EUSPC16AUG2023

▼ 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 Capsules 40mg
Retsevmo Capsules 80mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Retsevmo Capsules 40mg

Each hard capsule contains 40 mg selpercatinib.

Retsevmo Capsules 80mg

Each hard capsule contains 80 mg selpercatinib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

Retsevmo Capsules 40mg

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

Retsevmo Capsules 80mg

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 thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib

Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with 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 fusion (NSCLC and non-medullary thyroid cancer) or mutation (MTC) 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 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 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 NSCLC or thyroid cancer. Retsevmo is intended to be used from the age of 12 years for the treatment of patients with RET-mutant MTC (see section 5.1). In RET-mutant MTC, 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 H_2 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

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 medications 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 liothyronine (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 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 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 coadministered, 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, coadministration 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 coadministered with multiple daily doses of ranitidine (H_2 receptor antagonist) given 2 hours after the selpercatinib dose.

Coadministration with medicinal products that are proton pump inhibitors

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

when Retsevmo was administered with food.

Coadministration with medicinal products that are substrates of transporters

Selpercatinib inhibits the renal transporter multidrug and toxin extrusion protein 1 (MATE1). *In vivo* interactions of selpercatinib with clinically relevant substrates of MATE1, such as creatinine, may occur (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 liothyronine (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 serious adverse drug reactions (ADRs) are abdominal pain (2.5%), hypersensitivity (2.0%), diarrhoea (1.9%), ALT increased (1.5%) and AST increased (1.5%).
Permanent discontinuation of Retsevmo for treatment emergent adverse events, regardless of attribution occurred in 8.0% of patients. 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%).

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.

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; N=796)

MedDRA system organ class	MedDRA preferred term	Frequency of all Grades	Frequency of Grade ≥ 3
Immune system disorders [a]	Hypersensitivity [c]	Common	Common*
Endocrine disorders	Hypothyroidism	Very common	Uncommon*
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	Haemorrhage [n]	Very common	Common
	Hypertension [g]	Very common	Very common
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease/pneumonitis [o]	Common	Uncommon
	Chylothorax	Common	Uncommon
Gastrointestinal disorders	Abdominal pain [h]	Very common	Common*
	Diarrhoea [i]	Very common	Common*
	Nausea	Very common	Common*
	Vomiting	Very common	Common*
	Constipation	Very common	Uncommon*
	Dry Mouth [j]	Very common	-
	Chylous ascites	Common	-
Skin and subcutaneous tissue disorders	Rash [k]	Very common	Uncommon*
General disorders and administration site conditions	Pyrexia	Very common	Uncommon*
	Fatigue [l]	Very common	Common*
	Oedema [m]	Very common	Uncommon*
	AST increased	Very common	Very common

Investigations [b]	ALT increased	Very common	Very common
	Platelets decreased	Very common	Common
	Lymphocyte count decreased	Very common	Very common
	Magnesium decreased	Very common	Uncommon
	Creatinine increased	Very common	Common

[*] Only includes grade 3 adverse reactions.

[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] 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.

[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] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower and gastrointestinal pain.

[i] Diarrhoea includes diarrhoea, anal incontinence, defaecation urgency, frequent bowel movements and gastrointestinal hypermotility.

[j] Dry mouth includes dry mouth and mucosal dryness.

[k] Rash includes rash, rash maculo-papular, rash erythematous, rash macular, rash pruritic, rash papular, rash morbilliform.

[l] Fatigue includes fatigue, asthenia and malaise.

[m] Oedema includes oedema peripheral, face oedema, periorbital oedema, swelling face, peripheral swelling, localised oedema, eyelid oedema, eye swelling, lymphoedema, orbital oedema, eye oedema, oedema, swelling, scrotal oedema and scrotal swelling.

[n] Haemorrhage includes epistaxis, haematuria, contusion, haemoptysis, rectal haemorrhage, haematochezia, ecchymosis, petechiae, vaginal haemorrhage, blood urine present, gastric haemorrhage, traumatic haematoma, cerebral haemorrhage, gingival bleeding, mouth haemorrhage, purpura, blood blister, haemorrhage intracranial, spontaneous haematoma, subarachnoid haemorrhage, subdural haemorrhage, abdominal wall haematoma, anal haemorrhage, angina bullosa haemorrhagica, conjunctival haemorrhage, disseminated intravascular coagulation, diverticulum intestinal haemorrhagic, eye haemorrhage, gastrointestinal haemorrhage, haematemesis, haemorrhage, haemorrhage subcutaneous, haemorrhagic stroke, haemorrhoidal haemorrhage, hepatic haematoma, hepatic haemorrhage, intra-abdominal haemorrhage, laryngeal haemorrhage, lower gastrointestinal haemorrhage, melaena, occult blood positive, pelvic haematoma, periorbital haematoma, periorbital haemorrhage, pharyngeal haemorrhage, post procedural haemorrhage, postmenopausal haemorrhage, pulmonary contusion, retinal haemorrhage, retroperitoneal haematoma, scleral haemorrhage, skin haemorrhage, upper gastrointestinal haemorrhage, uterine haemorrhage and vessel puncture site haematoma.

[o] Interstitial lung disease/pneumonitis includes pneumonitis, radiation pneumonitis, alveolitis, bronchiolitis, and pulmonary radiation injury.

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).

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

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% of 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). 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, 24.7% (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.

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

Haemorrhages
Grade ≥3 haemorrhagic events occurred in 3.1% 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 life-threatening or recurrent severe haemorrhage (see section 4.2).

<u>Additional information on special populations</u>

Paediatric patients
There were 3 patients < 18 years (range: 15-17) of age in LIBRETTO-001. 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 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 to the Drug Office, Department of Health.

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 tumor cell lines. In *in vitro* and *in vivo* tumor models, selpercatinib demonstrated anti-tumor activity in cells harboring constitutive activation of RET protein resulting from gene fusions and mutations, including CCDC6-RET, KIF5B-RET, RET V804M, and RET M918T. In addition, selpercatinib showed anti-tumor activity in mice intracranially implanted with a patient-derived RET fusion-positive tumor.

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 and RET fusion-positive thyroid cancer 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 tumor, 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-naive RET fusion-positive NSCLC

Of the 356 *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-naive 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)	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)
Rate (%) of patients with duration of response	
≥ 6 months (95% CI)	87.7 (75.9, 93.9)
≥ 12 months (95% CI)	66.1 (51.6, 77.3)

NE = not estimable

*Median duration of follow-up was 20.27 months (25^{th}, 75^{th} percentile: 12.9, 26.7)

Data Cut-off date: 15 June 2021.

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 (97.2%) 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 (97.2%) 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

	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)
Rate (%) of patients with duration of response	
≥ 6 months (95% CI)	86.9 (80.3, 91.5)
≥ 12 months (95% CI)	73.1 (64.9, 79.7)

NE = not estimable
*Median duration of follow-up was 21.19 months (25^{th}, 75^{th} percentile: 16.6, 26.0)
Data Cut-off date: 15 June 2021

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 (57.7%) patients. The median CNS DOR was 9.36 months (95%CI: 7.4, 15.3).

RET fusion-positive thyroid cancer-previously treated
Of the *RET* fusion-positive thyroid cancer patients previously treated with systemic therapy other than Radioactive iodine, and enrolled in LIBRETTO-001, 22 patients had the opportunity to be followed for at least 6 months and were considered efficacy eligible. The primary assessment of efficacy was based on the first 19 of the 22 consecutively enrolled patients. For the primary analysis population, the median age was 54 years (range 25 to 88 years). 47.4% of patients were male. 73.7% of patients were White while 10.5% were Asian, 5.3% were Black and 5.3% were Hispanic/Latino. ECOG performance status was reported as 0-1 (89.5%) or 2 (10.5%). 100% of patients had metastatic disease. Patients had received a median of 4 prior systemic therapies (range: 1-7). Prior therapies included radioactive iodine (84.2%), MKI (78.9%). 42.1% had other systemic therapy. The different histologies represented in the 19 patients included: papillary (n = 13), poorly differentiated (n = 3), anaplastic (n = 2), and Hurthle cell (n = 1). The most common fusion partner was CCDC6 (47.4%) followed by NCOA4 (31.6%).
Efficacy results for previously treated RET fusion-positive thyroid cancer are summarised in Table 6

Table 6 Objective response and duration of response

	Primary analysis set IRC assessment	**Efficacy eligible patients IRC assessment**
n	19	22
Objective response (CR + PR)		
% (95% CI)	78.9 (54.4, 93.9)	77.3 (54.6, 92.2)
Complete response n (%)	2 (10.5)	2 (9.1)
Partial response n (%)	13 (68.4)	15 (68.2)
Duration of response (months)*		
Median (95% CI)	18.4 (7.6, NE)	18.4 (10.1, NE)

NE = not estimable

*Median duration of follow-up was 20.27 months (25th, 75th percentile: 12.9, 25.4) for the first 19 patients and 20.27 months (25th, 75th percentile: 12.6, 25.4) for the 22 efficacy evaluable patients.

Vandetanib and cabozantinib naïve RET-mutant medullary thyroid cancer

Of the 319 *RET*-mutant MTC patients enrolled in LIBRETTO-001, 142 were naïve to treatment with cabozantinib and vandetanib. Of these 115 were treatment naïve 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. 58.5% of patients were male. 86.6% of patients were White, 5.6% were Asian, 1.4% were Black. 4.9% were Hispanic/Latino. Most patients (97.9%) had metastatic disease at enrolment. ECOG performance status was reported as 0-1 (95.8%) or 2 (4.2%). The most common mutation was M918T (60%), followed by extracellular cysteine mutations (23.2%). Efficacy results for cabozantinib and vandetanib treatment-naive *RET*-mutant MTC patients are summarised in Table 7.

Table 7 Objective response and duration of response

	Efficacy eligible patients IRC assessment
n	142
Objective response (CR + PR)	
% (95% CI)	81.0 (73.6, 87.1)
Complete response n (%)	22 (15.5)
Partial response n (%)	93 (65.5)
Duration of response (months)*	
Median, 95% CI	NE (NE, NE)
Rate (%) of duration of response	
12 months (95% CI)	91.9 (85.0, 95.7)
24 months (95% CI)	83.7 (73.0, 90.4)

NE = not estimable,
*Median duration of follow-up was 20.3 months (25th, 75th percentile: 14.2, 25.8).
Data cut-off date 15 June 2021

Previously treated RET-mutant medullary thyroid cancer

Of the RET-mutant MTC patients enrolled in LIBRETTO-001, 151 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. 63.6% of patients were male. 90.1% of patients were white while 1.3% were Asian, and 1.3% were Black. 6.6% were Hispanic/Latino. ECOG performance status was reported as 0-1 (92.7%) or 2 (7.3%). 98.0% of patients had metastatic disease. The most common mutation was M918T (65.6%), followed by extracellular cysteine mutations (15.6%). 100% (n = 151) of patients received prior systemic therapy with a median of 2 prior systemic regimens and 27.8% (n = 42) received 3 or more prior systemic regimens.
Efficacy results for previously treated RET-mutant MTC are summarised in Table 8.

Table 8 Objective response and duration of response

	Efficacy eligible patients IRC assessment
n	151
Objective response (CR + PR)	
% (95% CI)	73.5 (65.7, 80.4)
Complete response n (%)	14 (9.3)
Partial response n (%)	97 (64.2)
Duration of response (months)*	
Median (95% CI)	NE (27.2, NE)
Rate (%) of duration of response	
12 months (95% CI)	82.8 (74.1, 88.8)
24 months (95% CI)	64.5 (52.9, 73.9)

NE = not estimable
*Median duration of follow-up was 22.93 months (25^{th}, 75^{th} percentile: 17.5, 29.4).
Data cut-off date 15 June 2021

5.2 Pharmacokinetic properties

The pharmacokinetics of selpercatinib were evaluated in patients with locally advanced or metastatic solid tumors administered 160 mg twice daily unless otherwise specified. Steady-state selpercatinib AUC and 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 AUC0-24h 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 [^{14}C] radiolabeled 160 mg dose of selpercatinib to healthy subjects, unchanged selpercatinib constituted 86% of the measured radioactive components in plasma.

Elimination

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

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 $AUC_{0-\infty}$ 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).

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.

Embryotoxicitiy / 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 embryolethality 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 embryolethality 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 Capsules 40mg
Gelatin
Titanium dioxide (E171)
Iron oxide black (E172)

Retsevmo Capsules 80mg
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

24 months

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Retsevmo Capsules 40mg
Supplied as PCTFE/PVC blisters sealed with an aluminium foil in a blister card, in packs of 14 hard capsules.

Retsevmo Capsules 80mg
Supplied as PCTFE/PVC blisters sealed with an aluminium foil in a blister card, in packs of 28 hard capsules.

6.6 Special precautions for disposal

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