▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – RETEVMO®(SELPERCATINIB) CAPSULE

1 NAME OF THE MEDICINE

Selpercatinib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

RETEVMO 40 mg immediate release hard capsule

Each immediate release capsule contains 40 mg selpercatinib

RETEVMO 80 mg immediate release hard capsule

Each immediate release capsule contains 80 mg selpercatinib

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

RETEVMO 40 mg immediate release hard capsule

Grey, opaque capsule imprinted with “Lilly 3977” and “40 mg” in black ink.

RETEVMO 80 mg immediate release hard capsule

Blue, opaque capsule imprinted with “Lilly 2980” and “80 mg” in black ink.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

RETEVMO has **provisional approval** for the treatment of adult patients with locally advanced or metastatic *RET* fusion positive non-small cell lung cancer (NSCLC).

The decision to approve this indication has been made on the basis of objective response rate (ORR) and duration of response (DOR) from a single arm study. Continued approval of this indication depends on verification and description of benefit in a confirmatory trial.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Dose

The recommended dose of RETEVMO 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.

Avoid concomitant use of strong CYP inhibitors (see Section 4.5 Interactions with other medicines and other forms of interactions). If coadministration with strong CYP3A inhibitor cannot be avoided, reduce the current selpercatinib dose by 50%. If the CYP3A inhibitor is discontinued, increase the selpercatinib dose (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. Generally, dose reductions should be in 40 mg decrements. RETEVMO dose modifications are summarised in Table 1 and Table 2.

Table 1 Recommended dose modifications for RETEVMO for adverse reactions based in body weight

Dose modification	Adults ≥50 kg	Adults <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 reactions (ADR)	Grade	Dose modifications
Increased ALT or AST	Grade 3 or Grade 4	• Suspend dose until toxicity resolves to baseline (see sections 4.4 Special warnings and precautions for use and 4.8 Adverse effects (Undesirable effects)). Resume at a dose reduced by 2 levels. • If after at least 2 weeks selpercatinib is tolerated without recurrent increased

Adverse drug reactions (ADR)	Grade	Dose modifications
		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 Special warnings and precautions for use and 4.8 Adverse effects (Undesirable effects)). 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 Special warnings and precautions for use). • 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 Special warnings and precautions for use and 4.8 Adverse effects (Undesirable effects)).

Adverse drug reactions (ADR)	Grade	Dose modifications
	Grade 4	• Selpercatinib should be discontinued permanently if medically significant hypertension cannot be controlled.
Haemorrhagic events	Grade 3 or Grade 4	• Selpercatinib should be suspended until recovery to baseline. • Discontinue selpercatinib for severe or life-threatening haemorrhagic events.
Interstitial lung disease/Pneumonitis	Grade 2 that is persistent or recurs	• If persistent or recurs despite maximal supportive measures and does not return to baseline or Grade 1 within 7 days, suspend selpercatinib until toxicity resolves to baseline or Grade 1. Dosing should be resumed at the next lower dose.
	Grade 3 or Grade 4	• Discontinue selpercatinib.
Hypothyroidism	Grade 3 or Grade 4	• Selpercatinib should be suspended until resolution to Grade 1 or baseline. • Discontinue selpercatinib based on severity.
Other adverse reactions	Grade 3 or Grade 4	• Selpercatinib should be suspended until recovery to baseline. • Discontinue selpercatinib for severe or life-threatening events.

Special populations

Elderly

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

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 Pharmacokinetic properties).

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 Pharmacokinetic properties).

Paediatric population

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

Method of administration

RETEVMO is for oral administration.

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.

RETEVMO concomitant use with strong CYP inducers should be avoided (see section 4.5 Interactions with other medicines and other forms of interactions).

RETEVMO must be accompanied by a meal if used concomitantly with a proton pump inhibitor (see section 4.5 Interactions with other medicines and other forms of interactions).

RETEVMO should be administered 2 hours before or 10 hours after concomitant H_2 receptor antagonists (see section 4.5 Interactions with other medicines and other forms of interactions).

Locally acting antacids should be administered 2 hours before or 2 hours after RETEVMO.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Interstitial lung disease/Pneumonitis

Interstitial lung disease (ILD) and/or pneumonitis, including severe and life-threatening disease, was reported in patients receiving selpercatinib (see section 4.8 Adverse effects (Undesirable effects)). Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis and treat as medically appropriate. Based on the severity of ILD/pneumonitis, selpercatinib may require dose interruption or discontinuation (see section 4.2 Dose and method of administration).

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 Adverse effects (Undesirable effects)). 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 Dose and method of administration).

Hypertension

Hypertension was reported in patients receiving selpercatinib (see section 4.8 Adverse effects (Undesirable effects)). 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 Dose and method of administration). 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 Pharmacodynamic properties). 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 (see section 4.5 Interactions with other medicines and other forms of interactions).

Patients should have a QTcF interval of ≤470 ms and serum electrolytes within normal range before starting selpercatinib treatment. Electrocardiograms and serum electrolytes should be monitored in all patients after 1 week of selpercatinib treatment, at least monthly for the first 6 months and otherwise, as clinically indicated, adjusting frequency based upon risk factors including diarrhoea, vomiting, and/or nausea. Hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiating selpercatinib and during treatment. Monitor the QT interval with ECGs more frequently in patients who require treatment with concomitant medications known to prolong the QT interval.

Selpercatinib may require dose interruption or modification (see section 4.2 Dose and method of administration).

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 Interactions with other medicines and other forms of interactions).

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, pregnancy and lactation).

Fertility

Based on nonclinical safety findings, male and female fertility may be compromised by treatment with RETEVMO (see sections 4.6 Fertility, pregnancy and lactation and 5.3 Preclinical safety data). 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 Adverse effects (Undesirable effects)). 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 Dose and method of administration). 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 Adverse effects (Undesirable effects)).

Permanently discontinue selpercatinib in patients with severe or life-threatening haemorrhage (see section 4.2 Dose and method of administration).

Hypothyroidism

Selpercatinib can cause hypothyroidism. Hypothyroidism occurred in 13% (53/423) of patients with other solid tumours including NSCLC; all reactions were Grade 1 or 2.

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 section 4.2 Dose and method of administration).

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.

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.

Use in the elderly

No dose adjustment is required based on age (see section 4.2 Dose and method of administration and 5.2 Pharmacokinetic properties).

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.

Paediatric use

The safety of selpercatinib in children aged less than 18 years has not been established.

Effects on laboratory tests

Hepatic transaminase should be monitored prior to the start of selpercatinib therapy, at every 2 weeks interval during the first 3 months, monthly for the next 3 months and as clinically indicated.

Serum electrolytes should be monitored in all patients after 1 week of selpercatinib treatment, at least monthly for the first 6 months and as clinically indicated (see Sections 4.4 Special warnings and precautions for use and 4.2 Dose and method of administration).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

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 AUC_{0-24} and C_{max}, respectively).

Agents that may increase selpercatinib plasma concentrations

Co-administration of a single 160 mg selpercatinib dose with itraconazole, a strong CYP3A4 inhibitor, increased the C_{max} and AUC of selpercatinib by 30% and 130%, respectively, compared to selpercatinib given alone, which may increase the risk of an ADR, including QTc prolongation. 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 Dose and method of administration and section 4.4 Special warnings and precautions for use; QT interval prolongation).

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, selexipag, 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.

Coadministration 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.

Coadministration with medicinal products that are proton pump inhibitors

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

Co-administration with medicinal products that are substrates of transporters

In vitro studies indicate that selpercatinib inhibits MATE1, P-gp, and BCRP, but does not inhibit OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BSEP, and MATE2-K at clinically relevant concentrations. *In vivo* interactions of selpercatinib with clinically relevant substrates of MATE1, such as creatinine, may occur.

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).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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 RETEVMO (see 4.6 Fertility, pregnancy and lactation, *Reproduction toxicity*). Both men and women should seek advice on fertility preservation before treatment.

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.

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. These effects were associated with reduced organ weights, reduced sperm motility, and an increase in the number of abnormal sperm exposures 2-fold the human exposure based on AUC at the maximum 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.

In a fertility and early embryonic study in female rats, a reduction in the number of oestrus cycles as well as embryolethality were observed at AUC-based exposure levels approximately equal to clinical exposure at the maximum recommended human dose. In repeat-dose studies in rats, reversible vaginal mucification with individual cell cornification and altered oestrus 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.

Use in pregnancy – Pregnancy Category D

There are no available data from the use of selpercatinib in pregnant women. Studies in animals have shown reproductive toxicity. RETEVMO 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.

Embryotoxicity/Teratogenicity

Based on data from animal reproduction studies and its mechanism of action, selpercatinib can cause fetal harm when administered to a pregnant woman. In an embryo-fetal development study, once daily oral administration of selpercatinib at a dose level of 50 mg/kg (approximately 1.4 times the human exposure based on AUC at the clinical dose of 160 mg twice daily) to pregnant rats during the period of organogenesis resulted in mean 96.4% post-implantation loss per litter and an increase in external malformations.

Use in lactation

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 RETEVMO and for at least one week after the last dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies have been conducted to determine the effects of selpercatinib on the ability to drive or use machines.

RETEVMO 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 RETEVMO (see section 4.8 Adverse effects (Undesirable effects)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The most common serious adverse events (SAE) occurring in >2% were pneumonia (4.1%), pleural effusion (3.0%), abdominal pain (2.5%), dyspnoea (2.3%) and hyponatraemia (2.3%).

Permanent discontinuation of RETEVMO for treatment emergent adverse events, regardless of attribution occurred in 8.0% of patients.

Tabulated list of adverse drug reactions

The ADRs reported in the 796 patients treated with selpercatinib are shown in Table 3, of these 356 patients had *RET* fusion positive NSCLC.

ADRs resulting in permanent discontinuation (2 or more patients) included increased ALT (0.6%), fatigue (0.6%), increased AST (0.5%), hypersensitivity (0.3%), and thrombocytopenia (0.3%).

The ADRs are classified according to MedDRA the system organ class. Frequency groups are defined by the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), and not known (cannot be estimated from available data).

Within each frequency group, undesirable effects are presented in order of decreasing seriousness. Median time on treatment with selpercatinib was 21.3 months.

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

System organ class	ADR	Selpercatinib (N=796)		
		All grades toxicity n (%)	Grade 3 toxicity n (%)	Grade 4 toxicity n (%)
Immune system disorders[a]	*Common*			
	Hypersensitivity[b]	47 (5.9)	15 (1.9)	0 (0.0)
Metabolism and nutrition disorders	*Very common*			
	Decreased appetite	150 (18.8)	3 (0.4)	0 (0.0)
Nervous system disorders	*Very common*			
	Headache[b]	220 (27.6)	11 (1.4)	0 (0.0)
	Dizziness[b]	152 (19.1)	2 (0.3)	0 (0.0)
Cardiac disorders	*Very common*			
	Electrocardiogram QT prolonged[b]	168 (21.1)	38 (4.8)	0 (0.0)
Vascular disorders	*Very common*			
	Hypertension[b]	326 (41.0)	156 (19.6)	1 (0.1)
Gastrointestinal disorders	*Very common*			
	Abdominal pain[b]	268 (33.7)	20 (2.5)	0 (0.0)
	Diarrhoea[b]	374 (47.0)	40 (5.0)	0 (0.0)
	Nausea	248 (31.2)	9 (1.1)	0 (0.0)
	Vomiting[b]	178 (22.4)	14 (1.8)	0 (0.0)
	Constipation	261 (32.8)	6 (0.8)	0 (0.0)
	Dry mouth[b]	344 (43.2)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	*Very common*			
	Rash[b]	261 (32.8)	5 (0.6)	0(0.0)
General disorders and administration site conditions	*Very common*			
	Pyrexia	135 (17.0)	1 (0.1)	0(0.0)
	Fatigue[b]	365 (45.9)	25 (3.1)	0 (0.0)
	Oedema[b]	386 (48.5)	6 (0.8)	0 (0.0)
Investigations[c]	*Very common*			
	ALT increased	439 (55.5)	85 (10.7)	8 (1.0)
	AST increased	466 (58.9)	77 (9.7)	7 (0.9)
	Platelets decreased	296 (37.4)	15 (1.9)	10 (1.3)
	Lymphocyte count decreased	396 (51.8)	135 (17.6)	14 (1.8)
	Magnesium decreased	259 (32.9)	3 (0.4)	2 (0.3)
	Creatinine increased	374 (47.3)	12 (1.5)	7 (0.9)
Blood and lymphatic system	*Very common*			
	Haemorrhage[b]	175 (22.0)	17 (2.1)	4 (0.5)

[a] 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).
[b] Composite terms
[c] 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 765 for Lymphocyte count decrease, 787 for Magnesium decreased and 791 for the others.

Additional adverse drug reactions from clinical trials

The following adverse reactions have been observed in selpercatinib-treated patients in on-going LIBRETTO-001 trial:

Chylothorax (1.4%) and chylous ascites (1.4%) (n=807).

Hypothyroidism (15.4%) (n=825)

Interstitial lung disease/pneumonitis (2.2%) (n=825)

Description of selected adverse reactions

Aminotransferase elevations (AST / ALT increased)

Based on laboratory assessment, ALT and AST elevations were reported in 55.5% and 58.9% patients, respectively. Grade 3 or 4 ALT or AST elevations were reported in 11.8% and 10.6% patients respectively.

The median time to first onset was: AST increase 4.3 weeks (range: 0.7, 151.7), ALT increase 4.3 weeks (range: 0.9, 144.0).

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

QT interval prolongation

In the 792 patients who had ECGs, review of data showed 7.3% of patients had >500 msec maximum post-baseline QTcF value, and 19.8% 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 2.1% of patients.

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

RETEVMO may require dose interruption or modification (see sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use).

Hypertension

In the 793 patients who had blood pressure measurements, the median maximum increase from baseline systolic pressure was 31 mm Hg (range: –12, +96). Only 10.8% of patients retained their baseline grade during treatment, 42.2% had an increasing shift of 1 grade, 37.1% of 2 grades, and 9.3% of 3 grades. A treatment emergent adverse event of hypertension was reported in 43.9% patients with history of hypertension (28.2% with grade 3, 4) and 38.8% of patients without history of hypertension (13.7% with grade 3, 4).

Overall, a total of 19.6% 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% patients. Diastolic blood pressure results were similar, but the increases were of lesser magnitude.

One patient was permanently discontinued due to hypertension. Dose modification is recommended in patients who develop hypertension (see section 4.2 Dose and method of administration). Selpercatinib should be discontinued permanently if medically significant hypertension cannot be controlled with antihypertensive therapy (see section 4.4 Special warnings and precautions for use).

Hypersensitivity

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

In study LIBRETTO-001, 24.7% (197/796) of patients treated with selpercatinib had previously received anti-PD-1/PD-L1 immunotherapy. Hypersensitivity occurred in a total of 5.9% (47/796) of patients receiving selpercatinib, including Grade 3 hypersensitivity in 1.9% (15/796) of patients.

Of the 47 patients with hypersensitivity, 55.3% (26/47) had NSCLC and had received prior anti-PD-1/PD-L1 immunotherapy.

Grade 3 hypersensitivity occurred in 3.6% (7/197) 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 112.1 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.

RETEVMO may require dose interruption or modification (see section 4.2 Dose and method of administration).

Haemorrhages

Grade ≥3 haemorrhagic events occurred in 3.1% (25/796) 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 24.3 weeks (range: 0.1 week to 147.6 weeks).

Selpercatinib should be discontinued permanently in patients with severe or life-threatening haemorrhage (see section 4.2 Dose and method of administration).

Additional information on special populations

Paediatric patients

The safety of selpercatinib in children aged less than 18 years has not been established.

Elderly

In patients receiving selpercatinib, 24.4% were ≥65-74 years of age, 8.3% 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 (51.5%), 75-84 years (56.1%), and ≥85 years (100.0%), than in patients <65 years (39.4%) of age.

The frequency of AE leading to discontinuation of selpercatinib was higher in patients ≥65-74 years (7.2%), 75-84 years (18.2%), and ≥85 years (25.0%), than in patients <65 years of age (6.8%).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, antineoplastic agents, protein kinase inhibitors.

ATC code: L01EX22

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 Dose and method of administration and 4.4 Special warnings and precautions for use).

Mechanism of action

Selpercatinib is an orally available, small molecule inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase. 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, promoting cell proliferation and survival in tumor cell lines. Point mutations in RET can also result in constitutively activated RET proteins that can promote cell growth and survival in tumor cell lines.

In RET enzyme assays, selpercatinib inhibits the kinase activity of RET, RET-V804L, RET-V804M, RET-A883F, RET-S904F, RET-A764T, RET-S891A and RET-M918T with IC50 values of 0.20 nM to 2.21 nM. In kinase screening assays, selpercatinib at a concentration of 100 nM inhibits only six of 329 non-RET kinases by more than 50% of the control. Among these, selpercatinib inhibits two kinases with IC50 values within 35-fold of RET: FLT4 (0.7-fold in an enzyme-based assay and 8-fold in a cell-based assay); and FLT1 (1.6-fold). Selpercatinib inhibits PDGFRB with an IC50 value of 2100 nM, and JAK1, JAK2, JAK3, TRKA, and TRKC with IC50 values greater than 5000 nM in enzyme assays.

Selpercatinib demonstrates *in vitro* inhibition of human cancer cell lines derived from multiple tumour types harbouring RET fusion genes and RET mutations with EC50 values equal to 10 nM or less. In *in vivo* mouse studies, selpercatinib demonstrates inhibition of tumor growth in RET fusion and RET mutant cancer cell lines, patient-derived RET fusion xenograft models, and a patient-derived RET fusion xenograft model harbouring a RET V804M mutation. Selpercatinib also exhibits intracranial anti-tumour activity of patient-derived RET fusion xenograft tumours implanted directly into the brain of mice.

In additional radioligand binding assays, selpercatinib inhibits two out of 54 non-kinase targets at a concentration of 1 μM: 5-HT transporter (70.2%) and α2c receptor (51.7%).

Clinical trials

Clinical efficacy and safety

The efficacy of RETEVMO was evaluated in adult patients with advanced RET fusion-positive NSCLC in a phase 1/2, multi-centre, 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 RETEVMO 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) and Nanostring technology. The major efficacy outcome measures were overall response rate (ORR) and duration

of response (DOR), as determined by a blinded independent review committee (IRC) according to RECIST v1.1.

Treatment-naïve RET fusion-positive NSCLC

Of the 356 *RET* fusion-positive NSCLC patients enrolled in LIBRETTO-001, 69 were treatment naïve. Most patients (98.6%) had metastatic disease at enrolment. 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. 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 for treatment naive

	Efficacy by IRC assessment
n	69
Objective response (CR+PR)	
% (95% CI)	84.1 (73.3, 91.8)
Complete response n (%)	4 (5.8)
Partial response n (%)	54 (78.3)
Duration of response (months)*	
Median, 95% CI	20.21 (13.0, NE)
Median duration of follow up	20.27
Progression-free survival (months)	
Median, 95% CI	21.95 (13.8, NE)
Median duration of follow-up (months)	21.91
Overall survival (OS) (months)*	
Median, 95% CI	NE (27.9, NE)
Median duration of follow-up (months)	25.20

NE = not estimable

*The OS rate was 92.7% (95% CI: 83.3, 96.9) at 12 months, 69.3% (95% CI: 55.2, 79.7) at 24 months, and 57.1% (95% CI: 35.9, 73.6) at 36 months.

Treatment-experienced RET fusion-positive NSCLC

A total of 247 patients had received prior platinum-based chemotherapy. Most patients (97.2%) had metastatic disease at enrolment. 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. 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) (34.4%) and taxanes (34.8%); 39.3% 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 for treatment experienced

	Efficacy eligible patients IRC assessment
n	247
Objective response (CR + PR)	
% (95% CI)	61.1 (54.7, 67.2)
Complete response n (%)	18 (7.3)
Partial response n (%)	133 (53.8)
Duration of response (months)*	
Median (95% CI)	28.58 (20.4, NE)
Median duration of follow-up (months)	21.19
Progression-free survival (months)	
Median (95% CI)	24.94 (19.3, NE)
Median duration of follow-up (months)	24.71
Overall survival (months)	
Median (95% CI)	NE (33.5, NE)
Median duration of follow-up (months)	26.41

NE = not estimable

* The OS rate was 87.9% (95% CI: 83.0, 91.4) at 12 moths, 68.9% (95%CI: 62.2, 74.7) at 24 months, and 58.5% (95%CI: 49.7, 66.3) at 36 months.

CNS response in RET fusion-positive NSCLC

A total of 106 RET fusion-positive NSCLC patients had CNS metastasis at baseline, including 26 patients with measurable CNS lesions according to IRC assessment. The CNS ORR in patients with measurable disease was 84.6% (22/26; 95% CI: 65.1, 95.6). CR was observed in 7 (26.9%) patients and PR in 15 (57.7%) patients. The median CNS DOR was 9.36 months (range: 7.4, 15.3).

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.

Selpercatinib may increase serum creatinine by decreasing renal tubular secretion of creatinine via inhibition of MATE1.

Absorption

After an oral dose of 160 mg, RETEVMO 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 L (69%) 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.

Metabolism

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

Excretion

The mean (CV%) clearance (CL/F) of selpercatinib is 6.0 L/h (49%) and the half-life is 22 hours following oral administration of selpercatinib in adult patients. Following oral administration of a single [^{14}C] radiolabelled 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 RETEVMO. Patients with a body weight ≤50 kg should start RETEVMO treatment with a dose of 120 mg twice daily, while patients>50 kg should start RETEVMO treatment with a dose of 160 mg twice daily.

Hepatic impairment

Selpercatinib is metabolised in the liver.

Selpercatinib $AUC_{0-\infty}$ 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 $AUC_{0-\infty}$ 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 Dose and method of administration).

Renal impairment

In a clinical pharmacology study using single dose selpercatinib 160 mg, exposure (AUC) was unchanged in subjects with mild, moderate, or severe renal impairment. End stage renal disease (eGFR <15 mL/min) and dialysis patients have not been studied.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Selpercatinib did not cause mutations in a bacterial mutagenicity assay and was negative in an *in vitro* micronucleus assay in human peripheral blood lymphocytes. 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.

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule content

Microcrystalline cellulose
Colloidal anhydrous silica

Capsule shell

RETEVMO 40 mg hard capsules
Gelatin
Titanium dioxide
Iron oxide black

RETEVMO 80 mg hard capsules
Gelatin
Titanium dioxide
Brilliant Blue FCF

Capsule black ink
TekPrint SW-9049 Black Ink

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

RETEVMO 40 mg immediate hard capsules

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

RETEVMO 80 mg immediate hard capsules

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

Not all pack sizes may be marketed.

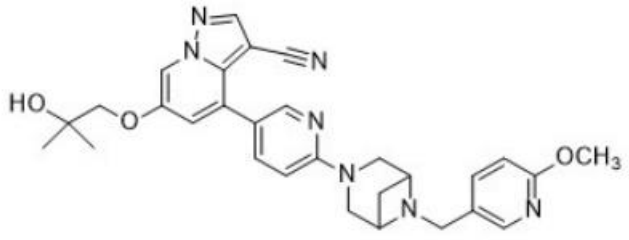
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The empirical formula for selpercatinib is $C_{29}H_{31}N_7O_3$ and it has the following structural formula.



CAS number

2152628-33-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

Eli Lilly Australia Pty Ltd
Level 9, 60 Margaret Street, Sydney, NSW 2000
AUSTRALIA
Phone: 1800 454 559

9 DATE OF FIRST APPROVAL

3 July 2023

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	New chemical entity