer, there are very limited data available in children or adolescents aged less than 18 years. Patients should be dosed according to body weight (see section 4.2). Based on results from a preclinical study (see section 5.3), open growth plates in adolescent patients should be monitored. Dose interruption or discontinuation should be considered based on the severity of any growth plate abnormalities and an individual risk-benefit assessment.

Method of administration

Retsevmo is for oral use.

The capsules 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 time every day.

Retsevmo must be accompanied by a meal if used concomitantly with a proton pump inhibitor (see section 4.5).

Retsevmo should be administered 2 hours before or 10 hours after H₂ receptor antagonists (see section 4.5).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Efficacy across tumour types

The benefit of selpercatinib has been established in single arm trials encompassing a relatively small sample of patients whose tumours exhibit RET gene fusions. Favourable effects of selpercatinib have been shown on the basis of overall response rate and response duration in a limited number of tumour types. The effect may be quantitatively different depending on tumour type, as well as on concomitant genomic alterations (see section 5.1). For these reasons, selpercatinib should only be used if there are no treatment options for which clinical benefit has been established, or where such treatment options have been exhausted (i.e., no satisfactory treatment options).

Interstitial Lung Disease (ILD)/Pneumonitis

Severe, life-threatening, or fatal cases of ILD/pneumonitis have been reported in patients treated with selpercatinib (see section 4.8). Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. Selpercatinib should be withheld, and patients should be promptly investigated for ILD if they present with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnoea, cough, and fever), and treated as medically appropriate. Based on the severity of ILD/pneumonitis, the dose of selpercatinib should be interrupted, reduced, or permanently discontinued (see section 4.2).

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

Grade ≥ 3 increased ALT and Grade ≥ 3 increased AST were reported in patients receiving selpercatinib (see section 4.8). 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 (see section 4.2).

Hypertension

Hypertension was reported in patients receiving selpercatinib (see section 4.8). 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 (see section 4.2). 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 (see section 5.1). 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 medicinal products known to prolong the QT interval.

Selpercatinib may require dose interruption or modification (see section 4.2).

Hypothyroidism

Hypothyroidism has been reported in patients receiving selpercatinib (see section 4.8). Baseline laboratory measurement of thyroid function is recommended in all patients. Patients with pre-existing hypothyroidism should be treated as per standard medical practice prior to the start of selpercatinib treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction during selpercatinib treatment. Thyroid function should be monitored periodically throughout treatment with selpercatinib. Patients who develop thyroid dysfunction should be treated as per standard medical practice, however patients could have an insufficient response to substitution with levothyroxine (T4) as selpercatinib may inhibit the conversion of levothyroxine to triiodothyronine (T3) and supplementation with liothyronine may be needed (see section 4.5).

Strong CYP3A4 inducers

Concomitant use of strong CYP3A4 inducers should be avoided due to the risk of decreased efficacy of selpercatinib (see section 4.5).

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 (see section 4.6).

Fertility

Based on nonclinical safety findings, male and female fertility may be compromised by treatment with Retsevmo (see sections 4.6 and 5.3). 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 (see section 4.8). 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 (see section 4.2). 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 (see section 4.8).

Permanently discontinue selpercatinib in patients with life-threatening or recurrent severe haemorrhage (see section 4.2).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on the pharmacokinetics of selpercatinib

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

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 AUC₀₋₂₄ and C_{max}, respectively).

Agents that may increase selpercatinib plasma concentrations

Co-administration of a single 160 mg selpercatinib dose with itraconazole, a strong CYP3A inhibitor, 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, telithromycin, posaconazole and nefazodone, have to be co-administered, the dose of selpercatinib should be reduced (see section 4.2).

Agents that may decrease selpercatinib plasma concentrations

Co-administration of rifampicin, a strong CYP3A4 inducer resulted in a decrease of approximately 87% and 70% in selpercatinib AUC and C_{max}, 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.

Effects of selpercatinib on the pharmacokinetics of other medicinal products (increase in plasma concentration)

Sensitive CYP2C8 substrates

Selpercatinib increased the $C_{\max}$ and AUC of repaglinide (a substrate of CYP2C8) by approximately 91% and 188% respectively. Therefore, co-administration with sensitive CYP2C8 substrates (e.g., odiaquine, cerivastatin, enzalutamide, paclitaxel, repaglinide, torasemide, sorafenib, rosiglitazone, buprenorphine, selezipag, dasabuvir and montelukast), should be avoided.

Sensitive CYP3A4 substrates

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, buspirone, conivaptan, darifenacin, darunavir, ebastine, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, tipranavir, triazolam, vardenafil), should be avoided.

Co-administration with medicinal products that affect gastric pH

Selpercatinib has pH-dependent solubility, with decreased solubility at higher pH. No clinically significant differences in selpercatinib pharmacokinetics were observed when co-administered with multiple daily doses of ranitidine (H_2 receptor antagonist) given 2 hours after the selpercatinib dose.

Co-administration with medicinal products that are proton pump inhibitors

Co-administration with multiple daily doses of omeprazole (a proton pump inhibitor) decreased selpercatinib AUC_{0-INF} and $C_{\max}$ when selpercatinib was administered fasting. Co-administration with multiple daily doses of omeprazole did not significantly change the selpercatinib AUC_{0-INF} and $C_{\max}$ when Retsevmo was administered with food.

Co-administration 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 (see section 5.2).

Selpercatinib is an *in vitro* inhibitor of P-gp and BCRP. *In vivo*, selpercatinib increased $C_{\max}$ and AUC of dabigatran, a P-gp substrate, by 43% and 38%, respectively. Therefore, caution should be used when taking a sensitive P-gp substrate (e.g., fexofenadine, dabigatran etexilate, colchicine, saxagliptin), and particularly those with a narrow therapeutic index (e.g., digoxin) (see section 5.2).

Medicinal products that may be less effective when given with selpercatinib

Selpercatinib could inhibit D2 deiodinase and thereby decrease the conversion of levothyroxine (T4) to triiodothyronine (T3). Patients could therefore have an insufficient response to substitution with levothyroxine and supplementation with liothyronine may be needed (see section 4.4).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females and males

Women of childbearing potential have to 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.

Pregnancy

There are no available data from the use of selpercatinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Retsevmo is not recommended during pregnancy and in women of childbearing potential not using contraception. It should only be used during pregnancy if the potential benefit justifies the potential risk to the foetus.

Breast-feeding

It is unknown whether selpercatinib is excreted in human milk. A risk to breast-fed newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Retsevmo and for at least one-week after the last dose.

Fertility

No human data on the effect of selpercatinib on fertility are available. Based on findings from animal studies, male and female fertility may be compromised by treatment with Retsevmo (see section 5.3). Both men and women should seek advice on fertility preservation before treatment.

4.7 Effects on ability to drive and use machines

Retsevmo may have minor influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines in case they experience fatigue or dizziness during treatment with Retsevmo (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most common ($\geq 1.0\%$) serious adverse drug reactions (ADRs) are pneumonia (6.6%), haemorrhage (3.2%), abdominal pain (2.9%), diarrhoea (2.0%), hypersensitivity (1.9%), vomiting (1.8%), blood creatinine increased (1.6%), ALT increased (1.3%), AST increased (1.3%), pyrexia (1.3%), fatigue (1.2%), nausea (1.2%), headache (1.1%), chylothorax (1.0%) and hypertension (1.0%). Permanent discontinuation of Retsevmo for treatment emergent adverse events, regardless of attribution occurred in 9.6% of patients. The most common ADRs resulting in permanent discontinuation (3 or more patients) were increased ALT (0.7%), fatigue (0.6%), increased AST (0.5%), blood bilirubin increased (0.4%), pneumonia (0.4%), thrombocytopenia (0.4%) and haemorrhage (0.4%).

Tabulated list of adverse drug reactions

The ADRs reported in patients treated with selpercatinib are shown in Table 3.

The ADRs are classified according to the MedDRA system organ class and frequency.

Frequency groups are defined by the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1\ 000$ to $< 1/100$); rare ($\geq 1/10\ 000$ to $< 1/1\ 000$); very rare ($< 1/10\ 000$), and not known (cannot be estimated from available data).

Median time on treatment with selpercatinib was 30.09 months.

Table 3 Adverse drug reactions in patients receiving single agent selpercatinib (LIBRETTO-001; N=837)

MedDRA system organ class	MedDRA preferred term	Frequency of all Grades	Frequency of Grade ≥ 3
Infections and infestations	Pneumonia ^a	Very common	Common
Immune system disorders ^b	Hypersensitivity ^c	Common	Common
Endocrine disorders	Hypothyroidism	Very common	-
Metabolism and nutrition disorders	Decreased appetite	Very common	Uncommon
Nervous system disorders	Headache ^d	Very common	Common
	Dizziness ^e	Very common	Uncommon
Cardiac disorders	Electrocardiogram QT prolonged ^f	Very common	Common
Vascular disorders	Hypertension ^g	Very common	Very common
	Haemorrhage ^h	Very common	Common
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease/pneumonitis ⁱ	Common	Uncommon
	Chylothorax	Common	Uncommon
Gastrointestinal disorders	Diarrhoea ^j	Very common	Common
	Dry Mouth ^k	Very common	-
	Abdominal pain ^l	Very common	Common
	Constipation	Very common	Uncommon
	Nausea	Very common	Common
	Vomiting ^m	Very common	Common
	Chylous ascites ⁿ	Common	Uncommon
Skin and subcutaneous tissue disorders	Rash ^o	Very common	Uncommon
General disorders and administration site conditions	Oedema ^p	Very common	Common
	Fatigue ^q	Very common	Common
	Pyrexia	Very common	Uncommon
Investigations ^r	AST increased	Very common	Very common
	ALT increased	Very common	Very common
	Lymphocyte count decreased	Very common	Very common
	Creatinine increased	Very common	Common
	White blood cell count decreased	Very common	Common
	Alkaline phosphatase increased	Very common	Common
	Platelets decreased	Very common	Common
	Magnesium decreased	Very common	Uncommon
	Haemoglobin decreased	Very common	Common
	Total bilirubin increased	Very common	Common
	Neutrophil count decreased	Very common	Common

- ^a Pneumonia includes pneumonia, lung infection, pneumonia aspiration, empyema, lung consolidation, pleural infection, pneumonia bacterial, pneumonia staphylococcal, atypical pneumonia, lung abscess, pneumocystis jirovecii pneumonia, pneumonia pneumococcal and pneumonia respiratory syncytial viral.
- ^b Hypersensitivity reactions were characterised 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).
- ^c Hypersensitivity includes drug hypersensitivity and hypersensitivity.
- ^d Headache includes headache, sinus headache and tension headache.
- ^e Dizziness includes dizziness, vertigo, presyncope and dizziness postural.
- ^f Electrocardiogram QT prolonged includes electrocardiogram QT prolonged and Electrocardiogram QT interval abnormal.
- ^g Hypertension includes hypertension and blood pressure increased.
- ^h Haemorrhage includes epistaxis, haemoptysis, contusion, haematuria, rectal haemorrhage, vaginal haemorrhage, cerebral haemorrhage, traumatic haematoma, blood urine present, conjunctival haemorrhage, ecchymosis, gingival bleeding, haematochezia, petechiae, blood blister, spontaneous haematoma, abdominal wall haematoma, anal haemorrhage, angina bullosa haemorrhagica, disseminated intravascular coagulation, eye haemorrhage, gastric haemorrhage, gastrointestinal haemorrhage, haemorrhage intracranial, haemorrhage subcutaneous, haemorrhoidal haemorrhage, hepatic haematoma, intra-abdominal haemorrhage, mouth haemorrhage, oesophageal haemorrhage, pelvic haematoma, periorbital haematoma, periorbital haemorrhage, pharyngeal haemorrhage, pulmonary contusion, purpura, retroperitoneal haematoma, skin haemorrhage, subarachnoid haemorrhage, diverticulum intestinal haemorrhagic, eye haematoma, haematemesis, haemorrhage, haemorrhagic stroke, hepatic haemorrhage, laryngeal haemorrhage, lower gastrointestinal haemorrhage, melaena, menorrhagia, occult blood positive, post procedural haemorrhage, postmenopausal haemorrhage, retinal haemorrhage, scleral haemorrhage, subdural haemorrhage, traumatic haemothorax, tumour haemorrhage, upper gastrointestinal haemorrhage, uterine haemorrhage and vessel puncture site haematoma.
- ⁱ Interstitial lung disease/pneumonitis includes pneumonitis, radiation pneumonitis, restrictive pulmonary disease, acute respiratory distress syndrome, alveolitis, bronchiolitis, langerhans' cell histiocytosis and pulmonary radiation injury.
- ^j Diarrhoea includes diarrhoea, anal incontinence, defaecation urgency, frequent bowel movements and gastrointestinal hypermotility.
- ^k Dry mouth includes dry mouth and mucosal dryness.
- ^l Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower and gastrointestinal pain.
- ^m Vomiting includes vomiting, retching and regurgitation.
- ⁿ Chylous ascites includes chylous ascites and ascites chylous (MedDRA LLTs).
- ^o Rash includes rash, rash maculo-papular, dermatitis, skin exfoliation, rash macular, rash erythematous, urticaria, dermatitis allergic, exfoliative rash, rash papular, rash morbilliform, rash pruritic, rash vesicular, butterfly rash, rash follicular, rash generalised, and rash pustular.
- ^p Oedema includes oedema peripheral, face oedema, periorbital oedema, swelling face, localised oedema, peripheral swelling, generalised oedema, eyelid oedema, eye swelling, lymphoedema, oedema genital, scrotal swelling, angioedema, eye oedema, oedema, scrotal oedema, skin oedema, swelling, orbital oedema, testicular swelling and vulvovaginal swelling.
- ^q Fatigue includes fatigue, asthenia and malaise.
- ^r Based on laboratory assessments. Percentage is calculated based on the number of patients with baseline assessment and at least one post-baseline assessment as the denominator, which was 806 for lymphocyte count decrease, 830 for magnesium decreased, 814 for neutrophil count decreased, and 834 for the others.

Description of selected adverse reactions

Aminotransferase elevations (AST / ALT increased)

Based on laboratory assessment, ALT and AST elevations were reported in 56.7% and 61.3% patients, respectively. Grade 3 or 4 ALT or AST elevations were reported in 12.2% and 10.4% patients respectively.

The median time to first onset was: AST increase 4.7 weeks (range: 0.7, 227.9), ALT increase 4.4 weeks (range: 0.9, 186.1).

Dose modification is recommended for patients who develop Grade 3 or 4 ALT or AST increase (see section 4.2).

QT interval prolongation

In the 837 patients who had ECGs, review of data showed 8.1% of patients had >500 msec maximum post-baseline QTcF value, and 21.6% of patients had a >60 msec maximum increase from baseline in QTcF intervals. At the time of the last post-baseline measurement, increase in QTc value >60 msec was reported in 2.0% of patients.

There were no reports of *Torsade de pointes*, sudden death, ventricular tachycardia, ventricular fibrillation, or ventricular flutter related to selpercatinib. One patient (0.1%) discontinued treatment due to QT prolongation.

Retsevmo may require dose interruption or modification (see sections 4.2 and 4.4).

Hypertension

In the 837 patients who had blood pressure measurements, the median maximum increase from baseline systolic pressure was 32 mm Hg (range: -15, +100). Only 10.3% of patients retained their baseline grade during treatment, 40.7% had an increasing shift of 1 grade, 38.5% of 2 grades, and 9.8% of 3 grades. A treatment emergent adverse event of hypertension was reported in 44.8% patients with history of hypertension (28.2% with grade 3, 4) and 41.7% of patients without history of hypertension (14.1% with grade 3, 4).

Overall, a total of 19.8% displayed treatment-emergent Grade 3 hypertension (defined as maximum systolic blood pressure greater than 160 mm Hg). Grade 4 treatment emergent hypertension was reported in 0.1% of patients. Diastolic blood pressure results were similar, but the increases were of lesser magnitude.

Two patients (0.2%) permanently discontinued treatment due to hypertension. Dose modification is recommended in patients who develop hypertension (see section 4.2). Selpercatinib should be discontinued permanently if medically significant hypertension cannot be controlled with antihypertensive therapy (see section 4.4).

Hypersensitivity

Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or increased aminotransferase.

In study LIBRETTO-001, 24.0% (201/837) of patients treated with selpercatinib had previously received anti-PD-1/PD-L1 immunotherapy. Hypersensitivity occurred in a total of 5.7% (48/837) of patients receiving selpercatinib, including Grade 3 hypersensitivity in 1.9% (16/837) of patients. Of the 48 patients with hypersensitivity, 54.2% (26/48) had NSCLC and had received prior anti-PD-1/PD-L1 immunotherapy.

Grade 3 hypersensitivity occurred in 3.5% (7/201) of the patients previously treated with anti-PD-1/PD-L1 immunotherapy.

The median time to onset was 1.9 weeks (range: 0.7 to 203.9 weeks): 1.7 weeks in patients with previous anti-PD-1/PD-L1 immunotherapy and 4.4 weeks in patients who were anti-PD-1/PD-L1 immunotherapy naïve.

Retsevmo may require dose interruption or modification (see section 4.2).

Haemorrhages

Grade ≥3 haemorrhagic events occurred in 3.5% of patients treated with selpercatinib, including 4 (0.5%) patients with fatal haemorrhagic events, two cases of cerebral haemorrhage, and one case

each of tracheostomy site haemorrhage, and haemoptysis. The median time to onset was 34.1 weeks (range: 0.1 week to 234.6 weeks).

Selpercatinib should be discontinued permanently in patients with life-threatening or recurrent severe haemorrhage (see section 4.2).

Additional information on special populations

Paediatric patients

There were 3 patients < 18 years (range: 15-17) of age with RET-mutant MTC in LIBRETTO-001. There were 8 patients < 18 years (range 12-17) of age with RET fusion-positive thyroid cancer in LIBRETTO-121. No unique safety findings in children aged less than 18 years have been identified.

Elderly

In patients receiving selpercatinib, 24.7% were ≥65-74 years of age, 8.6% were 75-84 years of age, and 1.0% ≥ 85 years of age. The frequency of serious adverse events reported was higher in patients ≥65-74 years (58.0%), 75-84 years (62.5%), and ≥85 years (100.0%), than in patients <65 years (46.7%) of age.

The frequency of AE leading to discontinuation of selpercatinib was higher in patients ≥65-74 years (10.1%), 75-84 years (19.4%), and ≥85 years (37.5%), than in patients <65 years of age (7.6%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, antineoplastic agents, protein kinase inhibitors, ATC code: L01EX22

Mechanism of action

Selpercatinib is an 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. In a binding assay at the concentration of 1 µM selpercatinib, significant antagonist binding activity (>50%) was observed for the 5-HT (serotonin) transporter (70.2% antagonist) and α₂C adrenoreceptor (51.7% antagonist). The concentration of 1 µM is approximately 7-fold higher than the maximum unbound plasma concentration of at the efficacious dose of selpercatinib.

Certain point mutations in RET or chromosomal rearrangements involving in-frame fusions of RET with various partners can result in constitutively activated chimeric RET fusion proteins that can act as oncogenic drivers by promoting cell proliferation of tumour cell lines. In *in vitro* and *in vivo* tumour models, selpercatinib demonstrated anti-tumour 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-tumour activity in mice intracranially implanted with a patient-derived RET fusion-positive tumour.

Pharmacodynamic properties

Cardiac electrophysiology

In a thorough QT study with positive control in 32 healthy subjects, no large change (that is, >20 ms) in the QTcF interval was detected at selpercatinib concentrations similar to those observed with a therapeutic dosing schedule. 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 sections 4.2 and 4.4).

Clinical efficacy and safety

The efficacy of Retsevmo was evaluated in adult patients with advanced RET fusion-positive NSCLC, RET fusion-positive thyroid cancer, other RET fusion-positive solid tumours, and in adult and adolescent patients with RET-mutant MTC enrolled in a phase 1/2, multicenter, open-label, single-arm clinical study: Study LIBRETTO-001. This study included two parts: phase 1 (dose escalation) and phase 2 (dose expansion). The primary objective of the phase 1 portion was to determine the recommended phase 2 dose of selpercatinib. The primary objective of the phase 2 part was to evaluate the anti-tumour activity of selpercatinib by determining ORR, as assessed by independent review committee. Patients with measurable or non-measurable disease as determined by RECIST 1.1, with evidence of a RET gene alteration in tumour and who had failed or were intolerant to standard of care were enrolled. Patients with CNS metastases were eligible if stable, while patients with symptomatic primary CNS tumour, metastases, leptomeningeal carcinomatosis or spinal cord compression were excluded. Patients with known primary driver alteration other than RET, clinically significant active cardiovascular disease or history of myocardial infarction, QTcF interval > 470 msec were excluded.

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 primary efficacy outcome measure was overall response rate (ORR) according to RECIST v1.1 as evaluated by a Blinded Independent Review Committee (IRC). Secondary efficacy outcomes included duration of response (DOR), progression free survival (PFS) and overall survival (OS).

Treatment-naïve RET fusion-positive NSCLC

Of the 362 RET fusion-positive NSCLC patients enrolled in LIBRETTO-001, 69 were treatment naïve. The median age was 63 years (range 23 years to 92 years). 62.3% of patients were female. 69.6% of patients were White, 18.8% were Asian, 5.8% were Black and 69.6% were never smokers. Most patients (98.6%) had metastatic disease at enrolment and 23.2% had CNS metastasis at baseline as assessed by investigator. ECOG performance status was reported as 0-1 (94.2%) or 2 (5.8%). The most common fusion partner was KIF5B (69.6%), followed by CCDC6 (14.5%) and then NCOA4 (1.4%). Efficacy results for treatment-naïve RET fusion-positive NSCLC patients are summarised in Table 4.

Table 4 Objective response and duration of response

	Efficacy eligible patients IRC assessment
N	69
Objective response (CR + PR)	
% (95% CI)	82.6 (71.6, 90.7)
Complete response n (%)	5 (7.2)
Partial response n (%)	52 (75.4)

Duration of response (months)*	
Median, 95% CI	20.23 (15.4, 29.5)
Rate (%) of patients with duration of response	
≥ 6 months (95% CI)	87.5 (75.5, 93.8)
≥ 12 months (95% CI)	66.7 (52.4, 77.6)

*Median duration of follow-up was 37.09 months (25th, 75th percentile: 24.0, 45.1)

Data Cut-off date: 13 January 2023.

Previously treated RET fusion-positive NSCLC

A total of 247 patients had received prior platinum-based chemotherapy. The median age was 61 years (range 23 years to 81 years). 56.7% of patients were female. 43.7% of patients were White, 47.8% were Asian, 4.9% were Black, and 66.8% were never smokers. Most patients (98.8%) had metastatic disease at enrolment and 31.2% had CNS metastasis at baseline as assessed by investigator. ECOG performance status was reported as 0-1 (97.1%) or 2 (2.8%). The most common fusion partner was KIF5B (61.9%), followed by CCDC6 (21.5%) and then NCOA4 (2.0%). The median number of prior systemic therapies was 2 (range 1–15) and 43.3% (n = 107/247) received 3 or more prior systemic regimens; prior treatments included anti PD1/PD-L1 therapy (58.3%), multi-kinase inhibitor (MKI) (31.6%) and taxanes (34.8%); 41.3% had other systemic therapy. Efficacy results for previously treated RET fusion-positive NSCLC patients are summarised in Table 5.

Table 5 Objective response and duration of response

	Efficacy eligible patients IRC assessment
N	247
Objective response (CR + PR)	
% (95% CI)	61.5 (55.2, 67.6)
Complete response n (%)	20 (8.1)
Partial response n (%)	132 (53.4)
Duration of response (months)*	
Median (95% CI)	31.6 (20.4, 42.3)
Rate (%) of patients with duration of response	
≥ 6 months (95% CI)	87.0 (80.4, 91.5)
≥ 12 months (95% CI)	73.0 (65.0, 79.5)

*Median duration of follow-up was 39.52 months (25th, 75th percentile: 24.6, 45.0)

Data Cut-off date: 13 January 2023.

CNS response in RET fusion-positive NSCLC

The CNS ORR assessed by IRC was 84.6% (22/26; 95% CI: 65.1, 95.6) in 26 patients with measurable disease. CR was observed in 7 (26.9%) patients and PR in 15 (57.5%) patients. The median CNS DOR was 9.36 months (95% CI: 7.4, 15.3).

Systemic treatment-naïve RET fusion-positive thyroid cancer

Of the RET fusion-positive thyroid cancer patients naïve to systemic therapy other than radioactive iodine, and enrolled in LIBRETTO-001, 24 patients had the opportunity to be followed for at least 6 months and were considered efficacy eligible. The median age was 60.5 years (range 20 to 84 years). 58.3% of patients were male. 75% of patients were White. ECOG performance status was reported as 0-1 (95.8%) or 2 (4.2%). 100% of patients had a history of metastatic disease. 22 out of the 24 patients (91.7%) received radioactive iodine prior to enrolment and therefore were considered radioactive iodine refractory. The different histologies represented in the 24 patients included: papillary (n=23) and poorly differentiated (n=1). The most common fusion partner was CCDC6 (45.8%) followed by

NCOA4 (20.8%). Efficacy results for systemic treatment-naïve *RET* fusion-positive thyroid cancer patients are summarised in Table 6.

Table 6 Objective response and duration of response

	Efficacy eligible patients IRC assessment
N	24
Objective response (CR + PR)	
% (95% CI)	95.8 (78.9, 99.9)
Complete response n (%)	5 (20.8)
Partial response n (%)	18 (75.0)
Duration of response (months)*	
Median (95% CI)	NE (42.8, NE)
Rate (%) of patients with duration of response	
≥ 12 months (95% CI)	100.0 (NE, NE)
≥ 24 months (95% CI)	90.9 (50.8, 98.7)

NE = not estimable

*Median duration of follow-up was 17.81 months (25th, 75th percentile: 9.2, 42.3)

Data Cut-off date: 13 January 2023

Previously treated RET fusion-positive thyroid cancer

Of the *RET* fusion-positive thyroid cancer patients previously treated with systemic therapy other than Radioactive iodine, and enrolled in LIBRETTO-001, 41 patients had the opportunity to be followed for at least 6 months and were considered efficacy eligible. The median age was 58 years (range 25 to 88 years). 43.9% of patients were male. 58.5% of patients were White while 29.3% were Asian and 7.3% were Black. ECOG performance status was reported as 0-1 (92.7%) or 2 (7.3%). 100% of patients had metastatic disease. Patients had received a median of 3 prior systemic therapies (range: 1-7). The most common prior therapies included radioactive iodine (73.2%), MKI (85.4%). 9.8% had other systemic therapy. The different histologies represented in the 41 patients included: papillary (n = 31), poorly differentiated (n = 5), anaplastic (n = 4), and Hurthle cell (n = 1). The most common fusion partner was CCDC6 (61.0%) followed by NCOA4 (19.5%).

Efficacy results for previously treated *RET* fusion-positive thyroid cancer are summarised in Table 7.

Table 7 Objective response and duration of response

	Efficacy eligible patients IRC assessment
N	41
Objective response (CR + PR)	
% (95% CI)	85.4 (70.8, 94.4)
Complete response n (%)	5 (12.2)
Partial response n (%)	30 (73.2)
Duration of response (months)*	
Median (95% CI)	26.7 (12.1, NE)
Rate (%) of patients with duration of response	
≥ 12 months (95% CI)	71.7 (52.4, 84.2)
≥ 24 months (95% CI)	50.7 (30.4, 67.8)

NE = not estimable

*Median duration of follow-up was 33.87 months (25th, 75th percentile: 12.9, 44.8)

Data Cut-off date: 13 January 2023.

Vandetanib and cabozantinib naïve RET-mutant medullary thyroid cancer

Of the 324 RET-mutant MTC patients enrolled in LIBRETTO-001, 143 were naïve to treatment with cabozantinib and vandetanib. Of these 116 were treatment naïve to other systemic therapy and 27 had previously received other systemic therapy. Among patients naïve to cabozantinib and vandetanib, the median age was 57 years (range 15 to 87 years). 2 patients (1.4%) were < 18 years of age. 58.0% of patients were male. 86.7% of patients were White, 5.6% were Asian, 1.4% were Black. Most patients (97.9%) had metastatic disease at enrolment. ECOG performance status was reported as 0-1 (95.9%) or 2 (4.2%). The most common mutation was M918T (60.1%), followed by extracellular cysteine mutations (23.8%). Efficacy results for cabozantinib and vandetanib treatment-naïve RET-mutant MTC patients are summarised in Table 8.

Table 8 Objective response and duration of response

	Efficacy eligible patients IRC assessment
N	143
Objective response (CR + PR)	
% (95% CI)	82.5 (75.3, 88.4)
Complete response n (%)	34 (23.8)
Partial response n (%)	84 (58.7)
Duration of response (months)*	
Median, 95% CI	NE (51.3, NE)
Rate (%) of duration of response	
≥ 12 months (95% CI)	91.4 (84.6, 95.3)
≥ 24 months (95% CI)	84.1 (75.9, 89.7)

NE = not estimable,

*Median duration of follow-up was 39.4 months (25th, 75th percentile: 32.3, 45.4).

Data cut-off date 13 January 2023.

Previously treated RET-mutant medullary thyroid cancer

Of the RET-mutant MTC patients enrolled in LIBRETTO-001, 152 were previously treated with cabozantinib and/or vandetanib, and considered efficacy eligible. The median age was 58 years (range 17 years to 90 years); 1 patient (0.7%) was < 18 years of age. 63.8% of patients were male. 90.1% of patients were White while 1.3% were Asian, and 1.3% were Black. ECOG performance status was reported as 0-1 (92.7%) or 2 (7.2%). 98.0% of patients had metastatic disease. The most common mutation was M918T (65.1%), followed by extracellular cysteine mutations (15.8%). 100% (n = 152) of patients received prior systemic therapy with a median of 2 prior systemic regimens and 27.6% (n = 42) received 3 or more prior systemic regimens.

Efficacy results for previously treated RET-mutant MTC are summarised in Table 9.

Table 9 Objective response and duration of response

	Efficacy eligible patients IRC assessment
N	152
Objective response (CR + PR)	
% (95% CI)	77.6 (70.2, 84.0)
Complete response n (%)	19 (12.5)
Partial response n (%)	99 (65.1)
Duration of response (months)*	
Median (95% CI)	45.3 (33.6, NE)
Rate (%) of duration of response	
≥ 12 months (95% CI)	83.0 (74.6, 88.8)
≥ 24 months (95% CI)	66.4 (56.3, 74.7)

NE = not estimable

*Median duration of follow-up was 38.3 months (25th, 75th percentile: 23.0, 46.1).

Data cut-off date 13 January 2023.

Other RET Fusion-Positive Solid Tumours

Efficacy was evaluated in 52 patients with *RET* fusion-positive tumours other than NSCLC and thyroid cancer with disease progression on or following prior systemic treatment or who had no satisfactory alternative treatment options. The median age was 54 years (range 21 to 85); 51.9% were female; 67.3% were White, 25.0% were Asian, and 5.8% were Black; ECOG performance status was 0-1 (92.3%) or 2 (7.7%) and 96.2% of patients had metastatic disease. Forty-seven patients (90.4%) received prior systemic therapy with a median of 2 prior systemic therapies (range 0 to 9) and 28.8% received 3 or more prior systemic therapies. No patients had been previously treated with a selective *RET* inhibitor. The most common cancers were pancreatic (25%), colon (25%), and salivary (7.7%). The most common fusion partners were NCOA4 (34.6%), CCDC6 (17.3%), and KIF5B (11.5%). Efficacy results for *RET* fusion-positive solid tumours other than NSCLC and thyroid cancer are summarized in Table 10 and Table 11.

Table 10 Objective response and duration of response

	Efficacy eligible patients IRC assessment
N	52
Overall response (CR+PR)	
% (95% CI)	44.2 (30.5, 58.7)
Complete response n (%)	3 (5.8)
Partial response n (%)	20 (38.5)
Duration of Response (months)*	
Median (95% CI)	37.19 (13.3, NE)
Rate (%) of duration of response	
6 months (95% CI)	84.7 (59.5, 94.8)
12 months (95% CI)	79 (53.1, 91.6)

* Median duration of follow-up was 28.55 months (25th, 75th percentile: 11.2, 40.9)

NE = not estimable

Data cut-off date 13 January 2023

Table 11 Objective response and duration of response by Tumour Type

Tumour Type	Patients (N = 52)	ORR (IRC assessment)		DOR Range (months)
		n (%)	95% CI	
Pancreatic	13	7 (53.8)	25.1, 80.8	2.50, 52.14
Colorectal	13	4 (30.8)	9.1, 61.4	1.84+, 13.31
Salivary	4	2 (50.0)	6.8, 93.2	5.72, 37.19
Cholangiocarcinoma	3	1 (33.3)	0.8, 90.6	14.82
Unknown primary	3	1 (33.3)	0.8, 90.6	9.23
Sarcoma	3	1 (33.3)	0.8, 90.6	31.44+
Breast	2	PR, CR	NA	2.30+, 17.28
Xanthogranuloma	2	NE, NE ^a	NA	NA
Carcinoma of the skin	2	NE, PR	NA	14.82+
Carcinoid	1	PR	NA	40.94+
Ovarian	1	PR	NA	28.55+
Pulmonary carcinosarcoma	1	NE	NA	NA
Rectal neuroendocrine	1	NE	NA	NA
Small intestine	1	CR	NA	24.54
Neuroendocrine	1	PR	NA	3.54+
Small cell lung cancer	1	SD	NA	NA

+ denotes ongoing response.

^a One xanthogranuloma patient had disease that could not be evaluated by IRC due to skin being the only site of disease. Based on investigator assessment, this patient had a CR.

CI = confidence interval, CR = complete response, DOR = duration of response, NA = not applicable, NE = not evaluable, ORR = overall response rate, PR = partial response, SD = stable disease.

Data cut-off date 13 January 2023

Due to the rarity of RET fusion-positive cancer, patients were studied across multiple tumour types with a limited number of patients in some tumour types, causing uncertainty in the ORR estimate per tumour type. The ORR in the total population may not reflect the expected response in a specific tumour type.

Paediatric population

As of 13 January 2023, 10 patients with *RET* fusion-positive thyroid cancer aged 12 to ≤ 21 years have been treated in LIBRETTO-121, an ongoing Phase 1/2 study in paediatric patients with an advanced solid or primary CNS tumour harbouring an activating RET alteration. Of these 10 patients, 8 patients were less than 18 years of age. Of the 10 patients, 4 were previously treated with radioactive iodine only, 2 had received prior systemic therapy that did not include radioactive iodine and 4 were not previously treated with any systemic therapy. For all 10 patients, per IRC, objective response rate was 60.0% (95% CI: 26.2, 87.8). 3 patients had confirmed complete response whilst 3 patients had confirmed partial response.

The European Medicines Agency has waived the obligation to submit the results of studies with selipercatinib in patients aged 6 months and below in solid tumours (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with selpercatinib in one or more subsets of the paediatric population in relapsed/refractory solid tumours, including RET fusion-positive solid tumours, RET-mutant medullary thyroid cancer, and other tumours with RET alteration/activation (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of selpercatinib were evaluated in patients with locally advanced or metastatic solid tumours administered 160 mg twice daily unless otherwise specified. Steady-state selpercatinib AUC and C_{max} increased in a linear to supra-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%)] C_{max} was 2,980 (53%) ng/mL and AUC_{0-24h} was 51,600 (58%) ng*h/mL.

In vivo studies indicate that selpercatinib is a mild inhibitor of P-gp.

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, 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 73.2% (range: 60.2-81.5%).

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), estimated by Population PK analysis, is 191 (69%) L following oral administration of selpercatinib in adult patients. Selpercatinib is 96% bound to human plasma proteins *in vitro* and binding is independent of concentration. The blood-to-plasma concentration ratio is 0.7.

Biotransformation

Selpercatinib is metabolized predominantly by CYP3A4. Following oral administration of a single [¹⁴C] 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 [¹⁴C] 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.

Special populations

Age, gender and body weight

Age (range: 15 years to 90 years) or gender had no clinically meaningful effect on the pharmacokinetics of Retsevmo. Patients with a body weight < 50 kg should start Retsevmo treatment with a dose of 120 mg twice daily, while patients ≥ 50 kg should start Retsevmo treatment with a dose of 160 mg twice daily.

Hepatic impairment

Selpercatinib AUC_{0-∞} increased by 7% in subjects with mild, 32% in subjects with moderate Child-Pugh classification. Thus, selpercatinib exposure (AUC) in subjects with mild and moderate hepatic impairment (Child-Pugh class A and B) is comparable to exposure in healthy subjects when a dose of 160 mg is administered.

Selpercatinib AUC_{0-∞} increased by 77% in subjects with severe hepatic impairment (Child-Pugh class C). 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 (section 4.2).

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 (eGFR <15 ml/min) and dialysis patients have not been studied.

Paediatric population

Based on limited pharmacokinetic data, the C_{max} and AUC was similar in adolescent patients, 12-18 years of age, and in adults.

5.3 Preclinical safety data

Repeat-dose studies were conducted in juvenile and adolescent/adult rats and adolescent/adult minipigs to characterize toxicity. Target organs of toxicity common to the rat and minipig were hematopoietic system, lymphoid tissues, tongue, pancreas, gastro-intestinal tract, epiphyseal growth plate, and male reproductive tissues. In general, toxicities in these organs were reversible; the exceptions were the testicular toxicity in adolescent/adult and juvenile animals, and changes in growth plates in juvenile rats. Reversible toxicity was observed in the ovaries 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 only occurring in these organs in rats were reversible.

Juvenile toxicity

Selpercatinib exposure approximately 0.5-2 times the exposure in adult humans caused mortality in rats younger than 21 days old. Comparable exposure was tolerated in rats aged 21 days and older.

Juvenile and adolescent/adult rats and adolescent/adult minipigs with open growth plates administered selpercatinib exhibited microscopic changes of hypertrophy, hyperplasia, and dysplasia of growth

plate cartilage (physis). In juvenile rats, the dysplasia at the growth plates was irreversible and associated with decreased femur length and reductions in bone mineral density. Skeletal changes were observed at exposure levels equivalent to those seen in adult patients taking the recommended dose of 160 mg BID.

Juvenile male rats administered selpercatinib and allowed to reach reproductive age after cessation of administration, exhibited decreased reproductive performance when mated with untreated female rats. Decreased fertility and copulation indices, increased pre- and post-implantation losses, and decreased number of viable embryos, were observed at an exposure approximately 3.4 times the efficacious exposure in adults.

Genotoxicity

Selpercatinib is not genotoxic at therapeutic doses. In an *in vivo* micronucleus assay in rats, selpercatinib was positive at concentrations >7 times the C_{max} 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 C_{max} at the human dose.

Mutagenesis

Selpercatinib did not cause mutations in a bacterial mutagenicity assay.

Carcinogenesis

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

Embryotoxicity / Teratogenicity

Based on data from animal reproduction studies and its mechanism of action, selpercatinib can cause foetal harm when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryoletality and malformations.

Reproduction toxicity

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

In a fertility study in male rats, dose-dependent germ cell depletion and spermatid retention were observed at subclinical AUC-based exposure levels (0.2 times the clinical exposure at the recommended human dose). These effects were associated with reduced organ weights, reduced sperm motility, and an increase in the number of abnormal sperm at AUC-based exposure levels approximately twice 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 subclinical 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, a reduction in the number of estrous cycles as well as embryoletality were observed at AUC-based exposure levels approximately equal to clinical exposure at the recommended human dose. In repeat-dose studies in rats, reversible vaginal mucification with individual cell cornification and altered estrous cycles were noted at clinically relevant AUC-based exposure levels. In minipigs, decreased corpora lutea and/or corpora luteal cysts were observed at subclinical AUC-based clinical exposure levels (0.07 to 0.3 times the clinical exposure at the recommended human dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Cellulose, microcrystalline
Silica, colloidal anhydrous

Capsule shell

Retsevmo 40 mg hard capsules

Gelatin
Titanium dioxide (E171)
Iron Oxide (E172)

Retsevmo 80 mg hard capsules

Gelatin
Titanium dioxide (E171)
Brilliant Blue FCF (E133)

Capsules black ink composition

Shellac
Ethanol (96 per cent),
Isopropyl alcohol
Butanol
Propylene glycol
Water, purified
Ammonia solution, concentrated
Potassium hydroxide
Iron oxide black

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Plastic bottle

Each pack contains 1 HDPE bottle with a plastic screw cap.

Retsevmo 40 mg hard capsules

Retsevmo 40 mg hard capsules is supplied as a 60 count HDPE bottle.

Retsevmo 80 mg hard capsules

Retsevmo 80 mg hard capsules is supplied as 60 count HDPE bottle or 120 count HDPE bottle.

Blister pack

Retsevmo 40 mg hard capsules

Supplied as PCTFE/PVC blisters sealed with an aluminium foil in a blister card, in packs of 14, 42, 56 or 168 hard capsules.

Retsevmo 80 mg hard capsules

Supplied as PCTFE/PVC blisters sealed with an aluminium foil in a blister card, in packs of 14, 28, 56 or 112 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83
3528BJ Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1527/001
EU/1/20/1527/002
EU/1/20/1527/003
EU/1/20/1527/004
EU/1/20/1527/005
EU/1/20/1527/006
EU/1/20/1527/007
EU/1/20/1527/008
EU/1/20/1527/009
EU/1/20/1527/010
EU/1/20/1527/011

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 February 2021
Date of latest renewal: 05 January 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Lilly, S.A.
Avda. de la Industria, 30
28108 Alcobendas, Madrid
Spain

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14a(4) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET fusion-positive non-small cell lung cancer, the MAH should submit the clinical study report of the Phase 3 study J2G-MC-JZJC	31 December 2024

Description	Due date
(LIBRETTO-431) comparing selpercatinib to platinum-based and pemetrexed therapy with or without pembrolizumab in patients with locally advanced or metastatic, RET-fusion-positive non-squamous NSCLC. The CSR should be submitted by	
In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET-mutant medullary thyroid carcinoma, the MAH should submit the clinical study report of the Phase 3 study J2G-MC-JZJB (LIBRETTO-531) comparing selpercatinib to physician's choice of cabozantinib or vandetanib in patients with progressive, advanced, kinase inhibitor-naïve, RET-mutant MTC. The CSR should be submitted by	30 September 2025
In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET fusion-positive thyroid cancer, the MAH should submit the final data from the study LIBRETTO-121.	30 June 2025
In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with systemic treatment naïve RET fusion-positive thyroid cancer, the MAH should submit the final data from the cohort 2 of the pivotal study LIBRETTO-001.	31 December 2025
In order to further confirm the efficacy and safety of selpercatinib in the treatment of patients with RET fusion-positive solid tumours other than NSCLC and thyroid cancer, the MAH should submit the final data from patients with RET-fusion positive solid tumours other than NSCLC and thyroid cancer enrolled in the pivotal study LIBRETTO-001.	31 December 2025

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PLASTIC BOTTLE - CARTONS FOR 40 MG HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 40 mg hard capsules
selpercatinib

2. STATEMENT OF ACTIVE SUBSTANCE

Each hard capsule contains 40 mg selpercatinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528BJ Utrecht, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/20/1527/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Retsevmo 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

PLASTIC BOTTLE - LABEL FOR 40 MG HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 40 mg hard capsules
selpercatinib

2. STATEMENT OF ACTIVE SUBSTANCE

Each hard capsule contains 40 mg selpercatinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

If inner seal is broken, do not use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Lilly logo

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/20/1527/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**BLISTER PACK - CARTONS FOR 40 MG HARD CAPSULES****1. NAME OF THE MEDICINAL PRODUCT**

Retsevmo 40 mg hard capsules
selpercatinib

2. STATEMENT OF ACTIVE SUBSTANCE

Each hard capsule contains 40 mg selpercatinib.

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

14 hard capsules
42 hard capsules
56 hard capsules
168 hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528BJ Utrecht, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/20/1527/004 (14 hard capsules)
EU/1/20/1527/005 (42 hard capsules)
EU/1/20/1527/006 (56 hard capsules)
EU/1/20/1527/007 (168 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Retsevmo 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER PACK - BLISTER CARD FOR 40 MG HARD CAPSULES
--

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 40 mg hard capsules
selpercatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

morning

evening

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

**BLISTER PACK - BLISTER TO BE USED INSIDE THE BLISTER CARDS FOR 40 MG
HARD CAPSULES**

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 40 mg
selpercatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PLASTIC BOTTLE - CARTONS FOR 80 MG HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 80 mg hard capsules
selpercatinib

2. STATEMENT OF ACTIVE SUBSTANCE

Each hard capsule contains 80 mg selpercatinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules
120 hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528BJ Utrecht, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/20/1527/002 (60 hard capsules)
EU/1/20/1527/003 (120 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Retsevmo 80 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

PLASTIC BOTTLE - LABEL FOR 80 MG HARD CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 80 mg hard capsules
selpercatinib

2. STATEMENT OF ACTIVE SUBSTANCE

Each hard capsule contains 80 mg selpercatinib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 hard capsules
120 hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

If inner seal is broken, do not use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Lilly logo

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/20/1527/002 (60 hard capsules)
EU/1/20/1527/003 (120 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**BLISTER PACK - CARTONS FOR 80 MG HARD CAPSULES****1. NAME OF THE MEDICINAL PRODUCT**

Retsevmo 80 mg hard capsules
selpercatinib

2. STATEMENT OF ACTIVE SUBSTANCE

Each hard capsule contains 80 mg selpercatinib.

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

14 hard capsules
28 hard capsules
56 hard capsules
112 hard capsules

5. METHOD AND ROUTE OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

Discard unused contents appropriately.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528BJ Utrecht, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/20/1527/008 (14 hard capsules)
EU/1/20/1527/009 (28 hard capsules)
EU/1/20/1527/010 (56 hard capsules)
EU/1/20/1527/011 (112 hard capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Retsevmo 80 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER PACK - BLISTER CARD FOR 80 MG HARD CAPSULES
--

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 80 mg hard capsules
selpercatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

morning

evening

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

**BLISTER PACK - BLISTER TO BE USED INSIDE THE BLISTER CARDS FOR 80 MG
HARD CAPSULES**

1. NAME OF THE MEDICINAL PRODUCT

Retsevmo 80 mg
selpercatinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Retsevmo 40 mg hard capsules

Retsevmo 80 mg hard capsules

selpercatinib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- This leaflet has been written as though the person taking the medicine is reading it. If you are giving this medicine to your child, please replace “you” with “your child” throughout.

What is in this leaflet

1. What Retsevmo is and what it is used for
2. What you need to know before you take Retsevmo
3. How to take Retsevmo
4. Possible side effects
5. How to store Retsevmo
6. Contents of the pack and other information

1. What Retsevmo is and what it is used for

Retsevmo is an anticancer medicine containing the active substance selpercatinib.

It is used to treat the following cancers which are caused by certain abnormal changes in the RET gene and which have spread and/or cannot be removed by surgery:

- A type of lung cancer called non-small cell lung cancer, in adults who have not previously been treated with a *RET* inhibitor medicine.
- Thyroid cancer (any type) in adults and adolescents 12 years and older if radioactive iodine treatment, when appropriate, has failed to control your cancer.
- A rare type of thyroid cancer called medullary thyroid cancer in adults and adolescents 12 years and older.
- Solid tumours (cancer) in other parts of the body in adults after prior therapies have failed to control the cancer.

Your doctor will perform a test to check if your cancer has a change in the RET gene to make sure that Retsevmo is right for you.

How Retsevmo works

In patients whose cancer has an altered RET gene, the change in the gene causes the body to make an abnormal RET protein, which can lead to uncontrolled cell growth and cancer. Retsevmo blocks the action of the abnormal RET protein and so may slow or stop the growth of the cancer. It may also help to shrink the cancer.

If you have any questions about how Retsevmo works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you take Retsevmo

Do not take Retsevmo

- if you are allergic to selipercatinib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor before taking Retsevmo:

- If you have lung or breathing problems other than lung cancer.
- If you have high blood pressure.
- If you have been told that you have an abnormality of your heart tracing after an electrocardiogram (ECG) known as prolonged QT interval.
- If you have problems with your thyroid or levels of thyroid hormone.
- Retsevmo may affect fertility in females and males, which may affect your ability to have children. Talk to your doctor if this is a concern for you.
- If you have a recent history of significant bleeding.

Retsevmo may cause hypersensitivity reactions such as fever, rash and pain. If you experience any of these reactions, talk to your doctor. After checking your symptoms, your doctor may ask you to take corticosteroids until your symptoms are better.

A fast breakdown of cancer cells (tumour lysis syndrome, TLS) can occur when you are taking Retsevmo. This can cause irregular heartbeat, kidney failure or abnormal blood test results. Talk to your doctor if you have a history of kidney problems or low blood pressure, because this may increase the risks associated with TLS.

See section 4, “Possible side effects”, and talk to your doctor if you have any symptoms.

What your doctor will check before and during your treatment

- Retsevmo may cause severe, life-threatening, or fatal inflammation of the lungs. Your doctor will monitor you before and during treatment with Retsevmo for symptoms. Tell your doctor right away if you notice any symptoms of lung problems including breathlessness, cough and raised temperature.
- Retsevmo may affect your blood pressure. You will have your blood pressure measured before and during treatment with Retsevmo.
- Retsevmo may affect the way your liver works. Tell your doctor right away if you develop symptoms of liver problems including: jaundice (yellow discoloration of the skin and eyes), loss of appetite, nausea or vomiting, or pain on the upper right side of your stomach area.
- Retsevmo may result in abnormal ECGs. You will have an ECG taken before and during your treatment with Retsevmo. Tell your doctor if you experience fainting as it may be a symptom of abnormal ECG.
- Retsevmo may affect how your thyroid works. Your doctor will monitor your thyroid function before and during treatment with Retsevmo.
- You will have regular blood tests before and during treatment with Retsevmo, to check your liver function and electrolytes (such as sodium, potassium, magnesium and calcium) in your blood.
- If you are 12-18 years of age, your doctor may monitor your growth during treatment.

Children and adolescents

Retsevmo is not intended for use in patients less than 18 years of age in lung cancer.

The thyroid cancer (including medullary thyroid cancer) indications do not cover children younger than 12 years of age.

Other medicines and Retsevmo

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor or pharmacist before taking Retsevmo if you are taking the following:

- medicines that may increase the concentration of Retsevmo in the blood:
 - Clarithromycin (used to treat bacterial infections)
 - Itraconazole, ketoconazole, posaconazole, voriconazole (used to treat fungal infections)
 - Atazanavir, ritonavir, cobicistat (used to treat HIV infections/AIDS)
- medicines that may reduce the effectiveness of Retsevmo:
 - Carbamazepine (used to treat epilepsy, nerve pain, bipolar disorder)
 - Rifampicin (used to treat tuberculosis (TB) and some other infections)
 - St. John's wort (a herbal product used to treat mild depression and anxiety)
 - Omeprazole, lansoprazole, or other proton pump inhibitors used to treat heartburn, ulcers, and acid reflux. If you are taking any of these medicines, then take Retsevmo with a full meal
 - Ranitidine, famotidine or other H2 blockers used to treat ulcers and acid reflux. If you are taking any of these medicines, then you need to take them 2 hours after taking Retsevmo
- medicines whose concentration in the blood might be increased by Retsevmo:
 - Repaglinide (used to treat type 2 diabetes and control blood sugar)
 - Dasabuvir (used to treat hepatitis C)
 - Selexipag (used to treat pulmonary arterial hypertension)
 - Digoxin (used to treat heart disorders)
 - Lovastatin and simvastatin (used to treat high cholesterol)
 - Dabigatran (used to prevent and treat blood clots)
- medicines that may be less effective when taken with Retsevmo:
 - Levothyroxine (used to treat hypothyroidism)

Pregnancy, breast-feeding and fertility

Pregnancy

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor before taking this medicine.

You should not use Retsevmo during pregnancy, since the effect of Retsevmo on the unborn is not known.

Breast-feeding

Do not breast-feed during treatment with Retsevmo as Retsevmo could harm a breast-fed baby. It is not known if Retsevmo passes into breast milk. You should not breast-feed for at least one week after your last dose of Retsevmo.

Contraception

It is recommended that women avoid becoming pregnant and that men do not father children during treatment with Retsevmo, because this medicine could harm the baby. If there is any possibility that the person taking this medicine may become pregnant or father a child, they must use adequate contraception during treatment and for at least one week after the last dose of Retsevmo.

Fertility

Retsevmo can affect your ability to have children. Talk to your doctor to seek advice about fertility preservation prior to treatment.

Driving and using machines

You should take special care when driving and using machines as you may feel tired or dizzy while taking Retsevmo.

3. How to take Retsevmo

Always take this medicine exactly as your doctor or pharmacist has told you, at the dose prescribed for you. Check with your doctor or pharmacist if you are not sure.

How much to take

Your doctor will prescribe the right dose for you. The maximum recommended dose is as follows:

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

Retsevmo is taken twice a day at about the same time every day, preferably in the morning and evening.

If you get certain side effects while you are taking Retsevmo your doctor may lower your dose or stop treatment temporarily or permanently.

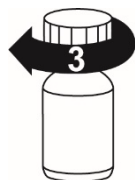
You can take the capsules either with or without food. Swallow the capsule whole with a glass of water. Do not chew, crush or split the capsule before swallowing.

Retsevmo is available in blister packs and in bottles. The bottle is protected by a plastic screw cap:

To open the bottle, push down the plastic screw cap while turning it anticlockwise as shown in the picture.



To close the bottle, turn the cap clockwise tightly.



If you take more Retsevmo than you should

If you take too many capsules, or if someone else takes your medicine, contact a doctor or hospital for advice. Medical treatment may be necessary.

If you forget to take Retsevmo

If you vomit after taking the dose or forget a dose, take your next dose at your usual time. Do not take a double dose to make up for the forgotten or vomited dose.

If you stop taking Retsevmo

Do not stop taking Retsevmo unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side-effects, although not everybody gets them.

Contact your doctor immediately for any of the following:

- Lung or breathing problems other than lung cancer with symptoms such as breathlessness, cough and raised temperature (which may affect more than 1 in 10 people)
- Liver problems (which may affect more than 1 in 10 people and can be associated with abnormalities in liver blood tests, such as increased liver enzymes) including: yellow discoloration of the skin and eyes (jaundice), darkening of the urine, loss of appetite, nausea or vomiting, or pain on the upper right side of your stomach area
- Allergic reaction typically shown by fever and muscle and joint pain followed by rash (which may affect up to 1 in 10 people)
- High blood pressure (which may affect more than 1 in 10 people)
- Bleeding with symptoms such as coughing up blood

Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people)

- Reduced number of white blood cells (e.g., lymphocytes, neutrophils, etc.)
- Fluid retention that may cause swelling in your hands or ankles (oedema)
- Increased blood levels of creatinine in tests, which may indicate that kidneys are not working properly (renal disorders)
- Diarrhoea
- Fatigue or tiredness
- Dry mouth
- Reduced number of blood platelets, which may cause bleeding and/ bruising
- Rash
- Pain in the belly
- Low blood levels of magnesium
- Constipation
- Nausea (feeling sick)
- Low levels of haemoglobin, which may cause anaemia
- Headache
- Vomiting
- Decreased appetite
- Dizziness
- Abnormal ECG
- Fever or high temperature
- Reduced thyroid activity
- Bleeding symptoms

Common (may affect more than 1 in 100 people)

- Lymph fluid may build up in the lining of your lungs or your stomach cavity, which may cause breathing problems or enlargement of the stomach

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Retsevmo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label or blister card and carton after “EXP”. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if you notice that the inner seal is broken or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Retsevmo contains

The active substance is selpercatinib. Each hard capsule contains 40 or 80 mg selpercatinib.

The other ingredients are:

- Capsule content: colloidal anhydrous silica, microcrystalline cellulose
- Capsule shell 40 mg: gelatin, titanium dioxide (E171), and iron oxide (E172).
- Capsule shell 80 mg: gelatin, titanium dioxide (E171), and brilliant blue FCF (E133).
- Black ink: Shellac, Ethanol (96 per cent), Isopropyl alcohol, Butanol, Propylene glycol, Water, purified, Ammonia solution (concentrated), Potassium hydroxide, Iron oxide black

What Retsevmo looks like and contents of the pack

Retsevmo 40 mg is supplied as grey opaque hard gelatin capsule, with black “Lilly”, “3977” and “40 mg” script.

Retsevmo 80 mg is supplied as blue opaque hard gelatin capsule, with black “Lilly”, “2980” and “80 mg” script.

Retsevmo is available in a white opaque bottle with a plastic screw cap, containing 60 hard capsules of 40 mg and either 60 or 120 hard capsules of 80 mg. Each carton contains one bottle.

Retsevmo is available in blister packs of 14, 42, 56 or 168 hard capsules of 40 mg and 14, 28, 56 or 112 hard capsules of 80 mg.

Not all the pack sizes may be marketed.

Marketing Authorisation Holder

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528BJ Utrecht, The Netherlands.

Manufacturer

Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Lietuva

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Eli Lilly Nederland B.V.
Tel: +372 6 817 280

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Eli Lilly Hrvatska d.o.o.
Tel: +385 1 2350 999

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Oy Eli Lilly Finland Ab
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Eli Lilly and Company (Ireland) Limited
Tel: + 353-(0) 1 661 4377

This leaflet was last revised in.

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

[illegible]

レットヴィモカプセル 40mg
レットヴィモカプセル 80mg

1.7 同種同効品一覧表

日本イーライリリー株式会社

目次

1.7 同種同効品一覧表.....	1
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1.7 同種同効品一覧表

セルベルカチニブは、選択的な RET（Rearranged during Transfection）受容体型チロシンキナーゼ阻害剤である。本剤は、非小細胞肺癌及び甲状腺癌を除く *RET* 融合遺伝子陽性の固形がんに対して新規の作用機序を有する経口治療薬となりうると考える。

非小細胞肺癌及び甲状腺癌を除く *RET* 融合遺伝子陽性の固形がんに対し特異的な分子標的薬はない。現在の治療では、*RET* 融合遺伝子の有無にかかわらず、化学療法や内分泌療法などの治療が実施されているか、もしくは、そのような治療が存在しない。

したがって、現時点で同種同効薬は存在しない。

レットヴィモカプセル 40mg

レットヴィモカプセル 80mg

1.8 添付文書（案）

日本イーライリリー株式会社

目次

1.8 添付文書（案）	1
1.8.1 添付文書（案）	1
1.8.2 効能・効果（案）及びその設定根拠	8
1.8.2.1 効能・効果（案）	8
1.8.2.2 効能又は効果に関連する注意（案）	8
1.8.2.3 設定根拠	9
1.8.3 用法・用量（案）及びその設定根拠	12
1.8.3.1 用法・用量（案）	12
1.8.3.2 用法及び用量に関連する注意（案）	12
1.8.3.3 設定根拠	13
1.8.4 使用上の注意（案）及びその設定根拠	15

1.8 添付文書（案）

1.8.1 添付文書（案）

レットヴィモカプセル 40mg、レットヴィモカプセル 80mg の添付文書（案）を以下に示す。

*20xx 年 x 月改訂（第 x 版、効能変更）
20xx 年 x 月改訂（第 x 版）

日本標準商品分類番号
874291

抗悪性腫瘍剤 RET^{注2)} 受容体型チロシンキナーゼ阻害剤

貯 法: 室温保存
有効期間: 24 カ月

セルベルカチニブカプセル

レットヴィモ[®] カプセル40mg **レットヴィモ[®] カプセル80mg** **Retevmo[®] Capsules**

劇薬

処方箋医薬品^{注1)}

注1) 注意—医師等の処方箋により使用すること

注2) RET: rearranged during transfection

	40mg	80mg
承認番号	30300AMX00448	30300AMX00449
販売開始	2021 年 12 月	2021 年 12 月

1. 警告

本剤は、緊急時に十分対応できる医療施設において、がん化学療法に十分な知識・経験を持つ医師のもとで、本剤の投与が適切と判断される症例についてのみ投与すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分説明し、同意を得てから投与すること。

2. 禁忌（次の患者には投与しないこと）

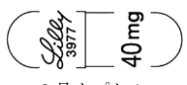
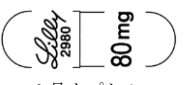
本剤の成分に対しアナフィラキシー等の重篤な過敏症の既往歴のある患者

3. 組成・性状

3.1 組成

販売名	レットヴィモカプセル 40mg	レットヴィモカプセル 80mg
有効成分	1 カプセル中 セルベルカチニブ 40mg	1 カプセル中 セルベルカチニブ 80mg
添加剤	内容物: 軽質無水ケイ酸、結晶セルロース カプセル本体: セラチン、酸化チタン、黒酸化鉄 (40mg のみ含有)、青色 1 号 (80mg のみ含有)	

3.2 製剤の性状

販売名	レットヴィモカプセル 40mg	レットヴィモカプセル 80mg
性状・剤形	灰色不透明の 硬カプセル剤	青色不透明の 硬カプセル剤
外形	 2 号カプセル	 0 号カプセル
寸法・重量	長径: 約 18.0mm 短径: 約 6.4mm 重量: 約 194mg	長径: 約 21.7mm 短径: 約 7.6mm 重量: 約 363mg
識別コード	 3977	 2980

*4. 効能又は効果

- RET 融合遺伝子陽性の進行・再発の固形腫瘍
- RET 遺伝子変異陽性の根治切除不能な甲状腺髄様癌

5. 効能又は効果に関連する注意

〈RET 融合遺伝子陽性の進行・再発の非小細胞肺癌〉

- 十分な経験を有する病理医又は検査施設における検査により、RET 融合遺伝子陽性が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器^{注)}を用いること。
- 「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、本剤以外の治療の実施についても慎重に検討し、適応患者の選択を行うこと。[17.1.1 参照]
- 本剤の術後補助療法における有効性及び安全性は確立していない。

〈RET 融合遺伝子陽性の進行・再発の甲状腺癌〉

- 十分な経験を有する病理医又は検査施設における検査により、RET 融合遺伝子陽性が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器^{注)}を用いること。
- 放射性ヨウ素による治療の適応となる患者においては、当該治療を優先すること。

〈RET 融合遺伝子陽性の進行・再発の固形腫瘍（非小細胞肺癌及び甲状腺癌を除く）〉

- 十分な経験を有する病理医又は検査施設における検査により、RET 融合遺伝子陽性が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器^{注)}を用いること。

- 組織球症患者は本剤の投与対象となり得る。

- 臨床試験に組み入れられた患者のがん種等について、「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、本剤以外の治療の実施についても慎重に検討し、適応患者の選択を行うこと。[17.1.1 参照]

- 本剤の手術の補助療法における有効性及び安全性は確立していない。

〈RET 遺伝子変異陽性の根治切除不能な甲状腺髄様癌〉

- 十分な経験を有する病理医又は検査施設における検査により、RET 遺伝子変異が確認された患者に投与すること。生殖細胞系列の RET 遺伝子変異が陰性又は不明の場合は、承認された体外診断用医薬品又は医療機器^{注)}を用いて検査を行うこと。
- 「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、本剤以外の治療の実施についても慎重に検討し、適応患者の選択を行うこと。[17.1.1 参照]

注) 承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である:

<https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html>

*6. 用法及び用量

通常、成人にはセルベルカチニブとして 1 回 160mg を 1 日 2 回経口投与する。なお、患者の状態により適宜減量する。

通常、12 歳以上の小児には体表面積に合わせて次の投与量（セルベルカチニブとして 1 回約 92mg/m²）を 1 日 2 回経口投与する。なお、患者の状態により適宜減量する。

小児の用量

体表面積	1 回投与量
1.2m ² 未満	80mg
1.2m ² 以上 1.6m ² 未満	120mg
1.6m ² 以上	160mg

7. 用法及び用量に関連する注意

- 他の抗悪性腫瘍剤との併用について、有効性及び安全性は確立していない。
- 本剤投与により副作用が発現した場合には、以下の基準を考慮して、休薬・減量・中止すること。

成人の場合 本剤の減量の目安

減量レベル	投与量
通常投与量	1 回 160mg 1 日 2 回
1 段階減量	1 回 120mg 1 日 2 回
2 段階減量	1 回 80mg 1 日 2 回
3 段階減量	1 回 40mg 1 日 2 回

小児の場合 本剤の減量の目安

体表面積	減量レベル	投与量
1. 2m ² 未満	通常投与量	1 回 80mg 1 日 2 回
	1 段階減量	1 回 40mg/1 回 80mg 1 日 2 回 (1 日量 120mg)
	2 段階減量	1 回 40mg 1 日 2 回
	3 段階減量 ^(注1)	1 回 40mg 1 日 1 回
1. 2m ² 以上 1. 6m ² 未満	通常投与量	1 回 120mg 1 日 2 回
	1 段階減量	1 回 80mg 1 日 2 回
	2 段階減量	1 回 40mg/1 回 80mg 1 日 2 回 (1 日量 120mg)
	3 段階減量 ^(注1)	1 回 40mg 1 日 1 回
1. 6m ² 以上	通常投与量	1 回 160mg 1 日 2 回
	1 段階減量	1 回 120mg 1 日 2 回
	2 段階減量	1 回 80mg 1 日 2 回
	3 段階減量	1 回 40mg 1 日 2 回

注 1) 過敏症発現時のみ（過敏症以外で 2 段階減量において忍容性が得られない場合、投与中止）

副作用に対する休薬、減量及び中止基準

副作用	程度 ^(注2)	処置
ALT 又は AST 増加	グレード 3 又は 4	グレード 1 以下に回復するまで休薬し、回復後は 2 段階減量して投与再開できる。 再開後に 2 週間以上再発しない場合には、1 段階増量することができる。更に 4 週間以上再発しない場合には、もう 1 段階増量することができる。 減量した用量で投与中に再発した場合には、中止する。
QT 間隔延長	QTc 間隔>500msec	QTc 間隔<470msec に回復するまで休薬し、回復後は 1 段階減量して投与再開できる。 2 段階減量した用量で投与中に再発した場合には、中止する。
	重篤な不整脈を疑う所見や症状が認められた場合	中止する。
高血圧	グレード 3 又は 4	回復するまで休薬し、回復後は 1 段階減量して投与再開できる。
過敏症（アナフィラキシー等の重篤な過敏症を除く） [11. 1. 3 参照]	グレード 1～4	回復するまで休薬し、副腎皮質ステロイドの全身投与を考慮する。回復後は副腎皮質ステロイドを併用しながら 3 段階減量して投与再開できる。 再開後に 7 日以上再発しない場合には、1 段階ずつ発現時の用量まで増量できる。増量後に 7 日以上再発しない場合には、副腎皮質ステロイドを漸減する。
間質性肺疾患	グレード 2	回復するまで休薬し、回復後は 1 段階減量して投与再開できる。
	グレード 3 又は 4	中止する。
上記以外の副作用	グレード 3 又は 4	回復するまで休薬し、回復後は 1 段階減量して投与再開できる。

注 2) グレードは NCI-CTCAE ver. 4. 03 に準じる。

8. 重要な基本的注意

8. 1 肝機能障害があらわれることがあるので、本剤の投与開始前

及び投与期間中は定期的に肝機能検査を行い、患者の状態を十分に観察すること。[11. 1. 1 参照]

8. 2 QT 間隔延長があらわれることがあるので、本剤の投与開始前には患者の QTc 間隔が 470msec 以下であることを確認するとともに血清電解質検査（カリウム、マグネシウム等）を行うこと。心電図及び血清電解質検査を投与開始後 1 週間時点及び投与開始後 6 ヶ月間は毎月 1 回行い、以降も必要に応じて行うこと。また、必要に応じて電解質補正を行うこと。[11. 1. 2、17. 3. 1 参照]
8. 3 高血圧があらわれることがあるので、本剤の投与開始前に血圧が適切に管理されていることを確認すること。本剤投与中は定期的に血圧を測定すること。
8. 4 間質性肺疾患があらわれることがあるので、本剤の投与にあたっては、初期症状（呼吸困難、咳嗽、発熱等）の確認及び胸部画像検査の実施等、患者の状態を十分に観察すること。また、患者に副作用について説明するとともに、間質性肺疾患の初期症状が発現した場合には、速やかに医療機関を受診するよう説明すること。[9. 1. 3、11. 1. 5 参照]

9. 特定の背景を有する患者に関する注意

9. 1 合併症・既往歴等のある患者

9. 1. 1 QT 間隔延長のおそれ又はその既往歴のある患者

QT 間隔延長が発現するおそれがある。先天性/後天性 QT 延長症候群又はその他不整脈の要因になる病態を有する患者には慎重に投与すること。[11. 1. 2、17. 3. 1 参照]

9. 1. 2 高血圧症の患者

高血圧が悪化するおそれがある。[11. 1. 4 参照]

9. 1. 3 間質性肺疾患のある患者又はその既往歴のある患者

間質性肺疾患が発現又は増悪するおそれがある。[8. 4、11. 1. 5 参照]

9. 3 肝機能障害患者

9. 3. 1 重度の肝機能障害のある患者（Child-Pugh 分類 C）

減量を考慮するとともに、患者の状態をより慎重に観察し、副作用の発現に十分注意すること。本剤の血中濃度が上昇し、副作用が増強されるおそれがある。[16. 6. 2 参照]

9. 4 生殖能を有する者

*9. 4. 1 妊娠する可能性のある女性には、本剤投与中及び最終投与後 1 ヶ月間において避妊する必要性及び適切な避妊法について説明すること。[9. 5 参照]

*9. 4. 2 男性には、本剤投与中及び最終投与後 1 週間においてバリア法（コンドーム）を用いて避妊する必要性について説明すること。[15. 2. 1 参照]

9. 4. 3 成長期にある若年男性又は男児に投与する場合には、造精機能の低下があらわれる可能性があることを考慮すること。幼若ラットにおいて、精巣の精上皮変性、精巣上体の精子枯渇、精子運動率低値、異常形態精子比率高値及び受胎能の低下が認められ、精巣及び精巣上体の所見に回復性は認められていない^{1), 2)}。

9. 5 妊婦

妊婦又は妊娠している可能性のある女性には治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。ラットを用いた胚・胎児発生毒性試験において、臨床曝露量（AUC）と同程度の曝露量で胎児死亡及び奇形が認められている¹⁾。[9. 4. 1 参照]

9. 6 授乳婦

授乳しないことが望ましい。乳汁移行に関するデータはないが、本剤は BCRP の基質であるため、乳汁移行の可能性はある。

9. 7 小児等

*9. 7. 1 成長期にある若年者においては、骨成長について以下の点に注意すること。

- ・骨端線に異常がないか十分に観察すること。骨端線に異常が認められた場合には、投与継続の可否を慎重に判断すること。
- ・関節痛及び歩行障害について十分に観察すること。大腿骨頭すべり症等の骨端離開があらわれることがある。

[15. 2. 2 参照]

9. 7. 2 12 歳未満の小児等を対象とした臨床試験は実施していない。

10. 相互作用

本剤は、主に CYP3A4 によって代謝され、CYP2C8 及び 3A の阻害作用を示す。また、本剤の溶解度は pH の上昇により低下する。

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
CYP2C8 の基質となる薬剤 レバグリニド ピオグリタゾン モンテルカスト等 [16.7.6 参照]	これらの薬剤の副作用が増強されるおそれがあるので、患者の状態を慎重に観察し、副作用の発現に十分注意すること。	本剤が CYP2C8 を阻害することにより、これらの薬剤の血中濃度が上昇する可能性がある。
CYP3A の基質となる薬剤 ミダゾラム トリアゾラム ロミタピド等 [16.7.5 参照]	これらの薬剤の副作用が増強されるおそれがあるので、患者の状態を慎重に観察し、副作用の発現に十分注意すること。	本剤が CYP3A を阻害することにより、これらの薬剤の血中濃度が上昇する可能性がある。
CYP3A 阻害剤 イトラコナゾール クラリスロマイシン エリスロマイシン等 [16.7.1、16.7.2 参照]	本剤の副作用が増強されるおそれがあるので、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、本剤の減量を考慮するとともに、患者の状態を慎重に観察し、副作用の発現に十分注意すること。	これらの薬剤が CYP3A を阻害することにより、本剤の血中濃度が上昇する可能性がある。
CYP3A 誘導剤 リファンピシン フェニトイン ボセンタン等 [16.7.3、16.7.4 参照]	本剤の有効性が減弱するおそれがあるので、これらの薬剤との併用は可能な限り避け、CYP3A 誘導作用のない薬剤への代替を考慮すること。	これらの薬剤等が CYP3A を誘導することにより、本剤の血中濃度が低下する可能性がある。
セイヨウオトギリソウ (St. John's Wort、セント・ジョーンズ・ワート) 含有製品	本剤の有効性が減弱するおそれがあるので、摂取しないよう注意すること。	
プロトンポンプ阻害剤 オメプラゾール ランソプラゾール エソメプラゾール等 [16.7.7 参照]	本剤の有効性が減弱するおそれがあるので、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、本剤とともに食後に投与すること。	これらの薬剤による胃内 pH の上昇により、本剤の吸収が低下し、本剤の血中濃度が低下する可能性がある。
H ₂ 受容体拮抗剤 ラニチジン ファモチジン シメチジン等 [16.7.8 参照]	本剤の有効性が減弱するおそれがあるので、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、本剤と服用時間をずらすこと（ラニチジンを本剤投与 10 時間前及び 2 時間後に投与したときの本剤の血中濃度への影響は限定的であった）。	
制酸剤 炭酸カルシウム 水酸化マグネシウム 水酸化アルミニウム等	本剤の有効性が減弱するおそれがあるので、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、本剤と服用時間をずらすこと（制酸剤を本剤投与 2 時間前又は 2 時間後に投与したときの本剤の血中濃度への影響は限定的であった）。	

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

*11.1 重大な副作用

11.1.1 肝機能障害（36.4%）

[8.1 参照]

11.1.2 QT 間隔延長（13.9%）

[8.2、9.1.1、17.3.1 参照]

11.1.3 過敏症（5.1%）

発疹、発熱等の症状を伴う遅発性の過敏症があらわれることがある。[7.2 参照]

11.1.4 高血圧（30.0%）

[9.1.2 参照]

11.1.5 間質性肺炎患（0.7%）

[8.4、9.1.3 参照]

11.2 その他の副作用

副作用分類	20%以上	5～20%未満	5%未満
*消化器	口内乾燥 (34.2%)、下痢	便秘、悪心、腹痛	嘔吐
*一般・全身及び投与部位反応	疲労	浮腫、発熱	
*呼吸器			鼻出血、肺炎
*内分泌			甲状腺機能低下症
代謝・栄養障害		食欲減退	
精神神経系		頭痛	浮動性めまい
皮膚		発疹	
*血液		血小板減少、白血球減少、好中球減少	リンパ球減少、貧血
*臨床検査値異常		血中クレアチニン増加	低マグネシウム血症

14. 適用上の注意

14.1 薬剤交付時の注意

PTP 包装の薬剤は PTP シートから取り出して服用するよう指導すること。PTP シートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔をおこして縦隔洞炎等の重篤な合併症を併発することがある。

15. その他の注意

15.2 非臨床試験に基づく情報

15.2.1 セルペルカチニブは、ラット小核試験において、臨床用量 160mg1 日 2 回で得られる C_{max} の 5.2 倍に相当する用量で遺伝毒性が陽性であった¹⁾。[9.4.2 参照]

15.2.2 動物試験（成長板が閉鎖していない幼若ラット、若齢ラット及び若齢ミニブタ）において、本剤の反復投与により骨端成長板の異常（骨端軟骨の肥大、過形成及び異形成）が、ヒトに 160mg1 日 2 回の用量で投与したときの臨床曝露量よりも低い曝露量で認められている。また、幼若ラットにおいて、骨端成長板の変化に関連して、骨密度及び大腿骨長の低値が、ヒトに 160mg1 日 2 回の用量で投与したときの臨床曝露量のそれぞれ 0.8 倍及び 1.9 倍で認められている^{1),2)}。[9.7.1 参照]

16. 薬物動態

16.1 血中濃度

16.1.1 単回及び反復投与

進行固形腫瘍患者 94 例に本剤 160mg を単回経口投与したときの血漿中濃度推移及び薬物動態パラメータは以下のとおりであった³⁾（外国人データ）。

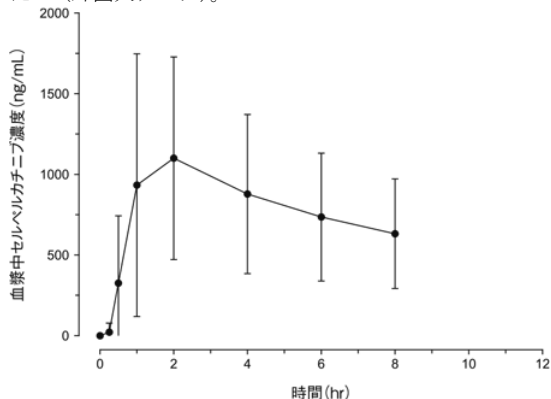


図 1) 本剤 160mg を単回経口投与後（第 1 サイクル第 1 日目）の血漿中濃度推移（平均値±標準偏差）

表 1) 本剤 160mg を単回経口投与後 (第 1 サイクル第 1 日目) の薬物動態パラメータ (幾何平均値及び変動係数%)

例数	94
C_{max} (ng/mL)	1120 (85.7)
t_{max} 注 1) (hr)	1.96 (0.50-7.83)
AUC_{τ} (ng・hr/mL)	7430 注 2) (67.5)

注 1) 中央値 (最小値-最大値)

注 2) 例数=71

τ : 投与間隔 (12 時間)

日本人の進行固形腫瘍患者 58 例に本剤 160mg を 1 日 2 回反復経口投与したときの定常状態における血漿中濃度推移及び薬物動態パラメータは以下のとおりであった³⁾。

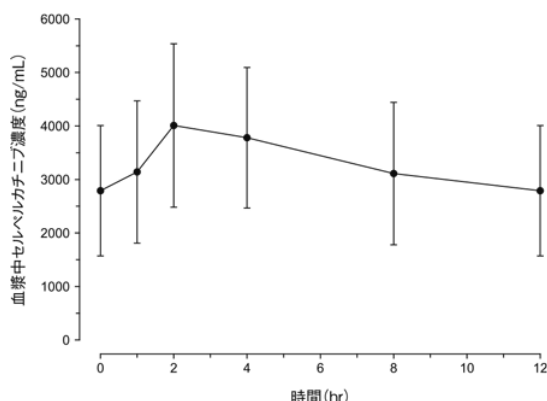


図 2) 本剤 160mg を 1 日 2 回反復経口投与後 (第 1 サイクル第 8 日目) の定常状態における血漿中濃度推移 (平均値±標準偏差)

表 2) 本剤 160mg を 1 日 2 回反復経口投与後 (第 1 サイクル第 8 日目) の定常状態における薬物動態パラメータ (幾何平均値及び変動係数%)

例数	58
$C_{max,ss}$ (ng/mL)	4060 (34.4)
$t_{max,ss}$ 注 3) (hr)	2.08 (0.00-8.10)
$AUC_{\tau,ss}$ (ng・hr/mL)	37100 (39.3)
CL_{ss}/F (L/hr)	4.31 (39.3)

注 3) 中央値 (最小値-最大値)

τ : 投与間隔 (12 時間)

血漿中濃度は反復投与後 8 日までに定常状態に到達した。また、本剤 160mg を 1 日 2 回反復経口投与した際の投与 8 日目におけるセルペルカチニブの蓄積率は 3.40 であった。

16.2 吸収

16.2.1 絶対的バイオアベイラビリティ

健康成人 6 例に本剤 160mg を単回経口投与したときの絶対的バイオアベイラビリティの幾何平均値は 73.2% であった⁴⁾ (外国人データ)。

16.2.2 食事の影響

健康成人 20 例に本剤 160mg を高脂肪食摂取後に単回経口投与したとき、空腹時投与に対する食後投与におけるセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比はそれぞれ 0.862 及び 1.09 であった⁵⁾ (外国人データ)。

16.3 分布

16.3.1 蛋白結合率

セルペルカチニブのヒト血漿タンパク結合率は約 96% であり、濃度依存性は認められなかった (*in vitro*)⁶⁾。

16.3.2 血液/血漿中濃度比

セルペルカチニブの血液/血漿中濃度比は約 0.7 であった (*in vitro*)⁷⁾。

16.4 代謝

セルペルカチニブは主として CYP3A4 により代謝される (*in vitro*)⁸⁾。健康成人 6 例に [¹⁴C]-セルペルカチニブ 160mg を単回経口投与したとき、投与 168 時間後までの血漿中には主に未変化体が検出された (血漿中総放射能に対する割合は、86.2%)⁴⁾ (外国人データ)。

16.5 排泄

健康成人 6 例に [¹⁴C]-セルペルカチニブ 160mg を単回経口投与したとき、投与 432 時間後までに投与した放射能の約 69% (未変化体は約 14%) が糞便中に排泄され、約 24% (未変化体は約 11.5%) が尿中に排泄された⁴⁾ (外国人データ)。

16.6 特定の背景を有する患者

16.6.1 腎機能障害患者

本剤 160mg を単回経口投与したとき、腎機能正常被験者 (10 例) に対する軽度の腎機能障害患者 (8 例) の非結合形セルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 1.30 及び 1.07 であった。腎機能正常被験者 (10 例) に対する中等度の腎機能障害患者 (8 例) の非結合形セルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 1.67 及び 1.89 であった。腎機能正常被験者 (10 例) に対する重度の腎機能障害患者 (7 例) の非結合形セルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 1.04 及び 1.54 であった⁹⁾ (外国人データ)。血液透析の有無によらず、末期腎不全患者に関するデータはない。

16.6.2 肝機能障害患者

本剤 160mg を単回経口投与したとき、肝機能正常被験者 (12 例) に対する軽度の肝機能障害患者 (8 例) の非結合形セルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 1.78 及び 1.33 であった。肝機能正常被験者 (12 例) に対する中等度の肝機能障害患者 (8 例) の非結合形セルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 0.989 及び 0.991 であった。肝機能正常被験者 (12 例) に対する重度の肝機能障害患者 (8 例) の非結合形セルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 2.32 及び 3.28 であった¹⁰⁾ (外国人データ)。^[9.3.1 参照]

*16.6.3 小児

国際共同第 I/II 相試験 (LIBRETTO-001 試験及び LIBRETTO-121 試験) に組み入れられた 830 例 (小児患者 24 例を含む) のデータを用いて母集団薬物動態モデルが構築された。構築された母集団薬物動態モデルを用いて、仮想患者の体表面積及び体重情報に基づく薬物動態シミュレーションを実施した結果、①体表面積 1.2m² 未満の患者に 80mg、②体表面積 1.2m² 以上 1.6m² 未満の患者に 120mg、③体表面積 1.6m² 以上の患者に 160mg をそれぞれ 1 日 2 回反復経口投与した際の、定常状態における本剤の C_{max} (ng/mL) 及び AUC_{24h} (ng・hr/mL) の中央値は、①2860 及び 47700、②3100 及び 54900 並びに③3670 及び 66900 と推定された¹¹⁾。

16.7 薬物相互作用

16.7.1 イトラコナゾール

健康成人 12 例にイトラコナゾール (強い CYP3A 阻害剤) 200mg を 1 日 1 回反復経口投与し、本剤 160mg を単回経口投与したとき、本剤単独投与時に対するイトラコナゾール併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、1.30 及び 2.33 であった¹²⁾ (外国人データ)。^[10.2 参照]

16.7.2 フルコナゾール、ジルチアゼム

生理学的薬物動態モデルに基づいたシミュレーションにおいて、本剤 (160mg を単回経口投与) 単独投与時に対するフルコナゾール (中程度の CYP3A 阻害剤) (200mg を 1 日 1 回反復経口投与) 併用投与時のセルペルカチニブの C_{max} 及び AUC の幾何平均値の比は、それぞれ 1.20 及び 2.48 と推定された。本剤 (160mg を単回経口投与) 単独投与時に対するジルチアゼム (中程度の CYP3A 阻害剤) (60mg を 1 日 3 回反復経口投与) 併用投与時のセルペルカチニブの C_{max} 及び AUC の幾何平均値の比は、それぞれ 1.17 及び 2.18 と推定された¹³⁾。^[10.2 参照]

16.7.3 リファンピシン

健康成人 12 例にリファンピシン (強い CYP3A 誘導剤) 600mg を 1 日 1 回反復経口投与し、本剤 160mg を単回経口投与したとき、本剤単独投与時に対するリファンピシン併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、0.301 及び 0.133 であった¹²⁾ (外国人データ)。^[10.2 参照]

16.7.4 ボセンタン、モダフィニル

生理学的薬物動態モデルに基づいたシミュレーションにおいて、本剤 (160mg を単回経口投与) 単独投与時に対するボセンタン (中程度の CYP3A 誘導剤) (125mg を 1 日 2 回反復経口投与) 併用投

与時のセルペルカチニブの C_{max} 及び AUC の幾何平均値の比は、それぞれ 0.71 及び 0.53 と推定された。本剤（160mg を単回経口投与）単独投与時に対するモダフィニル（中程度の CYP3A 誘導剤）（200mg を 1 日 1 回 7 日間経口投与後に 400mg を 1 日 1 回反復経口投与）併用投与時のセルペルカチニブの C_{max} 及び AUC の幾何平均値の比は、それぞれ 0.86 及び 0.64 と推定された¹³⁾。[10.2 参照]

16.7.5 ミダゾラム

健康成人 16 例に本剤 160mg を 1 日 2 回反復経口投与し、ミダゾラム（CYP3A の基質）2mg を単回経口投与したとき、ミダゾラム単独投与時に対する本剤併用投与時のミダゾラムの C_{max} 及び AUC_{inf} の幾何平均値の比は、1.39 及び 1.54 であった¹⁴⁾（外国人データ）。[10.2 参照]

16.7.6 レパグリニド

健康成人 16 例に本剤 160mg を 1 日 2 回反復経口投与し、レパグリニド（CYP2C8 の基質）0.5mg を単回経口投与したとき、レパグリニド単独投与時に対する本剤併用投与時のレパグリニドの C_{max} 及び AUC_{inf} の幾何平均値の比は、1.91 及び 2.88 であった¹⁵⁾（外国人データ）。[10.2 参照]

16.7.7 オメプラゾール

健康成人 20 例にオメプラゾール（プロトンポンプ阻害剤）40mg を 1 日 1 回反復経口投与し、本剤 160mg を空腹時に単回経口投与したとき、本剤単独投与時に対するオメプラゾール併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、0.123 及び 0.313 であった。また、オメプラゾールを反復経口投与し、本剤 160mg を高脂肪食摂取後に単回経口投与したとき、本剤単独投与時に対するオメプラゾール併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、0.586 及び 0.938 であった。オメプラゾールを反復経口投与し、本剤 160mg を低脂肪食摂取後に単回経口投与したとき、本剤単独投与時に対するオメプラゾール併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、0.782 及び 1.00 であった^{5), 16)}（外国人データ）。[10.2 参照]

16.7.8 ラニチジン

健康成人 20 例にラニチジン（ H_2 受容体拮抗剤）150mg を 1 日 2 回反復経口投与し、本剤 160mg をラニチジン投与 10 時間後及び 2 時間前に空腹時に単回経口投与したとき、本剤単独投与時に対するラニチジン併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、0.818 及び 0.932 であった¹⁶⁾（外国人データ）。[10.2 参照]

16.7.9 その他

- (1) セルペルカチニブは MATE1 を阻害する（*in vitro*）¹⁷⁾。
(2) 健康成人 12 例にリファンピシン（P-gp 阻害剤）600mg を単回経口投与し、本剤 160mg を単回経口投与したとき、本剤単独投与時に対するリファンピシン併用投与時のセルペルカチニブの C_{max} 及び AUC_{inf} の幾何平均値の比は、それぞれ 1.19 及び 1.06 であった¹²⁾（外国人データ）。

17. 臨床成績

*17.1 有効性及び安全性に関する試験

17.1.1 国際共同第 I/II 相試験（LIBRETTO-001 試験）

〈RET 融合遺伝子陽性の進行・再発の非小細胞肺癌及び甲状腺癌、RET 遺伝子変異陽性の根治切除不能な甲状腺髄様癌〉

①化学療法歴のある RET 融合遺伝子陽性の切除不能な進行・再発の非小細胞肺癌患者 134 例（日本人患者 25 例を含む）及び②化学療法歴のない RET 融合遺伝子陽性の切除不能な進行・再発の非小細胞肺癌患者 35 例（日本人患者 1 例を含む）に本剤 1 回 160mg を 1 日 2 回経口投与した。主要評価項目である RECIST ver. 1.1 に基づく独立評価委員会判定による奏効率は、それぞれ① 55.2%（95%信頼区間:46.4-63.8）及び② 71.4%（95%信頼区間:53.7-85.4）であった。

12 歳以上の③化学療法歴のある RET 融合遺伝子陽性の根治切除不能な甲状腺癌患者 10 例^{注 1)}（日本人患者 1 例を含む）、④化学療法歴のない RET 融合遺伝子陽性の根治切除不能な甲状腺癌患者 12 例^{注 2)}、⑤化学療法歴のある RET 遺伝子変異陽性の根治切除不能な甲状腺髄様癌患者 97 例（日本人患者 1 例を含む）及び⑥化学療法歴のない RET 遺伝子変異陽性の根治切除不能な甲状腺髄様癌患者 90 例に本剤 1 回 160mg ^{注 3)} を 1 日 2 回経口投与した。主要評価項目である RECIST ver. 1.1 に基づく独立評価委員会判定による奏効率は、それぞれ③ 50.0%（95%信頼区間:18.7-81.3）、④ 100%（95%信頼区間:73.5-100）、⑤ 68.0%（95%信頼区

間:57.8-77.1）及び⑥ 63.3%（95%信頼区間:52.5-73.2）であった³⁾。（2020 年 3 月 30 日データカットオフ）[5.2、5.11 参照]

注 1) 未分化癌 2 例、低分化癌 2 例を含む。

注 2) 低分化癌 1 例を含む。

注 3) 12 歳以上の小児に対する本剤の承認用法・用量は、(1) 体表面積 1.2m² 未満の患者に 80mg、(2) 体表面積 1.2m² 以上 1.6m² 未満の患者に 120mg、(3) 体表面積 1.6m² 以上の患者に 160mg をそれぞれ 1 日 2 回経口投与である。

安全性評価対象 400 例に認められた主な副作用は、口内乾燥（35.3%）、高血圧（31.8%）、ALT 増加（28.0%）、AST 増加（26.8%）、疲労（25.3%）等であった。（2020 年 3 月 30 日データカットオフ）

〈RET 融合遺伝子陽性の進行・再発の固形腫瘍（非小細胞肺癌及び甲状腺癌を除く）〉

RET 融合遺伝子陽性の進行・再発の固形腫瘍（非小細胞肺癌及び甲状腺癌を除く）患者として、本剤の忍容性の評価を目的とした⑦第 I 相パート（本剤 20mg を 1 日 1 回又は本剤 1 回 20、40、60、80、120、160、200 若しくは 240mg を 1 日 2 回経口投与）^{注 4)} の 5 例、本剤の有効性及び安全性を検討することを目的とした第 II 相パート（本剤 1 回 160mg を 1 日 2 回経口投与）のうち、⑧化学療法歴のある患者を対象としたコホートの 33 例（日本人患者 8 例を含む）、⑨化学療法歴のない患者を対象としたコホートの 2 例、⑩腫瘍組織検体以外で RET 融合遺伝子陽性が確認された患者等を対象としたコホートの 12 例（日本人患者 3 例を含む）が有効性の評価対象とされた。第 II 相パートの主要評価項目である RECIST ver. 1.1 に基づく独立評価委員会判定による奏効率は、それぞれ⑧ 57.6%（95%信頼区間:39.2-74.5）、⑨ 0%及び⑩ 16.7%であった³⁾。（2023 年 1 月 13 日データカットオフ）[5.8 参照]

注 4) 承認された用法・用量は本剤 1 回 160mg を 1 日 2 回経口投与である。

表) 有効性の評価対象におけるがん種別の有効性

がん種	奏効例数/評価例数	奏効率
大腸癌	4/13	30.8%
肺癌 ^{注 5)}	7/13	53.8%
唾液腺癌 ^{注 6)}	2/4	50.0%
肉腫 ^{注 7)}	1/3	33.3%
胆道癌 ^{注 8)}	1/3	33.3%
原発不明癌	1/3	33.3%
黄色肉芽腫 ^{注 9)}	0/2	0%
乳癌 ^{注 6)}	2/2	100%
皮膚癌 ^{注 9)}	1/2	50.0%
カルチノイド	1/1	100%
小腸癌	1/1	100%
直腸神経内分泌腫瘍 ^{注 10)}	0/1	0%
卵巣癌	1/1	100%
肺癌肉腫	0/1	0%
神経内分泌癌	1/1	100%
小細胞肺癌	0/1	0%

注 5) 本剤 80mg を 1 日 2 回で投与が開始された患者 1 例を含む。

注 6) 測定可能病変のない患者 1 例を含む。

注 7) 紡錘形細胞肉腫、多形肉腫及び高悪性度胸部肉腫が組入れられ、紡錘形細胞肉腫において奏効が認められた。

注 8) いずれも測定可能病変のない患者

注 9) 悪性黒色腫以外の皮膚癌（詳細不明）及び腺扁平上皮癌が組入れられ、悪性黒色腫以外の皮膚癌（詳細不明）において奏効が認められた。

注 10) 本剤 120mg を 1 日 2 回で投与が開始された患者

安全性評価対象 53 例に認められた主な副作用は、ALT 増加（35.8%）、AST 増加（28.3%）、口内乾燥（26.4%）、下痢（17.0%）、高血圧（17.0%）等であった。（2023 年 1 月 13 日データカットオフ）

17.3 その他

17.3.1 QT 間隔に対する影響

健康成人 32 例に本剤 320 又は 640mg ^{注 11)} を単回経口投与したとき、QTc 間隔のベースラインからの変化量のプラセボとの差における 90%信頼区間の上限値は、それぞれ 11.87 及び 12.47msec であった¹⁸⁾（外国人データ）。[8.2、9.1.1、11.1.2 参照]

注 11) 成人に対する本剤の承認用法・用量は 160mg の 1 日 2 回経口投与である。

18. 薬効薬理

18.1 作用機序

セルベルカチニブは、RET、血管内皮増殖因子受容体 (VEGFR)、線維芽細胞増殖因子受容体 (FGFR) 等のキナーゼ活性を阻害する。セルベルカチニブは、RET 融合タンパク等のリン酸化を阻害し、下流のシグナル伝達分子のリン酸化を阻害することにより、腫瘍増殖抑制作用を示すと考えられている¹⁹⁾。

18.2 抗腫瘍効果

セルベルカチニブは、*in vitro*において、RET 融合タンパクを発現するヒト非小細胞肺癌由来 LC-2/ad 細胞株及びヒト甲状腺乳頭癌由来 TPC-1 細胞株並びに変異型 RET (C634W 及び M918T) をそれぞれ発現するヒト甲状腺髄様癌由来 TT 及び MZ-CRC1 細胞株に対して増殖抑制作用を示した。また、セルベルカチニブは、*in vivo*において、LC-2/ad 細胞株、RET 融合タンパクを発現する非小細胞肺癌患者由来 CTG-0838 腫瘍組織片及び TT 細胞株をそれぞれ皮下移植した重症複合型免疫不全-ベージュマウス又はヌードマウスにおいて、腫瘍増殖抑制作用を示した¹⁹⁾。

19. 有効成分に関する理化学的知見

一般的名称:セルベルカチニブ (Selpercatinib) [JAN]

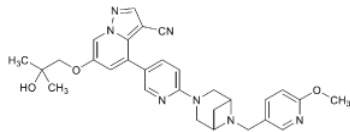
化 学 名: 6-(2-Hydroxy-2-methylpropoxy)-4-(6-{6-[(6-methoxypyridin-3-yl)methyl]-3,6-diazabicyclo[3.1.1]heptan-3-yl}pyridin-3-yl)pyrazolo[1,5-a]pyridine-3-carbonitrile

分 子 式: C₂₉H₃₁N₇O₃

分 子 量: 525. 60

性 状: 白色～淡黄色の粉末である。0. 1mol/L 塩酸にやや溶けにくく、アセトン及びエタノールに極めて溶けにくく、水にほとんど溶けない。

化学構造式:



融 点: 約 208℃

21. 承認条件

21.1 医薬品リスク管理計画を策定の上、適切に実施すること。

〈RET 融合遺伝子陽性の進行・再発の非小細胞肺癌及び甲状腺癌、RET 遺伝子変異陽性の根治切除不能な甲状腺髄様癌〉

21.2 国内での治験症例が極めて限られていることから、製造販売後、一定数の症例に係るデータが集積されるまでの間は、全症例を対象に使用成績調査を実施することにより、本剤の使用患者の背景情報を把握するとともに、本剤の安全性及び有効性に関するデータを早期に収集し、本剤の適正使用に必要な措置を講じること。

22. 包装

〈レットヴィモカプセル 40mg〉

56 カプセル [8 カプセル (PTP) × 7]

〈レットヴィモカプセル 80mg〉

56 カプセル [8 カプセル (PTP) × 7]

23. 主要文献

1) 社内資料: セルベルカチニブの毒性試験 (2021 年 9 月 27 日承認、CTD2. 6. 6)

*2) 社内資料: セルベルカチニブの幼若ラットを用いた試験 (2022 年 2 月 25 日承認、CTD2. 6. 6. 6. 4、審査報告書)

*3) 社内資料: 進行癌患者を対象としたセルベルカチニブの第 I/II 相試験 (LOXO-RET-17001 試験) (2021 年 9 月 27 日承認、CTD2. 7. 2. 4. 2、2. 7. 6. 12、審査報告書) (2022 年 2 月 25 日承認、審査報告書)

4) 社内資料: セルベルカチニブの絶対的バイオアベイラビリティ及びマスバランス試験 (LOXO-RET-18016 試験) (2021 年 9 月 27 日承認、CTD2. 7. 6. 3)

5) 社内資料: セルベルカチニブの薬物動態に及ぼす食事の影響及びオメプラゾールとの相互作用 (LOXO-RET-18015 試験) (2021 年 9 月 27 日承認、CTD2. 7. 6. 2)

6) 社内資料: セルベルカチニブのヒト血漿蛋白結合率 (LOXO-292-DMPK-060 試験) (2021 年 9 月 27 日承認、CTD2. 7. 2. 3. 2)

7) 社内資料: セルベルカチニブのヒト血液中/血漿中濃度比 (LOXO-292-DMPK-013 試験) (2021 年 9 月 27 日承認、CTD2. 7. 2. 3. 3)

8) 社内資料: セルベルカチニブの CYP 代謝 (LOXO-292-DMPK-017 試験) (2021 年 9 月 27 日承認、CTD2. 7. 2. 3. 5)

9) 社内資料: 様々な重症度の腎機能障害を有する被験者におけるセルベルカチニブの薬物動態 (LOXO-RET-18023 試験) (2021 年 9 月 27 日承認、CTD2. 7. 6. 6)

10) 社内資料: 様々な重症度の肝機能障害を有する被験者におけるセルベルカチニブの薬物動態 (LOXO-RET-18022 試験) (2021 年 9 月 27 日承認、CTD2. 7. 6. 5)

*11) 社内資料: セルベルカチニブの母集団薬物動態解析 (2022 年 2 月 25 日承認、審査報告書)

12) 社内資料: セルベルカチニブとイトラコナゾール及びリファンピシンの相互作用 (LOXO-RET-18014 試験) (2021 年 9 月 27 日承認、CTD2. 7. 6. 7)

13) 社内資料: セルベルカチニブの生理学的薬物動態モデル解析 (LOXO-292-DMPK-052 試験) (2021 年 9 月 27 日承認、CTD2. 7. 2. 2. 12)

14) 社内資料: セルベルカチニブとミダゾラムの相互作用 (LOXO-RET-18017 試験) (2021 年 9 月 27 日承認、CTD2. 7. 6. 8)

15) 社内資料: セルベルカチニブとレバグリニドの相互作用 (LOXO-RET-18026 試験) (2021 年 9 月 27 日承認、CTD2. 7. 6. 9)

16) 社内資料: セルベルカチニブとラニチジン及びオメプラゾールの相互作用 (LOXO-RET-19075 試験) (2021 年 9 月 27 日承認、CTD2. 7. 6. 10)

17) 社内資料: セルベルカチニブによるトランスポータ阻害 (LOXO-292-DMPK-035 試験) (2021 年 9 月 27 日承認、CTD2. 7. 2. 3. 8)

18) 社内資料: セルベルカチニブの QT/QTc 評価 (LOXO-RET-18032 試験) (2021 年 9 月 27 日承認、CTD2. 7. 2. 2. 8)

19) 社内資料: セルベルカチニブの薬理試験 (2021 年 9 月 27 日承認、CTD2. 6. 2)

24. 文献請求先及び問い合わせ先

日本イーライリリー株式会社 医薬情報問合せ窓口

〒651-0086 神戸市中央区磯上通 5 丁目 1 番 28 号

TEL: 0120-360-605 (医療関係者向け)

medical.lilly.com/jp

26. 製造販売業者等

26.1 製造販売元

日本イーライリリー株式会社
神戸市中央区磯上通 5 丁目 1 番 28 号

®: 登録商標

RET-I001 (Rx)

1.8.2 効能・効果（案）及びその設定根拠

1.8.2.1 効能・効果（案）

~~RET融合遺伝子陽性の切除不能な進行・再発の非小細胞肺癌~~
~~RET融合遺伝子陽性の根治切除不能な甲状腺癌~~
~~RET融合遺伝子陽性の進行・再発の固形腫瘍~~
~~RET遺伝子変異陽性の根治切除不能な甲状腺髄様癌~~

下線部：追加 取消線部：削除

1.8.2.2 効能又は効果に関連する注意（案）

- 〈~~RET融合遺伝子陽性の切除不能な進行・再発の非小細胞肺癌~~〉
- 5.1 十分な経験を有する病理医又は検査施設における検査により、~~RET融合遺伝子陽性~~が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器^注）を用いること。
- 5.2 「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、本剤以外の治療の実施についても慎重に検討し、適応患者の選択を行うこと。
- 5.3 本剤の術後補助療法における有効性及び安全性は確立していない。
- 〈~~RET融合遺伝子陽性の根治切除不能な進行・再発の甲状腺癌~~〉
- 5.4 十分な経験を有する病理医又は検査施設における検査により、~~RET融合遺伝子陽性~~が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器^注）を用いること。
- 5.5 放射性ヨウ素による治療の適応となる患者においては、当該治療を優先すること。
- 〈~~RET融合遺伝子陽性の進行・再発の固形腫瘍（非小細胞肺癌及び甲状腺癌を除く）~~〉
- 5.6 十分な経験を有する病理医又は検査施設における検査により、~~RET融合遺伝子陽性~~が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器^注）を用いること。
- 5.7 組織球症患者は本剤の投与対象となり得る。
- 5.8 臨床試験に組み入れられた患者のがん種等について、「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、本剤以外の治療の実施についても慎重に検討し、適応患者の選択を行うこと。
- 5.9 本剤の手術の補助療法における有効性及び安全性は確立していない。
- 〈~~RET遺伝子変異陽性の根治切除不能な甲状腺髄様癌~~〉
- 5.106 十分な経験を有する病理医又は検査施設における検査により、~~RET遺伝子変異~~が確認された患者に投与すること。生殖細胞系列の~~RET遺伝子変異~~が陰性又は不明の場合は、承認された体外診断用医薬品又は医療機器^注）を用いて検査を行うこと。
- 5.117 「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、本剤以外の治療の実施についても慎重に検討し、適応患者の選択を行うこと。

注）承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である：

<https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html>

下線部：追加 取消線部：削除

1.8.2.3 設定根拠

セルペルカチニブは、RET（rearranged during transfection）のアデノシン三リン酸（ATP）結合部位を競合的に阻害するよう設計された低分子であり、RET に対して選択性の高い阻害剤である。

発がん性の RET の活性化は、主に RET 融合遺伝子及び RET 遺伝子変異によって起こると考えられる。RET 融合遺伝子に関して、非臨床研究のデータより、がん種に関わらず発がんやがん細胞の増殖、生存のためのシグナル伝達経路の異常な活性化に寄与すると考えられる。

セルペルカチニブが複数の異なる RET 融合パートナー及びがん種を背景とする RET 融合遺伝子陽性がんに対して有効であることが、非臨床データにより示唆されている。また、12 歳以上の RET 融合遺伝子陽性の固形がん、RET 遺伝子変異陽性の MTC、及びその他の RET 活性化腫瘍を含む進行性の固形がんを対象とした国際共同第 I/II 相試験である LOXO-RET-17001 試験（LIBRETTO-001、以下 17001 試験）では、セルペルカチニブは RET 融合遺伝子のパートナーに関係なく、NSCLC 及び複数の組織型を有する TC 患者にベネフィットをもたらすことが示された。

セルペルカチニブの作用機序、非臨床データ、及び、臨床的知見から、がん種に関わらず遺伝子の構造再編成によって RET 融合遺伝子が形成されると、恒常的な RET 活性化が生じ、がん細胞の増殖及び生存が RET シグナル伝達経路に強く依存した状態になること、これに対してセルペルカチニブによる治療が有効であることが期待される。

17001 試験より、既承認の NSCLC 及び TC を除いた RET 融合遺伝子陽性の固形がんに対する有効性及び安全性を評価した。17001 試験は、完了した第 I 相パート及び進行中の第 II 相パートで構成された。第 I 相パートの主な目的は、セルペルカチニブの最大耐用量（MTD）と第 II 相推奨用量（RP2D）を確認することであった。第 II 相パートは複数のコホートから成り、第 I 相パートの結果から決定された RP2D の 160 mg BID を用いた。第 II 相パートの主な目的は、IRC 判定によるがん種に応じた Response Evaluation Criteria in Solid Tumors（RECIST）v1.1 又は Response Assessment in Neuro-Oncology（RANO）に基づく奏効率（ORR）によるセルペルカチニブの抗腫瘍効果を評価することであった。

本申請で提示する解析対象集団は NSCLC 及び TC を除く RET 融合遺伝子陽性の固形がん患者で構成するため、コホート 1、2、5 を横断的に解析した。

- コホート 1：RET 融合遺伝子陽性の固形がんで、過去に少なくとも 1 種類の標準的なファーストライン療法を行った後、がんが進行した患者、又はこれを忍容しない患者
- コホート 2：RET 融合遺伝子陽性の固形がんで、標準的なファーストライン療法の治療経験のない患者。以下の基準のいずれかを満たす。
 - 標準治療が存在しない
 - 患者が標準治療の候補ではない、又は標準治療に対して忍容性を示したり、標準治療から有意な臨床的ベネフィットが得られたりする可能性が低いと治験責任医師が判断した
 - 標準治療を拒否した
- コホート 5：
 - コホート 1~4 に該当するが、測定可能病変のない患者
 - コホート 3 又は 4 の要件を満たさない MTC の患者

- 他の *RET* 遺伝子の変化／活性化を有する MTC 症候群スペクトラム癌（例えば、MTC、褐色細胞腫）、神経内分泌特性／分化を示す癌、又は低分化甲状腺癌で事前に治験依頼者の了解が得られた患者
- cfDNA で *RET* 遺伝子の変化が陽性で腫瘍検体中でその変化の存在が確認されない患者

有効性について、20██年██月のカットオフデータでは、有効性解析対象集団として NSCLC 及び TC を除いた *RET* 融合遺伝子陽性の固形がん患者 41 例（コホート 1：30 例、コホート 2：1 例、コホート 5：10 例）が含まれた。37 例（90.2%）が、1 つ以上の治療ラインを前治療として受け、9 例（22.0%）がセルペルカチニブを 2 次治療として、28 例（68.3%）が、セルペルカチニブを 3 次以上の治療として投与された。NSCLC 及び TC を除いた *RET* 融合遺伝子陽性の固形がん患者 41 例に対して全体で 43.9%（95%CI：28.5 - 60.3%）の ORR が得られ、14 がん種中 10 がん種において臨床的に意義のある抗腫瘍効果が認められた。また、IRC 判定による奏効期間（DOR）の中央値は 24.5 ヶ月（95%CI：9.2 - NE）とがん種に関わらず持続的な奏効を示した。日本人 9 例に対して 77.8% の ORR が得られ、7 がん種中 6 がん種において臨床的に意義のある抗腫瘍効果が認められた。IRC 判定による DOR の中央値は 17.3 ヶ月と日本人においても全体集団と同様に良好な結果が認められた。2023 年 1 月のカットオフデータの結果は、20██年██月のカットオフデータの結果と同等であった。有効性解析対象集団として NSCLC 及び TC を除いた *RET* 融合遺伝子陽性の固形がん患者 52 例（コホート 1：38 例、コホート 2：2 例、コホート 5：12 例）が含まれた。47 例（90.4%）が、1 つ以上の治療ラインを前治療として受けていた。12 例（23.1%）が、セルペルカチニブを 2 次治療として、35 例（67.3%）が、セルペルカチニブを 3 次治療以降として投与された。NSCLC 及び TC を除いた *RET* 融合遺伝子陽性の固形がん患者 52 例に対して全体で 44.2%（95%CI：30.5 - 58.7%）の ORR が得られ、16 がん種中 12 がん種において臨床的に意義のある抗腫瘍効果が認められた。また、IRC 判定による DOR の中央値は 37.19 ヶ月（95%CI：13.3 - NE）と持続的な奏効を示した。日本人 11 例に対して 63.6% の ORR が得られ、7 がん種中 6 がん種において臨床的に意義のある抗腫瘍効果が認められた。また、いずれのカットオフデータの結果においても、多くの *RET* 融合パートナーで奏効例が認められた。これらを踏まえ、第 2.5.6.1.3 項記載のように、NSCLC 及び TC を除いた *RET* 融合遺伝子陽性の固形がんに対して、現在推奨されている 2 次治療以上の標準治療と比較した場合、セルペルカチニブは十分な臨床的意義がある治療と考えられた。

安全性について、NSCLC 及び TC を除いた *RET* 融合遺伝子陽性の固形がん患者に対するセルペルカチニブの安全性プロファイルは、既知の安全性プロファイルと大きく異ならず、新たな安全性上の懸念は認められなかった。セルペルカチニブは多くの前治療を使用していた場合でも忍容性が高く、治験薬との因果関係が否定できないと判断された有害事象による中止の割合は低かったことから、発現が認められた有害事象は適切なモニタリング、注意喚起及び用量調節で管理可能と考えられた。また、全体集団と日本人集団の安全性プロファイルには、臨床的に意味のある違いは認められなかった。以上から、セルペルカチニブは既承認の NSCLC 及び TC を除いた *RET* 融合遺伝子陽性の固形がんに対して良好なベネフィット・リスクバランスを示した。また、既承認の効能・効果である「*RET* 融合遺伝子陽性の切除不能な進行・再発の非小細胞肺癌」及び

「*RET* 融合遺伝子陽性の根治切除不能な甲状腺癌」は「*RET* 融合遺伝子陽性の進行・再発の固形腫瘍」に包含され、非小細胞肺癌、甲状腺癌、固形腫瘍（非小細胞肺癌及び甲状腺癌を除く）に対する各々の関連する注意について添付文書等で注意喚起を行うことで、本剤の適切な使用を推進することができる考える。

上記を踏まえ、既承認の効能・効果である「*RET* 融合遺伝子陽性の切除不能な進行・再発の非小細胞肺癌」及び「*RET* 融合遺伝子陽性の根治切除不能な甲状腺癌」と纏めて、本剤の効能又は効果（案）を「*RET* 融合遺伝子陽性の進行・再発の固形腫瘍」と設定することが妥当と考えた。

非小細胞肺癌及び甲状腺癌を除く *RET* 融合遺伝子陽性の固形腫瘍に対し、本剤は *RET* 遺伝子異常を有する患者を対象とし、遺伝子異常の検査にコンパニオン診断薬を必要とすることから、効能又は効果に関連する注意（案）として 5.6 を設定した。また、組織球症が本薬の投与対象となり得る旨を明確にするために 5.7 を設定し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うことが必要と考えられたことから 5.8 を設定した。更に、本剤の手術の補助療法における臨床試験成績を有していないことから 5.9 を設定した。

1.8.3 用法・用量（案）及びその設定根拠

1.8.3.1 用法・用量（案）

~~〈RET融合遺伝子陽性の切除不能な進行・再発の非小細胞肺癌〉~~
通常、成人にはセルペルカチニブとして1回160mgを1日2回経口投与する。なお、
~~患者の状態により適宜減量する。~~
~~〈RET融合遺伝子陽性の根治切除不能な甲状腺癌、RET遺伝子変異陽性の根治切除不
能な甲状腺髄様癌〉~~
通常、成人にはセルペルカチニブとして1回160mgを1日2回経口投与する。なお、
患者の状態により適宜減量する。
通常、12歳以上の小児には体表面積に合わせて次の投与量（セルペルカチニブとして
1回約92mg/m²）を1日2回経口投与する。なお、患者の状態により適宜減量する。

小児の用量

体表面積	1回投与量
1.2m ² 未満	80mg
1.2m ² 以上1.6m ² 未満	120mg
1.6m ² 以上	160mg

取消線部：削除

1.8.3.2 用法及び用量に関連する注意（案）

7.1 他の抗悪性腫瘍剤との併用について、有効性及び安全性は確立していない。
7.2 本剤投与により副作用が発現した場合には、以下の基準を考慮して、休薬・減量・
中止すること。

成人の場合 本剤の減量の目安

減量レベル	投与量
通常投与量	1回160mg 1日2回
1段階減量	1回120mg 1日2回
2段階減量	1回80mg 1日2回
3段階減量	1回40mg 1日2回

小児の場合 本剤の減量の目安

体表面積	減量レベル	投与量
1.2m ² 未満	通常投与量	1回80mg 1日2回
	1段階減量	1回40mg/1回80mg 1日2回 (1日量120mg)
	2段階減量	1回40mg 1日2回
	3段階減量 ^{注1)}	1回40mg 1日1回
1.2m ² 以上1.6m ² 未満	通常投与量	1回120mg 1日2回
	1段階減量	1回80mg 1日2回
	2段階減量	1回40mg/1回80mg 1日2回 (1日量120mg)
	3段階減量 ^{注1)}	1回40mg 1日1回
1.6m ² 以上	通常投与量	1回160mg 1日2回
	1段階減量	1回120mg 1日2回
	2段階減量	1回80mg 1日2回
	3段階減量	1回40mg 1日2回

注1) 過敏症発現時のみ（過敏症以外で2段階減量において忍容性が得られない場合、投与中止）

副作用に対する休薬、減量及び中止基準

副作用	程度 ^{注2)}	処置
ALT 又は AST 増加	グレード 3 又は 4	グレード 1 以下に回復するまで休薬し、回復後は 2 段階減量して投与再開できる。 再開後に 2 週間以上再発しない場合には、1 段階増量することができる。更に 4 週間以上再発しない場合には、もう 1 段階増量することができる。 減量した用量で投与中に再発した場合には、中止する。
QT 間隔延長	QTc 間隔>500msec	QTc 間隔<470msec に回復するまで休薬し、回復後は 1 段階減量して投与再開できる。 2 段階減量した用量で投与中に再発した場合には、中止する。
	重篤な不整脈を疑う所見や症状が認められた場合	中止する。
高血圧	グレード 3 又は 4	回復するまで休薬し、回復後は 1 段階減量して投与再開できる。
過敏症（アナフィラキシー等の重篤な過敏症を除く）	グレード 1～4	回復するまで休薬し、副腎皮質ステロイドの全身投与を考慮する。回復後は副腎皮質ステロイドを併用しながら 3 段階減量して投与再開できる。 再開後に 7 日以上再発しない場合には、1 段階ずつ発現時の用量まで増量できる。増量後に 7 日以上再発しない場合には、副腎皮質ステロイドを漸減する。
間質性肺疾患	グレード 2	回復するまで休薬し、回復後は 1 段階減量して投与再開できる。
	グレード 3 又は 4	中止する。
上記以外の副作用	グレード 3 又は 4	回復するまで休薬し、回復後は 1 段階減量して投与再開できる。

注2) グレードは NCI-CTCAE ver. 4.03 に準じる。

1.8.3.3 設定根拠

17001 試験の第 I 相パートにおいて 20 mg 1 日 1 回～240 mg 1 日 2 回（BID）までの用量漸増を行い、RP2D を 160 mg BID と決定した。

また、17001 試験の結果、*RET* 融合遺伝子陽性固形がん患者における定常状態での PK はセルペルカチニブの既知の PK と一致しており、有効性又は注目すべき有害事象に関する曝露-反応解析では、有効性に及ぼす有意な予測因子は認められず、注目すべき有害事象に関してはセルペルカチニブの曝露の増加に伴うリスクの増加を示さなかった。また、第 1.8.2.3 項に記載のように、既承認の非小細胞肺癌及び甲状腺癌を除いた *RET* 遺伝子陽性の固形がんに対してセルペルカチニブ 1 回 160 mg BID の有効性及び安全性が示されたことから、*RET* 融合遺伝子陽性の固形腫瘍を有する成人患者には 160 mg BID 投与が適切と考えた。17001 試験（15 歳から 17 歳までの *RET* 遺伝子変異陽性の甲状腺髄様癌患者 3 例を含む）の結果から、すべてのがん種で PK は概ね同様であった（CTD 第 2.7.2.3.2 項、及び初回申請資料第 2.7.2.4.3 項）。*RET* 融合遺伝子陽性の固形腫瘍を有する 12 歳以上の小児患者に対しては、*RET* 融合遺伝子陽性甲状腺癌又は *RET* 遺伝子変異陽性甲状腺髄様癌を有する 12 歳以上の小児患者に対して承認された用法・用量と同じく、成人にセルペルカチニブ 1 回 160 mg BID 投与した際と同程度の曝露量が期待できる用法・用量（160 mg BID/1.73m² = 92 mg/m² BID）として、体表面積が 1.2 m² 未満の患者には 80 mg BID 投与、体表面

積が 1.2 m^2 以上 1.6 m^2 未満の患者には 120 mg BID 投与、体表面積が 1.6 m^2 以上の患者には 160 mg BID 投与が適切と考えた。

本剤は他の抗悪性腫瘍剤との併用に関する臨床成績が得られていないことから、既承認効能効果と同様、用法及び用量に関連する注意（案）として 7.1 を設定した。また、各種副作用が認められた場合には休薬、減量等の対応が必要であることから、既承認効能効果と同様 7.2 を設定した。

1.8.4 使用上の注意（案）及びその設定根拠

使用上の注意（案）は、本剤の国際共同臨床試験及びその他試験結果並びに企業中核データシート [Company Core Data Sheet (CCDS)] を参考にして設定した。

使用上の注意（案）	設定根拠
1. 警告 本剤は、緊急時に十分対応できる医療施設において、がん化学療法に十分な知識・経験を持つ医師のもとで、本剤の投与が適切と判断される症例についてのみ投与すること。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分説明し、同意を得てから投与すること。	変更なし
2. 禁忌（次の患者には投与しないこと） 本剤の成分に対しアナフィラキシー等の重篤な過敏症の既往歴のある患者	変更なし
8. 重要な基本的注意 8.1 肝機能障害があらわれることがあるので、本剤の投与開始前及び投与期間中は定期的に肝機能検査を行い、患者の状態を十分に観察すること。 [11.1.1 参照]	変更なし
8.2 QT 間隔延長があらわれることがあるので、本剤の投与開始前には患者の QTc 間隔が 470msec 以下であることを確認するとともに血清電解質検査（カリウム、マグネシウム等）を行うこと。心電図及び血清電解質検査を投与開始後 1 週間時点及び投与開始後 6 ヶ月間は毎月 1 回行い、以降も必要に応じて行うこと。また、必要に応じて電解質補正を行うこと。 [11.1.2、17.3.1 参照]	
8.3 高血圧があらわれることがあるので、本剤の投与開始前に血圧が適切に管理されていることを確認すること。本剤投与中は定期的に血圧を測定すること。	
8.4 間質性肺疾患があらわれることがあるので、本剤の投与にあたっては、初期症状（呼吸困難、咳嗽、発熱等）の確認及び胸部画像検査の実施等、患者の状態を十分に観察すること。また、患者に副作用について説明するとともに、間質性肺疾患の初期症状が発現した場合には、速やかに医療機関を受診するよう説明すること。 [9.1.3、11.1.5 参照]	
9. 特定の背景を有する患者に関する注意 9.1 合併症・既往歴等のある患者 9.1.1 QT 間隔延長のおそれ又はその既往歴のある患者 QT 間隔延長が発現するおそれがある。先天性/後天性 QT 延長症候群又はその他不整脈の要因になる病態を有する患者には慎重に投与すること。 [11.1.2、17.3.1 参照] 9.1.2 高血圧症の患者 高血圧が悪化するおそれがある。 [11.1.4 参照] 9.1.3 間質性肺疾患のある患者又はその既往歴のある患者 間質性肺疾患が発現又は増悪するおそれがある。 [8.4、11.1.5 参照]	変更なし
9.3 肝機能障害患者 9.3.1 重度の肝機能障害のある患者（Child-Pugh 分類 C） 減量を考慮するとともに、患者の状態をより慎重に観察し、副作用の発現に十分注意すること。本剤の血中濃度が上昇し、副作用が増強されるおそれがある。 [16.6.2 参照]	変更なし

使用上の注意（案）	設定根拠												
9.4 生殖能を有する者 9.4.1 <u>妊娠する可能性のある女性</u>には、本剤投与中及び最終投与後 1 ヶ月間において避妊する必要性及び適切な避妊法について説明すること。 [9.5 参照] 9.4.2 男性には、本剤投与中及び最終投与後 1 週間においてバリア法（コンドーム）を用いて避妊する必要性について説明すること。 [15.2.1 参照] 9.4.3 成長期にある若年男性又は男児に投与する場合には、造精機能の低下があらわれる可能性があることを考慮すること。幼若ラットにおいて、精巣の精上皮変性、精巣上体の精子枯渇、精子運動率低値、異常形態精子比率高値及び受胎能の低下が認められ、精巣及び精巣上体の所見に回復性は認められていない。	2021 年 9 月 27 日の NSCLC 効能効果承認時に設定された避妊文言に関して、以下の観点から避妊ガイダンスを勘案し、避妊期間を設定した。 - 本剤は復帰突然変異試験で変異原性を示さず、ヒト末梢リンパ球を用いた小核試験で染色体異常誘発性を示さなかった。 - ラット小核試験において、遺伝毒性が陽性であったが、このときの用量は骨髄に影響を生じ、かつ臨床用量 160mg1 日 2 回で得られる Cmax の 5.2 倍に相当する十分な高い用量であった。 - ラットの胚・胎児発生毒性は試験された最低用量で認められたため、危険性が除外できない。 - 本剤の半減期は 31.5 時間であり 5 倍すると約 1 週間である。												
9.5 妊婦 妊婦又は妊娠している可能性のある女性には治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。ラットを用いた胚・胎児発生毒性試験において、臨床曝露量（AUC）と同程度の曝露量で胎児死亡及び奇形が認められている。 [9.4.1 参照]	変更なし												
9.6 授乳婦 授乳しないことが望ましい。乳汁移行に関するデータはないが、本剤は BCRP の基質であるため、乳汁移行の可能性はある。	変更なし												
9.7 小児等 9.7.1 成長期にある若年者においては、<u>骨成長について以下の点に注意すること。</u> ・骨端線に異常がないか十分に観察すること。骨端線に異常が認められた場合には、投与継続の可否を慎重に判断すること。 ・関節痛及び歩行障害について十分に観察すること。大腿骨頭すべり症等の骨端離開があらわれることがある。 [15.2.2 参照] 9.7.2 12 歳未満の小児等を対象とした臨床試験は実施していない。	・非臨床試験において、骨の成長への影響が示唆されたため、ヒトでの影響は不明であるが注意喚起が必要と考え設定した。骨端離開については、臨床試験における集積状況や非臨床試験における知見等から本剤との因果関係が否定できない事象と判断したため、今後の日本人での発現リスクが否定できないと考えられることから設定した。 ・12 歳未満の小児等を対象とした臨床試験結果に基づき用量設定されていないことから設定した。												
10. 相互作用 本剤は、主に CYP3A4 によって代謝され、CYP2C8 及び 3A の阻害作用を示す。また、本剤の溶解度は pH の上昇により低下する。 10.2 併用注意（併用に注意すること） <table><tr><th>薬剤名等</th><th>臨床症状・措置方法</th><th>機序・危険因子</th></tr><tr><td>CYP2C8 の基質となる薬剤 レバグリニド ピオグリタゾン モンテルカスト等 [16.7.6 参照]</td><td>これらの薬剤の副作用が増強されるおそれがあるので、患者の状態を慎重に観察し、副作用の発現に十分注意すること。</td><td>本剤が CYP2C8 を阻害することにより、これらの薬剤の血中濃度が上昇する可能性がある。</td></tr><tr><td>CYP3A の基質となる薬剤 ミダゾラム トリアゾラム ロミタピド等 [16.7.5 参照]</td><td>これらの薬剤の副作用が増強されるおそれがあるので、患者の状態を慎重に観察し、副作用の発現に十分注意すること。</td><td>本剤が CYP3A を阻害することにより、これらの薬剤の血中濃度が上昇する可能性がある。</td></tr><tr><td>CYP3A 阻害剤 イトラコナゾール クラリスロマイシン エリスロマイシン等</td><td>本剤の副作用が増強されるおそれがあるので、これらの薬剤との併用は可能な限り避けること。や</td><td>これらの薬剤が CYP3A を阻害することにより、本剤の血中濃度が上昇する可能性がある。</td></tr></table>	薬剤名等	臨床症状・措置方法	機序・危険因子	CYP2C8 の基質となる薬剤 レバグリニド ピオグリタゾン モンテルカスト等 [16.7.6 参照]	これらの薬剤の副作用が増強されるおそれがあるので、患者の状態を慎重に観察し、副作用の発現に十分注意すること。	本剤が CYP2C8 を阻害することにより、これらの薬剤の血中濃度が上昇する可能性がある。	CYP3A の基質となる薬剤 ミダゾラム トリアゾラム ロミタピド等 [16.7.5 参照]	これらの薬剤の副作用が増強されるおそれがあるので、患者の状態を慎重に観察し、副作用の発現に十分注意すること。	本剤が CYP3A を阻害することにより、これらの薬剤の血中濃度が上昇する可能性がある。	CYP3A 阻害剤 イトラコナゾール クラリスロマイシン エリスロマイシン等	本剤の副作用が増強されるおそれがあるので、これらの薬剤との併用は可能な限り避けること。や	これらの薬剤が CYP3A を阻害することにより、本剤の血中濃度が上昇する可能性がある。	変更なし
薬剤名等	臨床症状・措置方法	機序・危険因子											
CYP2C8 の基質となる薬剤 レバグリニド ピオグリタゾン モンテルカスト等 [16.7.6 参照]	これらの薬剤の副作用が増強されるおそれがあるので、患者の状態を慎重に観察し、副作用の発現に十分注意すること。	本剤が CYP2C8 を阻害することにより、これらの薬剤の血中濃度が上昇する可能性がある。											
CYP3A の基質となる薬剤 ミダゾラム トリアゾラム ロミタピド等 [16.7.5 参照]	これらの薬剤の副作用が増強されるおそれがあるので、患者の状態を慎重に観察し、副作用の発現に十分注意すること。	本剤が CYP3A を阻害することにより、これらの薬剤の血中濃度が上昇する可能性がある。											
CYP3A 阻害剤 イトラコナゾール クラリスロマイシン エリスロマイシン等	本剤の副作用が増強されるおそれがあるので、これらの薬剤との併用は可能な限り避けること。や	これらの薬剤が CYP3A を阻害することにより、本剤の血中濃度が上昇する可能性がある。											

使用上の注意（案）			設定根拠													
[16.7.1、16.7.2 参照]	むを得ず併用する場合には、本剤の減量を考慮するとともに、患者の状態を慎重に観察し、副作用の発現に十分注意すること。		これらの薬剤等が CYP3A を誘導することにより、本剤の血中濃度が低下する可能性がある。													
CYP3A 誘導剤 リファンピシン フェニトイン ボセンタン等 [16.7.3、16.7.4 参照]	本剤の有効性が減弱するおそれがあるので、これらの薬剤との併用は可能な限り避け、CYP3A 誘導作用のない薬剤への代替を考慮すること。															
セイヨウオトギリソウ(St. John's Wort、セント・ジョーンズ・ワート)含有製品	本剤の有効性が減弱するおそれがあるので、摂取しないよう注意すること。															
プロトンポンプ阻害剤 オメプラゾール ランソプラゾール エソメプラゾール等 [16.7.7 参照]	本剤の有効性が減弱するおそれがあるので、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、本剤とともに食後に投与すること。	これらの薬剤による胃内 pH の上昇により、本剤の吸収が低下し、本剤の血中濃度が低下する可能性がある。														
H ₂ 受容体拮抗剤 ラニチジン ファモチジン シメチジン等 [16.7.8 参照]	本剤の有効性が減弱するおそれがあるので、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、本剤と服用時間をずらすこと(ラニチジンを本剤投与 10 時間前及び 2 時間後に投与したときの本剤の血中濃度への影響は限定的であった)。															
制酸剤 炭酸カルシウム 水酸化マグネシウム 水酸化アルミニウム等	本剤の有効性が減弱するおそれがあるので、これらの薬剤との併用は可能な限り避けること。やむを得ず併用する場合には、本剤と服用時間をずらすこと(制酸剤を本剤投与 2 時間前又は 2 時間後に投与したときの本剤の血中濃度への影響は限定的であった)。															
11. 副作用 次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。 11.1 重大な副作用 11.1.1 肝機能障害（36.4%） [8.1 参照] 11.1.2 QT 間隔延長（13.9%） [8.2、9.1.1、17.3.1 参照] 11.1.3 過敏症（5.1%） 発疹、発熱等の症状を伴う遅発性の過敏症があらわれることがある。 [7.2 参照] 11.1.4 高血圧（30.0%） [9.1.2 参照] 11.1.5 間質性肺疾患（0.7%） [8.4、9.1.3 参照] 11.2 その他の副作用			本剤の副作用として臨床試験の結果から本剤投与との間に関連性があると判断された事象を CCDS の記載を参考に設定した。なお、事象の頻度は LIBRETTO-001 試験の第 II 相パートに組み入れられた NSCLC 及び甲状腺癌患者並びに第 I 相パート及び第 II 相パートに組み入れられ開始用量として本剤 160mg1 日 2 回を投与された NSCLC 及び甲状腺癌以外の固形癌患者（Tissue-Agnostic Safety Population）の頻度に基づき算出した。													
<table><tr><td>副作用分類</td><td>20%以上</td><td>5～20%未満</td><td>5%未満</td></tr><tr><td>消化器</td><td>口内乾燥 (34.2%)、下痢</td><td>便秘、悪心、腹痛</td><td>嘔吐</td></tr><tr><td>一般・全身及び投与部位反応</td><td>疲労</td><td>浮腫、発熱</td><td></td></tr></table>			副作用分類	20%以上	5～20%未満	5%未満	消化器	口内乾燥 (34.2%)、下痢	便秘、悪心、腹痛	嘔吐	一般・全身及び投与部位反応	疲労	浮腫、発熱			
副作用分類	20%以上	5～20%未満	5%未満													
消化器	口内乾燥 (34.2%)、下痢	便秘、悪心、腹痛	嘔吐													
一般・全身及び投与部位反応	疲労	浮腫、発熱														

使用上の注意（案）				設定根拠
呼吸器			鼻出血、肺炎	
内分泌			甲状腺機能低下症	
代謝・栄養障害		食欲減退		
精神神経系		頭痛	浮動性めまい	
皮膚		発疹		
血液		血小板減少、白血球減少、好中球減少	リンパ球減少、貧血	
臨床検査値異常		血中クレアチニン増加	低マグネシウム血症	
14. 適用上の注意 14.1 薬剤交付時の注意 PTP 包装の薬剤は PTP シートから取り出して服用するよう指導すること。PTP シートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔をおこして縦隔洞炎等の重篤な合併症を併発することがある。				変更なし
15. その他の注意 15.2 非臨床試験に基づく情報 15.2.1 セルペルカチニブは、ラット小核試験において、臨床用量 160mg1 日 2 回で得られる C_{max} の 5.2 倍に相当する用量で遺伝毒性が陽性であった。[9.4.2 参照] 15.2.2 動物試験（成長板が閉鎖していない幼若ラット、若齢ラット及び若齢ミニブタ）において、本剤の反復投与により骨端成長板の異常（骨端軟骨の肥大、過形成及び異形成）が、ヒトに 160mg1 日 2 回の用量で投与したときの臨床曝露量よりも低い曝露量で認められている。また、幼若ラットにおいて、骨端成長板の変化に関連して、骨密度及び大腿骨長の低値が、ヒトに 160mg1 日 2 回の用量で投与したときの臨床曝露量のそれぞれ 0.8 倍及び 1.9 倍で認められている。[9.7.1 参照]				変更なし

レットヴィモカプセル 40mg
レットヴィモカプセル 80mg

1.9 一般的名称に係る文書

日本イーライリリー株式会社

目次

1.9 一般的名称に係る文書.....	1
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1.9 一般的名称に係る文書

International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names: List 82

Notice is hereby given that, in accordance with paragraph 7 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances [*Off. Rec. Wld Health Org.*, 1955, **60**, 3 (Resolution EB15.R7); 1969, **173**, 10 (Resolution EB43.R9); Resolution EB115.R4 (EB115/2005/REC/1)], the following names are selected as Recommended International Nonproprietary Names. The inclusion of a name in the lists of Recommended International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.

Lists of Proposed (1–1117) and Recommended (1–78) International Nonproprietary Names can be found in *Cumulative List No. 17, 2017* (available in CD-ROM only).

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Dénominations communes internationales RECOMMANDÉES: Liste 82

Il est notifié que, conformément aux dispositions du paragraphe 7 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques [*Actes off. Org. mond. Santé*, 1955, **60**, 3 (résolution EB15.R7); 1969, **173**, 10 (résolution EB43.R9); résolution EB115.R4 (EB115/2005/REC/1)] les dénominations ci-dessous sont choisies par l'Organisation mondiale de la Santé en tant que dénominations communes internationales recommandées. L'inclusion d'une dénomination dans les listes de DCI recommandées n'implique aucune recommandation en vue de l'utilisation de la substance correspondante en médecine ou en pharmacie.

On trouvera d'autres listes de Dénominations communes internationales proposées (1–117) et recommandées (1–78) dans la *Liste récapitulative No. 17, 2017* (disponible sur CD-ROM seulement).

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS: Lista 82

De conformidad con lo que dispone el párrafo 7 del Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas [*Act. Of. Mund. Salud*, 1955, **60**, 3 (Resolución EB15.R7); 1969, **173**, 10 (Resolución EB43.R9); Resolución EB115.R4 (EB115/2005/REC/1) EB115.R4 (EB115/2005/REC/1)], se comunica por el presente anuncio que las denominaciones que a continuación se expresan han sido seleccionadas como Denominaciones Comunes Internacionales Recomendadas. La inclusión de una denominación en las listas de las Denominaciones Comunes Recomendadas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia.

Las listas de Denominaciones Comunes Internacionales Propuestas (1–117) y Recomendadas (1–78) se encuentran reunidas en *Cumulative List No. 17, 2017* (disponible sólo en CD-ROM).

selitrectinibum

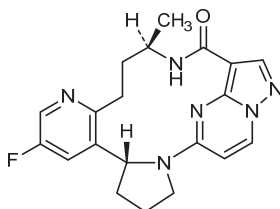
selitrectinib

(2²*R*,6*R*)-3⁵-fluoro-6-methyl-1(5,3)-pyrazolo[1,5-*a*]pyrimidina-3(3,2)-pyridina-2(1,2)-pyrrolidinacyclooctaphan-8-one

sélitrectinib

(2²*R*,6*R*)-3⁵-fluoro-6-méthyl-1(5,3)-pyrazolo[1,5-*a*]pyrimidina-3(3,2)-pyridina-2(1,2)-pyrrolidinacyclooctaphan-8-one

selitrectinib

(2²*R*,6*R*)-3⁵-fluoro-6-metil-1(5,3)-pirazolo[1,5-*a*]pyrimidina-3(3,2)-piridina-2(1,2)-pirrolidinaciclooctafan-8-onaC₂₀H₂₁FN₆O**selpercatinibum**

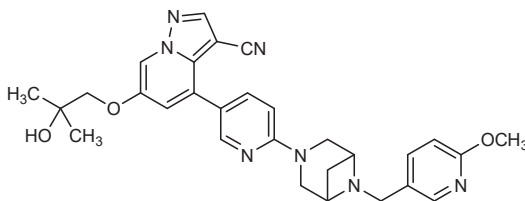
selpercatinib

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

selpercatinib

6-(2-hydroxy-2-méthylpropoxy)-4-(6-{6-[(6-méthoxypyridin-3-yl)méthyl]-3,6-diazabicyclo[3.1.1]heptan-3-yl}pyridin-3-yl)pyrazolo[1,5-*a*]pyridine-3-carbonitrile

selpercatinib

6-(2-hidroxi-2-metilpropoxi)-4-(6-{6-[(6-metoxipiridin-3-il)metil]-3,6-diazabicyclo[3.1.1]heptan-3-il}piridin-3-il)pirazolo[1,5-*a*]piridina-3-carbonitriloC₂₉H₃₁N₇O₃**semorinemabum #**

semorinemab

immunoglobulin G4-kappa, anti-[*Homo sapiens* MAPT (microtubule-associated protein tau, tau)], monoclonal antibody;

薬生薬審発 0310 第 1 号
令和 2 年 3 月 10 日

各都道府県衛生主管部（局）長 殿

厚生労働省医薬・生活衛生局医薬品審査管理課長
（ 公 印 省 略 ）

医薬品の一般的名称について

標記については、「医薬品の一般的名称の取扱いについて（平成 18 年 3 月 31 日薬食発第 0331001 号厚生労働省医薬食品局長通知）」等により取り扱っているところです。今般、我が国における医薬品の一般的名称（以下「JAN」という。）について、新たに別添のとおり定めたので、御了知の上、貴管下関係業者に周知方よろしく御配慮願います。

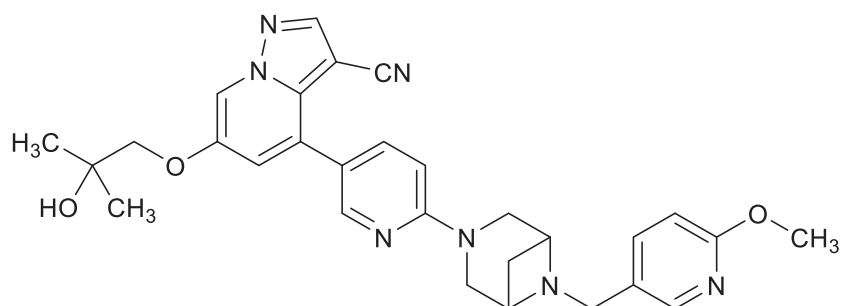
（参照）

「日本医薬品一般的名称データベース」<https://jpd.b.nihs.go.jp/jan/Default.aspx>
（別添の情報のうち、JAN 以外の最新の情報は、当該データベースの情報で対応することとしています。なお、本年 2 月末より当該 URL を変更しており、令和 2 年 4 月初頭以降は従前 URL でのアクセスは不可となります。）

登録番号 301-4-B4

JAN（日本名）：セルペルカチニブ

JAN（英名）：Selpercatinib



C₂₉H₃₁N₇O₃

6-(2-ヒドロキシ-2-メチルプロポキシ)-4-(6-{6-[(6-メトキシピリジン-3-イル)メチル]-3,6-ジアザビシクロ[3.1.1]ヘプタン-3-イル}ピリジン-3-イル)ピラゾロ[1,5-*a*]ピリジン-3-カルボニトリル

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

レットヴィモカプセル 40mg

レットヴィモカプセル 80mg

1.10 毒薬・劇薬等の指定審査資料のまとめ

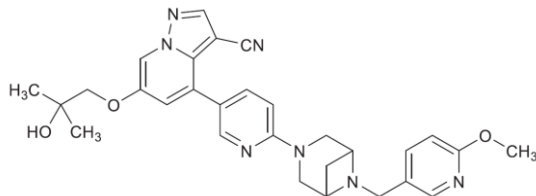
日本イーライリリー株式会社

目次

1.10 毒薬・劇薬等の指定審査資料のまとめ	1
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1.10 毒薬・劇薬等の指定審査資料のまとめ

表 1.10-1 毒薬・劇薬等の指定審査資料のまとめ（現行）

化学名・別名	化学名: 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 (別名: セルペルカチニブ及びその製剤)															
構造式																
効能・効果	RET 融合遺伝子陽性の切除不能な進行・再発の非小細胞肺癌 RET 融合遺伝子陽性の根治切除不能な甲状腺癌 RET 遺伝子変異陽性の根治切除不能な甲状腺髄様癌															
用法・用量	〈RET 融合遺伝子陽性の切除不能な進行・再発の非小細胞肺癌〉 通常、成人にはセルペルカチニブとして1回 160 mg を1日2回経口投与する。なお、患者の状態により適宜減量する。 〈RET 融合遺伝子陽性の根治切除不能な甲状腺癌、RET 遺伝子変異陽性の根治切除不能な甲状腺髄様癌〉 通常、成人にはセルペルカチニブとして1回 160 mg を1日2回経口投与する。なお、患者の状態により適宜減量する。 通常、12歳以上の小児には体表面積に合わせて次の投与量（セルペルカチニブとして1回約 92 mg/m²）を1日2回経口投与する。なお、患者の状態により適宜減量する。 小児の用量 <table><tr><td>体表面積</td><td>1回投与量</td></tr><tr><td>1.2m²未満</td><td>80mg</td></tr><tr><td>1.2m²以上 1.6m²未満</td><td>120mg</td></tr><tr><td>1.6m²以上</td><td>160mg</td></tr></table>			体表面積	1回投与量	1.2m ² 未満	80mg	1.2m ² 以上 1.6m ² 未満	120mg	1.6m ² 以上	160mg					
体表面積	1回投与量															
1.2m ² 未満	80mg															
1.2m ² 以上 1.6m ² 未満	120mg															
1.6m ² 以上	160mg															
劇薬等の指定	原薬及び製剤：劇薬 処方箋医薬品															
市販名及び有効成分・分量	原体：セルペルカチニブ 製剤： レットヴィモカプセル 40mg（1カプセル中 40 mg 含有） レットヴィモカプセル 80mg（1カプセル中 80 mg 含有）															
毒性	単回投与毒性（経口） <table><tr><td>動物種</td><td>概略の致死量 (mg/kg)</td></tr><tr><td>ラット</td><td>>2000^a</td></tr><tr><td>ミニブタ</td><td>>65^b</td></tr></table> a：ラット小核予備試験（単回投与）の成績から推定した。 b：ミニブタ 14日間投与毒性試験の初回投与後の成績から推定した。 反復投与毒性（経口） <table><tr><td>動物種</td><td>用量 (mg/kg)</td><td>NOAEL (mg/kg)</td><td rowspan="2">主な毒性所見</td></tr><tr><td>期間</td><td></td><td></td></tr></table>			動物種	概略の致死量 (mg/kg)	ラット	>2000 ^a	ミニブタ	>65 ^b	動物種	用量 (mg/kg)	NOAEL (mg/kg)	主な毒性所見	期間		
動物種	概略の致死量 (mg/kg)															
ラット	>2000 ^a															
ミニブタ	>65 ^b															
動物種	用量 (mg/kg)	NOAEL (mg/kg)	主な毒性所見													
期間																

セルベルカチニブ（固形がん）

	ラット 28日間	雄：5, 20, 75/45 ^a 雌：15, 50, 150/120 ^b	雄：20 雌：50	死亡又は切迫屠殺：75/45（雄2例）、150/120（雌1例） 75/45（雄）、150/120（雌）：円背位、立毛、削瘦（雄）、斜視（雌）、透明口腔内分泌物（雌）、被毛の汚れ（雌）、不正咬合及び白色切歯、粗毛（雌）、体重↓（雄）、体重増加量↓、摂餌量↓、総白血球数↑（雌）、好中球数↑（雌）、単球数↑（雌）、大型非染色細胞数↑（雌）、A/G比↓（雌）、総タンパク↓、アルブミン↓、Ca↓、AST↑、γ-GTP↑、グルコース↓（雄）、尿素窒素↑（雌）、肝臓重量↓（雄）、胸腺重量↓（雄）、骨端軟骨異形成、骨髓細胞数減少、組織鉍質沈着、膵腺房細胞の変性／壊死（雄） 以下、非毒性的変化： 75/45（雄）、150/120（雌）：ブルンナー腺の陰窩／導管拡張（雄）、舌の上皮萎縮、肺泡マクロファージの増加、膵腺房細胞の変性／壊死（雌） ≥20（雄）：網状赤血球数↓、平均赤血球容積↑、平均赤血球ヘモグロビン↑、ALT↑、ALP↑、コレステロール↑、無機リン↑、ヘモグロビン↑、ヘマトクリット↑ 20（雄）：骨端軟骨異形成、膵腺房細胞の変性／壊死 ≥5（雄）：血小板数↓ ≥50（雌）：平均赤血球容積↑、平均赤血球ヘモグロビン↑、ALT↑、ALP↑、無機リン↑、ヘモグロビン↑、ヘマトクリット↑
	ラット 91日間	雄：2, 7.5, 20 雌：7.5, 25, 75	雄：7.5 雌：25	死亡又は切迫屠殺：2（雄1例）、25（雌1例）、いずれもセルベルカチニブ投与と関連しない 20（雄）、75（雌）：切歯の異常（不正咬合、白色切歯及び切歯喪失）、被毛菲薄化、骨髓細胞数減少、精巣の小型化又は軟化、精巣重量↓、精細管変性／萎縮、精巣上体の管腔内細胞残屑・管腔内精子↓、精巣上体重量↓、膈上皮の粘液分泌↑、性周期の変化（判定不能） 以下、非毒性的変化： 20（雄）、75（雌）：肺泡マクロファージ浸潤、総タンパク↓（雌）、A/G比↓（雌）、無機リン↑、尿pH↑、ヘモグロビン↑（雄）、ヘマトクリット↑（雄）、平均赤血球容積↑（雄）、平均赤血球ヘモグロビン↑（雄） ≥7.5（雄）：網状赤血球数↓ 7.5（雄）：精細管変性／萎縮 ≥25（雌）：膈上皮の粘液分泌↑及び性周期判定不能（1例）、平均赤血球容積↑、平均赤血球ヘモグロビン↑、アルブミン↓ ≥7.5（雌）：ヘモグロビン又はヘマトクリット↑
	ミニブ タ 28日間	2, 5, 12	12	死亡又は切迫屠殺：なし 以下、非毒性的変化： 12：尿素窒素↑（雌）、ALP↑、カリウム↑、無機リン↑ ≥5：赤血球量↑、下顎リンパ節及び腸間膜リンパ節のリンパ球低細胞性 ≥2：舌及び前胃の上皮萎縮

セルペルカチニブ（固形がん）

	ミニブ タ 91 日間	2, 5, 15 ^c	雄：＜2 雌：5	死亡又は切迫屠殺：15（雄 3 例、雌 4 例）、2（雌 1 例：セル ペルカチニブ投与と関連しない） 15：跛行、起立不同意、横臥位、疼痛、赤色口腔内分泌物、 活動性低下、食欲不振、前胃粘膜上皮の萎縮、変性／壊死、 びらん／潰瘍及び／又は好中球性炎症、大腿骨の骨端軟骨の 肥厚（骨端軟骨異形成）、卵巣の黄体減少及び黄体嚢胞、食 道の粘膜萎縮、粘膜変性／壊死、好中球性炎症及び／又は潰 瘍／びらん）、舌の粘膜萎縮、ALP↑、無機リン↑、尿素窒 素↑、Na↑、尿検査値の変化（尿比重↑、尿タンパク↑） ≥2：精細管変性／萎縮、精巣上体の管腔内細胞残屑、精巢 重量↓、精巣上体重量↓ 以下、非毒性的変化： 5：QTc（雌）↑ 2及び5：黄体嚢胞																												
略語：↑＝増加、↓＝減少、A/G 比＝アルブミン：グロブリン比、ALP＝アルカリフォスファターゼ、ALT＝アラニンアミノトランスフェラーゼ、AST＝アスパラギン酸アミノトランスフェラーゼ、Ca＝カルシウム、Na＝ナトリウム、γ-GTP＝γ-グルタミルトランスフェラーゼ活性、QTc＝心拍数で補正した QT a. 75 mg/kg の用量で投与を開始したが、Day 8～10 に休薬した後、Day 11 に 45 mg/kg に減量した。 b. 150 mg/kg の用量で投与を開始したが、Day 16 に 120 mg/kg に減量し、Day 18～20 に休薬した後、Day 21 に 120 mg/kg で投与を再開した。 c. Day 27 に雄 3 例、Day 26 に雌 4 例をそれぞれ瀕死屠殺した。同群の残りの動物についてはこの時点で投与を終了し、4 週間の回復期間の後剖検した。																																
副作用	<table><tr><td colspan="2">副作用発現率 566/653 例 (86.7%)</td><td colspan="2">臨床検査値異常発現率 342/653 例 (52.4%)</td></tr><tr><td>副作用 の種類</td><td>件数／評価例数 (発現割合)</td><td>臨床検査値異常 の種類</td><td>件数／評価例数 (発現割合)</td></tr><tr><td>口内乾燥</td><td>234/653 (35.8%)</td><td>ALT 増加</td><td>184/653 (28.2%)</td></tr><tr><td>ALT 増加</td><td>184/653 (28.2%)</td><td>AST 増加</td><td>177/653 (27.1%)</td></tr><tr><td>AST 増加</td><td>177/653 (27.1%)</td><td>心電図 QT 延長</td><td>97/653 (14.9%)</td></tr><tr><td>高血圧</td><td>175/653 (26.8%)</td><td>血中クレアチニン増加</td><td>81/653 (12.4%)</td></tr><tr><td>下痢</td><td>147/653 (22.5%)</td><td>血中 ALP 増加</td><td>51/653 (7.8%)</td></tr></table>				副作用発現率 566/653 例 (86.7%)		臨床検査値異常発現率 342/653 例 (52.4%)		副作用 の種類	件数／評価例数 (発現割合)	臨床検査値異常 の種類	件数／評価例数 (発現割合)	口内乾燥	234/653 (35.8%)	ALT 増加	184/653 (28.2%)	ALT 増加	184/653 (28.2%)	AST 増加	177/653 (27.1%)	AST 増加	177/653 (27.1%)	心電図 QT 延長	97/653 (14.9%)	高血圧	175/653 (26.8%)	血中クレアチニン増加	81/653 (12.4%)	下痢	147/653 (22.5%)	血中 ALP 増加	51/653 (7.8%)
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会社	日本イーライリリー株式会社 製剤：輸入																															

表 1.10-2 毒薬・劇薬等の指定審査資料のまとめ（変更）

化学名・別名																												
構造式																												
効能・効果	<u>RET</u> 融合遺伝子陽性の切除不能な進行・再発の非小細胞肺癌 <u>RET</u> 融合遺伝子陽性の根治切除不能な甲状腺癌 <u>RET</u> 融合遺伝子陽性の進行・再発の固形腫瘍 <u>RET</u> 遺伝子変異陽性の根治切除不能な甲状腺髄様癌 下線部：追加 取消線部：削除																											
用法・用量	~~〈RET融合遺伝子陽性の切除不能な進行・再発の非小細胞肺癌〉~~ 通常、成人にはセルペルカチニブとして1回160mgを1日2回経口投与する。なお、患者の状態により適宜減量する。 ~~〈RET融合遺伝子陽性の根治切除不能な甲状腺癌、RET遺伝子変異陽性の根治切除不能な甲状腺髄様癌〉~~ 通常、成人にはセルペルカチニブとして1回160mgを1日2回経口投与する。なお、患者の状態により適宜減量する。 通常、12歳以上の小児には体表面積に合わせて次の投与量（セルペルカチニブとして1回約92mg/m ² ）を1日2回経口投与する。 なお、患者の状態により適宜減量する。 小児の用量 <table><tr><td>体表面積</td><td>1回投与量</td></tr><tr><td>1.2m²未満</td><td>80mg</td></tr><tr><td>1.2m²以上1.6m²未満</td><td>120mg</td></tr><tr><td>1.6m²以上</td><td>160mg</td></tr></table> 取消線部：削除				体表面積	1回投与量	1.2m ² 未満	80mg	1.2m ² 以上1.6m ² 未満	120mg	1.6m ² 以上	160mg																
体表面積	1回投与量																											
1.2m ² 未満	80mg																											
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1.6m ² 以上	160mg																											
劇薬等の指定																												
市販名及び有効成分・分量																												
毒性																												
副作用	国際共同第1/2相試験（LOXO-RET-17001試験） 対象：RET融合遺伝子陽性の進行・再発の固形腫瘍（非小細胞肺癌及び甲状腺癌を除く） 副作用発現率 50/55例（90.9%） 臨床検査値異常発現率 <table><tr><td>副作用の種類</td><td>件数／評価例数 （発現割合）</td><td>臨床検査値異常の種類</td><td>件数／評価例数 （発現割合）</td></tr><tr><td>ALT増加</td><td>19/55（34.5%）</td><td>AST増加</td><td>36/54（66.7%）</td></tr><tr><td>AST増加</td><td>15/55（27.3%）</td><td>ALT増加</td><td>31/54（57.4%）</td></tr><tr><td>口内乾燥</td><td>15/55（27.3%）</td><td>血中ALP増加</td><td>26/54（48.1%）</td></tr><tr><td>下痢</td><td>10/55（18.2%）</td><td>血中アルブミン減少</td><td>26/54（48.1%）</td></tr><tr><td>高血圧</td><td>9/55（16.4%）</td><td>血中ナトリウム減少</td><td>26/54（48.1%）</td></tr></table>				副作用の種類	件数／評価例数 （発現割合）	臨床検査値異常の種類	件数／評価例数 （発現割合）	ALT増加	19/55（34.5%）	AST増加	36/54（66.7%）	AST増加	15/55（27.3%）	ALT増加	31/54（57.4%）	口内乾燥	15/55（27.3%）	血中ALP増加	26/54（48.1%）	下痢	10/55（18.2%）	血中アルブミン減少	26/54（48.1%）	高血圧	9/55（16.4%）	血中ナトリウム減少	26/54（48.1%）
副作用の種類	件数／評価例数 （発現割合）	臨床検査値異常の種類	件数／評価例数 （発現割合）																									
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会社																												

レットヴィモカプセル 40mg
レットヴィモカプセル 80mg

1.12 添付資料一覧

日本イーライリリー株式会社

1.12 添付資料一覧

第4部（モジュール4）：非臨床試験報告書

4.3 参考文献

添付資料 番号	タイトル	著者	試験実施期間 (報告書承認年月)	試験 実施場所	報種類 (国内、 国外)	掲載誌	参考文献	申請電子 データの 提出有無
4.3.1	Early cellular abnormalities induced by RET/PTC1 oncogene in thyroid-targeted transgenic mice.	Cho JY. et al.	-	-	-	Oncogene. 1999;18(24):3659-65.	参考文献	-
4.3.2	Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes.	Drilon A.et al.	-	-	-	Nat Rev Clin Oncol. 2018;15(3):151-67.	参考文献	-
4.3.3	RET fusions observed in lung and colorectal cancers are sensitive to ponatinib.	Gozgit JM .et al.	-	-	-	Oncotarget. 2018;9(51):29654-64.	参考文献	-
4.3.4	Preclinical Modeling of KIF5B-RET Fusion Lung Adenocarcinoma.	Huang Q.et al.	-	-	-	Mol Cancer Ther. 2016;15(10):2521-9.	参考文献	-
4.3.5	Aberrant melanogenesis and melanocytic tumour development in transgenic mice that carry a metallothionein/ret fusion gene.	Iwamoto T.et al.	-	-	-	EMBO J. 1991;10(11):3167-75.	参考文献	-
4.3.6	Neuroblastoma in a transgenic mouse carrying a metallothionein/ret fusion gene.	Iwamoto T.et al.	-	-	-	Br J Cancer. 1993;67(3):504-7.	参考文献	-
4.3.7	OLFM4-RET fusion is an oncogenic driver in small intestine adenocarcinoma.	Liu W.et al.	-	-	-	Oncogene. 2022;41(1):72-82.	参考文献	-
4.3.8	Identification of CCDC6-RET fusion in the human lung adenocarcinoma cell line, LC-2/ad.	Matsubara D.et al.	-	-	-	J Thorac Oncol. 2012;7(12):1872-6.	参考文献	-
4.3.9	RET revisited: expanding the oncogenic portfolio	Mulligan LM.	-	-	-	Nat Rev Cancer. 2014;14:173-86.	参考文献	-

セルペルカチニブ（固形がん）

4.3.10	c-RET molecule in malignant melanoma from oncogenic RET-carrying transgenic mice and human cell lines.	Ohshima Y.et al.	-	-	-	PLoS ONE. 2010;5(4):e10279.	参考文献	-
4.3.11	RET rearrangements are actionable alterations in breast cancer.	Paratala BS.et al.	-	-	-	Nat Commun. 2018;9(1):4821.	参考文献	-
4.3.12	Development of mammary and cutaneous gland tumors in transgenic mice carrying the RET/PTC1 oncogene.	Portella G.et al.	-	-	-	Oncogene. 1996;13(9):2021-6.	参考文献	-
4.3.13	The RET/PTC3 oncogene: metastatic solid-type papillary carcinomas in murine thyroids.	Powell DJ.et al.	-	-	-	Cancer Res. 1998;58(23):5523-8.	参考文献	-
4.3.14	A mouse model of KIF5B-RET fusion-dependent lung tumorigenesis.	Saito M.et al.	-	-	-	Carcinogenesis. 2014;35(11):2452-6.	参考文献	-
4.3.15	Selective RET kinase inhibition for patients with RET-altered cancers.	Subbiah V.et al.	-	-	-	Ann Oncol. 2018;29(8):1869-76.	参考文献	-

第5部（モジュール5）：臨床試験報告書

5.2 全臨床試験一覧表

添付資料番号	タイトル	著者	試験実施期間 (報告書承認年月)	試験実施場所	報種類 (国内、国外)	掲載誌	評価資料 参考資料	申請電子データの 提出有無
5.2	全臨床試験一覧表	-	-	-	-	-	-	-

5.3 臨床試験報告書

5.3.3 臨床薬物動態（PK）試験報告書

5.3.3.5 ポピュレーションPK試験報告書

添付資料番号	タイトル	著者	試験実施期間 (報告書承認年月)	試験実施場所	報種類 (国内、国外)	掲載誌	評価資料 参考資料	申請電子データの 提出有無
5.3.3.5.1	LOXO-RET-17001 (J2G-OX-JZJA) /J2G-GH-JZJK : Population Pharmacokinetic and Safety/Efficacy Exposure-Response Analysis of Selpercatinib	-	(20██年██月)	-	国外	-	評価	有

セルペルカチニブ（固形がん）

5.3.5 有効性及び安全性試験報告書

5.3.5.2 非対照試験報告書

添付資料 番号	タイトル	著者	試験実施期間 (報告書承認年月)	試験 実施場所	報種類 (国内、 国外)	掲載誌	評価資料 参考資料	申請電子 データの 提出有無
5.3.5.2.1	治験総括報告書LOXO-RET-17001: Rearranged during Transfection (RET) 融合遺伝子陽性の非小細胞肺癌、甲状腺髄様癌、及びRET活性が亢進したその他の癌を含む進行固形癌患者を対象としたセルペルカチニブの第I/II相試験 (loxo-ret-17001- 20 試験)	-	20 年 月 日 - 20 年 月 日	日本、米国 他	国内外	-	評価	有
5.3.5.2.2	治験総括報告書補遺LOXO-RET-17001: Rearranged during Transfection (RET) 融合遺伝子陽性の非小細胞肺癌、甲状腺髄様癌、及びRET活性が亢進したその他の癌を含む進行固形癌患者を対象としたセルペルカチニブの第I/II相試験 (loxo-ret-17001- 20 試験)	-	20 年 月 日 - 20 年 月 日	日本、米国 他	国内外	-	評価	有

5.3.6 市販後の使用経験に関する報告書

添付資料 番号	タイトル	著者	試験実施期間 (報告書承認年月)	試験 実施場所	報種類 (国内、 国外)	掲載誌	評価資料 参考資料	申請電子 データの 提出有無
5.3.6.1	PSUR-PBRER: SELPERCATINIB (LY3527723) PERIODIC SAFETY UPDATE REPORT (PSUR) in the Format of ICH E2C (R2)	-	20 年 月 - 20 年 月 (20 年 月)	-	国外	-	参考資料	無
5.3.6.2	新医療用医薬品に関する安全性定期報告書	-	20 年 月 - 20 年 月 (20 年 月)	-	国内	-	参考資料	無

5.3.7 患者データ一覧表及び症例記録

5.3.7.2 有害事象発現症例一覧表

添付資料 番号	タイトル	著者	試験実施期間 (報告書承認年月)	試験 実施場所	報種類 (国内、 国外)	掲載誌	評価資料 参考資料	申請電子 データの 提出有無
5.3.7.2.1	有害事象発現症例一覧表 loxo-ret-17001-20 試験	-	-	-	国内外	-	評価	有
5.3.7.2.2	有害事象発現症例一覧表 loxo-ret-17001-20 試験	-	-	-	国内外	-	評価	有

セルペルカチニブ（固形がん）

5.3.7.3 重篤な有害事象発現症例一覧表

添付資料 番号	タイトル	著者	試験実施期間 (報告書承認年月)	試験 実施場所	報種類 (国内、 国外)	掲載誌	評価資料 参考資料	申請電子 データの 提出有無
5.3.7.3.1	重篤な有害事象発現症例一 覧表 loxo-ret-17001- XXXX -20 XXXX 試験	-	-	-	国内外	-	評価	有
5.3.7.3.2	重篤な有害事象発現症例一 覧表 loxo-ret-17001- XXXX -20 XXXX 試験	-	-	-	国内外	-	評価	有

5.3.7.4 臨床検査値異常症例一覧表

添付資料 番号	タイトル	著者	試験実施期間 (報告書承認年月)	試験 実施場所	報種類 (国内、 国外)	掲載誌	評価資料 参考資料	申請電子 データの 提出有無
5.3.7.4.1	臨床検査値異常症例一 覧表 loxo-ret-17001- XXXX -20 XXXX 試験	-	-	-	国内外	-	評価	有
5.3.7.4.2	臨床検査値異常症例一 覧表 loxo-ret-17001- XXXX -20 XXXX 試験	-	-	-	国内外	-	評価	有

5.4 参考文献

添付資料 番号	タイトル	著者	試験実施期間 (報告書承認年月)	試験 実施場所	報種類 (国内、 国外)	掲載誌	参考文献	申請電子 データの 提出有無
5.4.1	OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer.	Aghajanian C. et al.	-	-	-	J Clin Oncol. 2012;30(17):2039-45.	参考文献	-
5.4.2	Carboplatin plus etoposide versus topotecan as second-line treatment for patients with sensitive relapsed small-cell lung cancer: an open-label, multicentre, randomised, phase 3 trial.	Baize N. et al.	-	-	-	Lancet Oncol. 2020;21(9):1224-33.	参考文献	-
5.4.3	Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial.	Bennouna J. et al.	-	-	-	Lancet Oncol. 2013;14(1):29-37.	参考文献	-
5.4.4	RIBBON-2: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer.	Brufsky AM. et al.	-	-	-	J Clin Oncol. 2011;29(32):4286-93.	参考文献	-

セルペルカチニブ（固形がん）

5.4.5	Treatment of patients with late stage colorectal cancer: ASCO resource-stratified guideline.	Chiorean E. et al.	-	-	-	JCO Global Oncol. 2020;6:414-38.	参考文献	-
5.4.6	Early cellular abnormalities induced by RET/PTC1 oncogene in thyroid-targeted transgenic mice.	Cho JY. et al.	-	-	-	Oncogene. 1999;18(24):3659-65.	参考文献	-
5.4.7	NTRK fusion-positive cancers and TRK inhibitor therapy.	Cocco E. et al.	-	-	-	Nat Rev Clin Oncol. 2018;15(12):731-47.	参考文献	-
5.4.8	FDA drug approval summary: gefitinib (ZD1839) (Iressa) tablets.	Cohen MH. Et al.	-	-	-	Oncologist. 2003;8(4):303-6.	参考文献	-
5.4.9	Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial.	Coleman RL. et al.	-	-	-	Lancet Oncol. 2017;18(6):779-91.	参考文献	-
5.4.10	Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer.	Cortés J. et al.	-	-	-	N Engl J Med. 2022;386(12):1143-54.	参考文献	-
5.4.11	Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study.	Cortes J. et al.	-	-	-	Lancet. 2011;377(9769):914-23.	参考文献	-
5.4.12	Overall Survival With Palbociclib And Fulvestrant in Women With HR+/HER2-ABC: Updated Exploratory Analyses of PALOMA-3, a Double-Blind, Phase 3 Randomized Study.	Cristofanilli M. et al.	-	-	-	Clin Cancer Res. 2022;28(16):3433-42.	参考文献	-

セルペルカチニブ（固形がん）

5.4.13	Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial.	Cristofanilli M.et al.	-	-	-	Lancet Oncol. 2016;17(4):425-39.	参考文献	-
5.4.14	Recurrent RET gene fusions in paediatric spindle mesenchymal neoplasms.	Davis JL.et al.	-	-	-	Histopathology. 2020;76(7):1032-41.	参考文献	-
5.4.15	Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes.	Drilon A.et al.	-	-	-	Nat Rev Clin Oncol. 2018;15(3):151-67.	参考文献	-
5.4.16	Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer.	Eckardt JR.et al.	-	-	-	J Clin Oncol. 2007;25(15):2086-92.	参考文献	-
5.4.17	New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).	Eisenhauer EA.et al.	-	-	-	Eur J Cancer. 2009;45(2):228-47.	参考文献	-
5.4.18	Phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in progressive or recurrent ovarian cancer.	Ferrandina G.et al.	-	-	-	J Clin Oncol. 2008;26(6):890-6.	参考文献	-
5.4.19	Characteristics and survival outcomes of patients with RET fusion-positive (RET-fp) solid tumours receiving non-RET inhibitor therapy in a real-world setting.	Garrido P.et al.	-	-	-	Poster presented at: ESMO Congress 2022; September 9-13, 2022; Paris, France.	参考文献	-
5.4.20	Palliative effect of chemotherapy: objective tumor response is associated with symptom improvement in patients with metastatic breast cancer.	Geels P.et al.	-	-	-	J Clin Oncol. 2000;18(12):2395-405.	参考文献	-

セルペルカチニブ（固形がん）

5.4.21	Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200.	Giantonio BJ.et al.	-	-	-	J Clin Oncol. 2007;25(12):1539-44.	参考文献	-
5.4.22	Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan.	Gordon AN.et al.	-	-	-	J Clin Oncol. 2001;19(14):3312-22.	参考文献	-
5.4.23	Combined chemotherapy with cisplatin, etoposide, and irinotecan versus topotecan alone as second-line treatment for patients with sensitive relapsed small-cell lung cancer (JCOG0605): a multicentre, open-label, randomised phase 3 trial.	Goto K.et al.	-	-	-	Lancet Oncol. 2016;17(8):1147-57.	参考文献	-
5.4.24	RET fusions observed in lung and colorectal cancers are sensitive to ponatinib.	Gozgit JM .et al.	-	-	-	Oncotarget. 2018;9(51):29654-64.	参考文献	-
5.4.25	Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer.	Gradishar WJ.et al.	-	-	-	J Clin Oncol. 2005;23(31):7794-803.	参考文献	-
5.4.26	Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial.	Grothey A.et al.	-	-	-	Lancet. 2013;381(9863):303-12.	参考文献	-
5.4.27	Preclinical Modeling of KIF5B-RET Fusion Lung Adenocarcinoma.	Huang Q.et al.	-	-	-	Mol Cancer Ther. 2016;15(10):2521-9.	参考文献	-
5.4.28	Randomized phase II trial comparing amrubicin with topotecan in patients with previously treated small-cell lung cancer: North Japan Lung Cancer Study Group Trial 0402.	Inoue A.et al.	-	-	-	J Clin Oncol. 2008;26(33):5401-6.	参考文献	-

セルペルカチニブ（固形がん）

5.4.29	Expression of glial cell line-derived neurotrophic factor family members and their receptors in pancreatic cancers.	Ito Y.et al.	-	-	-	Surgery. 2005;138(4):788-94.	参考文献	-
5.4.30	Aberrant melanogenesis and melanocytic tumour development in transgenic mice that carry a metallothionein/ret fusion gene.	Iwamoto T.et al.	-	-	-	EMBO J. 1991;10(11):3167-75.	参考文献	-
5.4.31	Neuroblastoma in a transgenic mouse carrying a metallothionein/ret fusion gene.	Iwamoto T.et al.	-	-	-	Br J Cancer. 1993;67(3):504-7.	参考文献	-
5.4.32	Randomized phase II trial of single-agent amrubicin or topotecan as second-line treatment in patients with small-cell lung cancer sensitive to first-line platinum-based chemotherapy.	Jotte R.et al.	-	-	-	J Clin Oncol. 2011;29(3):287-93.	参考文献	-
5.4.33	RET aberrations in diverse cancers: next-generation sequencing of 4,871 patients.	Kato S.et al.	-	-	-	Clin Cancer Res. 2017;23(8):1988-97.	参考文献	-
5.4.34	A phase II trial of docetaxel in platinum pre-treated patients with advanced epithelial ovarian cancer: a Japanese cooperative study.	Katsumata N.et al.	-	-	-	Ann Oncol. 2000;11(12):1531-6.	参考文献	-
5.4.35	Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomised, open-label, phase 2 study.	Kawai A.et al.	-	-	-	Lancet Oncol. 2015;16(4):406-16.	参考文献	-
5.4.36	FOLFIRINOX as second-line chemotherapy for advanced pancreatic cancer: A subset analysis of data from a nationwide multicenter observational study in Japan.	Kobayashi N.et al.	-	-	-	Pancreatology. 2020;20(7):1519-25.	参考文献	-
5.4.37	REToma: a cancer subtype with a shared driver oncogene.	Kohno T.et al.	-	-	-	Carcinogenesis. 2020;41(2):123-9.	参考文献	-

セルペルカチニブ（固形がん）

5.4.38	TAS-102 plus bevacizumab for patients with metastatic colorectal cancer refractory to standard therapies (C-TASK FORCE): an investigator-initiated, open-label, single-arm, multicentre, phase 1/2 study.	Kuboki Y.et al.	-	-	-	Lancet Oncol. 2017;18(9):1172-81.	参考文献	-
5.4.39	Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade.	Le DT.et al.	-	-	-	Science. 2017;357(6349):409-13.	参考文献	-
5.4.40	Phase II Open-Label Study of Pembrolizumab in Treatment-Refractory, Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: KEYNOTE-164.	Le DT.et al.	-	-	-	J Clin Oncol. 2020;38(1):11-9.	参考文献	-
5.4.41	PD-1 Blockade in Tumors with Mismatch-Repair Deficiency.	Le DT.et al.	-	-	-	N Engl J Med. 2015;372(26):2509-20.	参考文献	-
5.4.42	First FDA Approval Agnostic of Cancer Site - When a Biomarker Defines the Indication.	Lemery S.et al.	-	-	-	N Engl J Med. 2017;377(15):1409-12.	参考文献	-
5.4.43	OLFM4-RET fusion is an oncogenic driver in small intestine adenocarcinoma.	Liu W.et al.	-	-	-	Oncogene. 2022;41(1):72-82.	参考文献	-
5.4.44	Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study.	Marabelle A.et al.	-	-	-	Lancet Oncol. 2020a;21(10):1353-65.	参考文献	-
5.4.45	Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study.	Marabelle A.et al.	-	-	-	J Clin Oncol. 2020b;38(1):1-10.	参考文献	-
5.4.46	Identification of CCDC6-RET fusion in the human lung adenocarcinoma cell line, LC-2/ad.	Matsubara D.et al.	-	-	-	J Thorac Oncol. 2012;7(12):1872-6.	参考文献	-

セルペルカチニブ（固形がん）

5.4.47	The safety and efficacy of the weekly dosing of irinotecan for platinum- and taxanes-resistant epithelial ovarian cancer.	Matsumoto K.et al.	-	-	-	Gynecol Oncol. 2006;100(2):412-6.	参考文献	-
5.4.48	Randomized trial of TAS-102 for refractory metastatic colorectal cancer.	Mayer RJ.et al.	-	-	-	N Engl J Med. 2015;372(20):1909-19.	参考文献	-
5.4.49	Second-Line Gemcitabine Plus Nab-Paclitaxel for Patients with Unresectable Advanced Pancreatic Cancer after First-Line FOLFIRINOX Failure.	Mita N.et al.	-	-	-	J Clin Med. 2019;8(6):761.	参考文献	-
5.4.50	A phase II study of S-1 in gemcitabine-refractory metastatic pancreatic cancer.	Morizane C.et al.	-	-	-	Cancer Chemother Pharmacol. 2009;63(2):313-9.	参考文献	-
5.4.51	A single-arm confirmatory study of amrubicin therapy in patients with refractory small-cell lung cancer: Japan Clinical Oncology Group Study (JCOG0901).	Murakami H.et al.	-	-	-	Lung Cancer. 2014;84(1):67-72.	参考文献	-
5.4.52	Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer.	Mutch DG.et al.	-	-	-	J Clin Oncol. 2007;25(19):2811-8.	参考文献	-
5.4.53	Circulating tumor DNA-guided treatment with pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer: a phase 2 trial.	Nakamura Y.et al.	-	-	-	Nat Med. 2021;27(11):1899-903.	参考文献	-
5.4.54	c-RET molecule in malignant melanoma from oncogenic RET-carrying transgenic mice and human cell lines.	Ohshima Y.et al.	-	-	-	PLoS ONE. 2010;5(4):e10279.	参考文献	-
5.4.55	Phase III trial of paclitaxel at two dose levels, the higher dose accompanied by filgrastim at two dose levels in platinum-pretreated epithelial ovarian cancer: an intergroup study.	Omura GA.et al.	-	-	-	J Clin Oncol. 2003;21(15):2843-8.	参考文献	-

セルペルカチニブ（固形がん）

5.4.56	Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer.	Overman MJ.et al.	-	-	-	J Clin Oncol. 2018;36(8):773-9.	参考文献	-
5.4.57	Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study.	Overman MJ.et al.	-	-	-	Lancet Oncol. 2017;18(9):1182-91.	参考文献	-
5.4.58	RET rearrangements are actionable alterations in breast cancer.	Paratala BS.et al.	-	-	-	Nat Commun. 2018;9(1):4821.	参考文献	-
5.4.59	Genomic landscape of 891 RET fusions detected across diverse solid tumor types.	Parimi V.et al.	-	-	-	NPJ Precis Oncol. 2023;7(1):10.	参考文献	-
5.4.60	Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer.	Peeters M.et al.	-	-	-	J Clin Oncol. 2010;28(31):4706-13.	参考文献	-
5.4.61	Bevacizumab and platinum-based combinations for recurrent ovarian cancer: a randomised, open-label, phase 3 trial.	Pfisterer J.et al.	-	-	-	Lancet Oncol. 2020;21(5):699-709.	参考文献	-
5.4.62	Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2†.	Piccart M.et al.	-	-	-	Ann Oncol. 2014;25(12):2357-62.	参考文献	-
5.4.63	RET fusions in a small subset of advanced colorectal cancers at risk of being neglected.	Pietrantonio F.et al.	-	-	-	Ann Oncol. 2018;29(6):1394-401.	参考文献	-
5.4.64	Nab-paclitaxel plus gemcitabine for metastatic pancreatic adenocarcinoma after Folfirinox failure: an AGEO prospective multicentre cohort.	Portal A.et al.	-	-	-	Br J Cancer. 2015;113(7):989-95.	参考文献	-

セルペルカチニブ（固形がん）

5.4.65	Development of mammary and cutaneous gland tumors in transgenic mice carrying the RET/PTC1 oncogene.	Portella G.et al.	-	-	-	Oncogene. 1996;13(9):2021-6.	参考文献	-
5.4.66	Bevacizumab Combined With Weekly Paclitaxel, Pegylated Liposomal Doxorubicin, or Topotecan in Platinum-Resistant Recurrent Ovarian Cancer: Analysis by Chemotherapy Cohort of the Randomized Phase III AURELIA Trial.	Poveda AM.et al.	-	-	-	J Clin Oncol. 2015;33(32):3836-8.	参考文献	-
5.4.67	The RET/PTC3 oncogene: metastatic solid-type papillary carcinomas in murine thyroids.	Powell DJ.et al.	-	-	-	Cancer Res. 1998;58(23):5523-8.	参考文献	-
5.4.68	Prolonged oral etoposide as second-line therapy for platinum-resistant and platinum-sensitive ovarian carcinoma: a Gynecologic Oncology Group study.	Rose PG.et al.	-	-	-	J Clin Oncol. 1998;16(2):405-10.	参考文献	-
5.4.69	A mouse model of KIF5B-RET fusion-dependent lung tumorigenesis.	Saito M.et al.	-	-	-	Carcinogenesis. 2014;35(11):2452-6.	参考文献	-
5.4.70	RET gene fusions in malignancies of the thyroid and other tissues.	Santoro M.et al.	-	-	-	Genes. 2020;11(4):424.	参考文献	-
5.4.71	Multicenter phase II study of S-1 monotherapy as second-line chemotherapy for advanced biliary tract cancer refractory to gemcitabine.	Sasaki T.et al.	-	-	-	Invest New Drugs. 2012;30(2):708-13.	参考文献	-
5.4.72	Modified FOLFIRINOX as a second-line therapy following gemcitabine plus nab-paclitaxel therapy in metastatic pancreatic cancer.	Sawada M.et al.	-	-	-	BMC Cancer. 2020;20(1):449.	参考文献	-
5.4.73	Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial.	Schöffski P.et al.	-	-	-	Lancet. 2016;387(10028):1629-37.	参考文献	-

セルペルカチニブ（固形がん）

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セルペルカチニブ（固形がん）

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セルペルカチニブ（固形がん）

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1.12 添付資料一覧

