ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Lazcluze 80 mg film-coated tablets
Lazcluze 240 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lazcluze 80 mg film-coated tablets

Each film-coated tablet contains 80 mg lazertinib (as mesylate monohydrate).

Lazcluze 240 mg film-coated tablets

Each film-coated tablet contains 240 mg lazertinib (as mesylate monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Lazcluze 80 mg film-coated tablets

Yellow, 14 mm, oval tablet, debossed with “LZ” on one side and “80” on the other side.

Lazcluze 240 mg film-coated tablets

Reddish purple, 20 mm, oval tablet, debossed with “LZ” on one side and “240” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lazcluze in combination with amivantamab is indicated for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations.

4.2 Posology and method of administration

Treatment with Lazcluze should be initiated by a physician experienced in the use of anticancer medicinal products.

Before initiation of Lazcluze, EGFR mutation-positive status in tumour tissue or plasma specimens must be established using a validated test method. If no mutation is detected in a plasma specimen, tumour tissue should be tested if available in sufficient amount and quality due to the potential for false negative results using a plasma test.

Posology

The recommended dose of Lazcluze is 240 mg once daily in combination with amivantamab.

It is recommended to administer Lazcluze any time prior to amivantamab when given on the same day. Refer to section 4.2 of the amivantamab Summary of Product Characteristics for recommended amivantamab dosing information.

Venous thromboembolic (VTE) events with concomitant use with amivantamab

At the initiation of treatment, prophylactic anticoagulants should be administered to prevent venous thromboembolic (VTE) events in patients receiving Lazcluze in combination with amivantamab. Consistent with clinical guidelines, patients should receive prophylactic dosing of either a direct acting oral anticoagulant (DOAC) or a low molecular weight heparin (LMWH). Use of Vitamin K antagonists is not recommended.

Skin and nail reactions

Patients should be instructed to limit sun exposure during and for 2 months after Lazcluze combination therapy and alcohol-free emollient cream is recommended for dry areas. For further information about prophylaxis for skin and nail reactions, see section 4.4.

Duration of treatment

Treatment should continue until disease progression or unacceptable toxicity.

Missed dose

If a planned dose of Lazcluze is missed, it can be administered within 12 hours. If more than 12 hours have passed since the dose was to be given, the missed dose should **not** be administered and the next dose should be administered per the usual dosing schedule.

Dose modifications

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

Table 1: Recommended Lazcluze dose reductions for adverse reactions

Dose reduction	**Recommended dose**
Initial dose	240 mg once daily
1st dose reduction	160 mg once daily
2nd dose reduction	80 mg once daily
3rd dose reduction	Discontinue Lazcluze

Dose modifications for specific adverse reactions are presented in Table 2.

Refer to section 4.2 of the amivantamab Summary of Product Characteristics for information about dose modifications for amivantamab.

Table 2: Recommended Lazcluze and amivantamab dose modifications for adverse reactions*

Adverse reaction	**Severity**	**Dose modification**
Interstitial lung disease (ILD)/pneumonitis	Any grade	• Withhold Lazcluze and amivantamab if ILD/pneumonitis is suspected. • Permanently discontinue Lazcluze and amivantamab if ILD/pneumonitis is confirmed.

Venous thromboembolic (VTE) events (see section 4.4)	Events with clinical instability (e.g., respiratory failure or cardiac dysfunction)	• Withhold Lazcluze and amivantamab until the patient is clinically stable. Thereafter, both medicinal products can be resumed at the same dose.
	Recurrent VTE event despite therapeutic level anticoagulation	• Permanently discontinue amivantamab. Treatment can continue with Lazcluze at the same dose.
Skin and nail reactions (see section 4.4)	Grade 1	• Supportive care should be initiated. • Reassess after 2 weeks.
	Grade 2	• Supportive care should be initiated. • If there is no improvement after 2 weeks, reduce amivantamab dose and continue Lazcluze. • Reassess every 2 weeks, if no improvement, reduce Lazcluze dose until ≤ Grade 1 (Table 1).
	Grade 3	• Supportive care should be initiated. • Withhold Lazcluze and amivantamab. • Upon recovery to ≤ Grade 2, resume both medicinal products at the same dose or consider dose reduction, preferentially reducing the dose of amivantamab first. • If there is no improvement within 2 weeks, permanently discontinue both Lazcluze and amivantamab.
	Grade 4 (including severe bullous, blistering or exfoliating skin conditions, e.g., Toxic epidermal necrolysis)	• Permanently discontinue amivantamab and hold Lazcluze. • Withhold Lazcluze until ≤ Grade 2 or baseline. • Upon recovery to ≤ Grade 2, resume Lazcluze at the same dose.
Hepatotoxicity	Grade 3-4	• Withhold Lazcluze and amivantamab. • Upon recovery to ≤ Grade 1, resume both medicinal products at the same dose or consider dose reduction, preferentially reducing the dose of amivantamab first.
Paraesthesia	Grade 3-4	• Supportive care should be initiated. • Withhold Lazcluze until ≤ Grade 1 or baseline. Resume Lazcluze at the same dose or consider dose reduction. • Consider permanently discontinuing Lazcluze if recovery does not occur within 4 weeks.

Diarrhoea	Grade 3	• Supportive care should be initiated. • Withhold Lazcluze and amivantamab. • Upon recovery to ≤ Grade 1, resume both medicinal products at the same dose or consider dose reduction, preferentially reducing the dose of amivantamab first.
	Grade 4	• Supportive care should be initiated. • Withhold Lazcluze and amivantamab. • Upon recovery to ≤ Grade 1, reduce the dose, preferentially reducing the dose of amivantamab first.
Stomatitis	Grade 3-4	• Withhold Lazcluze and amivantamab. • Upon recovery to ≤ Grade 2, resume both medicinal products at the same dose or consider dose reduction, preferentially reducing the dose of amivantamab first.
Other adverse reactions	Grade 3-4	• Withhold Lazcluze and amivantamab until the adverse reaction resolves to ≤ Grade 1 or baseline. • Resume one or both medicinal products, preferentially resuming Lazcluze first at a reduced dose, unless the adverse reaction is strongly suspected to be related to Lazcluze. • Consider permanently discontinuing both Lazcluze and amivantamab if recovery does not occur within 4 weeks.

* Refer to section 4.2 of the amivantamab Summary of Product Characteristics for recommended amivantamab dosing information.

Special populations

Elderly

No dose adjustment is required (see sections 4.8, 5.1 and 5.2).

Renal impairment

Based on population pharmacokinetics (PK) analysis, no dose adjustment is required for patients with mild, moderate or severe renal impairment. Data in patients with severe renal impairment are limited. The PK of lazertinib in patients with end stage renal disease is unknown. Caution is required in patients with end-stage renal disease (see section 5.2).

Hepatic impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment. The PK of lazertinib in patients with severe hepatic impairment is unknown. Caution is required in patients with severe hepatic impairment (see section 5.2).

Paediatric population

There is no relevant use of lazertinib in the paediatric population for the treatment of non-small cell lung cancer.

Method of administration

Lazcluze is for oral use. The tablets should be swallowed whole with or without food. Tablets should not be crushed, split, or chewed.

If vomiting occurs any time after taking Lazcluze, the next dose should be taken the next day.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Interstitial lung disease/pneumonitis

Interstitial lung disease (ILD) or ILD-like adverse reactions (e.g., pneumonitis), including fatal events, have been reported in patients treated with lazertinib and amivantamab (see section 4.8). Patients with a medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD were excluded from the pivotal clinical study.

Patients should be monitored for symptoms indicative of ILD/pneumonitis (e.g., dyspnoea, cough, fever). If symptoms develop, treatment with Lazcluze should be interrupted pending investigation of these symptoms. Suspected ILD or ILD-like adverse reactions should be evaluated and appropriate treatment should be initiated as necessary. Lazcluze should be permanently discontinued in patients with confirmed ILD or ILD-like adverse reactions (see section 4.2).

Venous thromboembolic (VTE) events

In patients receiving Lazcluze in combination with amivantamab, venous thromboembolic (VTE) events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), including fatal events, were reported (see section 4.8). Consistent with clinical guidelines, patients should receive prophylactic dosing of either a direct acting oral anticoagulant (DOAC) or a low-molecular weight heparin (LMWH). Use of Vitamin K antagonists is not recommended.

Signs and symptoms of VTE events should be monitored. Patients with VTE events should be treated with anticoagulation as clinically indicated. For VTE events associated with clinical instability, treatment should be withheld until the patient is clinically stable. Thereafter, both medicinal products can be resumed at the same dose.

In the event of recurrence despite appropriate anticoagulation, amivantamab should be discontinued. Treatment can continue with Lazcluze at the same dose (see section 4.2).

Skin and nail reactions

Rash (including dermatitis acneiform), pruritus and dry skin occurred in patients treated with lazertinib in combination with amivantamab (see section 4.8). Patients should be instructed to limit sun exposure during and for 2 months after Lazcluze combination therapy. Protective clothing and use of broad-spectrum UVA/UVB sunscreen are advisable. Alcohol-free emollient cream is recommended for dry areas. A prophylactic approach to rash prevention should be considered. This includes prophylactic therapy with an oral antibiotic (e.g., doxycycline or minocycline, 100 mg twice daily) starting on Day 1 for the first 12 weeks of treatment and after completion of oral antibiotic therapy, topical antibiotic lotion to the scalp (e.g., clindamycin 1%) for the next 9 months of treatment.

Non-comedogenic skin moisturiser on the face and whole body (except scalp) and chlorhexidine solution to wash hands and feet should be considered beginning on Day 1 and continued for the first 12 months of treatment.

Prescriptions for additional topical and/or oral antibiotics and topical corticosteroids are recommended to be available at the time of initial dosing to minimise any delay in reactive management should rash develop despite prophylactic treatment. If skin or nail reactions develop, topical corticosteroids and topical and/or oral antibiotics should be administered. For Grade 3 or poorly-tolerated Grade 2 events, systemic antibiotics and oral steroids should also be administered and dermatologic consultation should be considered. Lazcluze should be dose reduced, interrupted, or permanently discontinued based on severity (see section 4.2).

Eye disorders

Eye disorders, including keratitis, occurred in patients treated with lazertinib in combination with amivantamab (see section 4.8). Patients presenting with worsening eye symptoms should promptly be referred to an ophthalmologist and should discontinue use of contact lenses until symptoms are evaluated.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Strong CYP3A4 inducers can decrease lazertinib plasma concentrations. Lazertinib may increase the plasma concentrations of CYP3A4 and BCRP substrates.

Agents that may alter lazertinib plasma concentrations

CYP3A4 inducers

The co-administration of multiple doses of rifampicin (strong CYP3A4 inducer) decreased lazertinib C_{max} by 72% and AUC by 83% in healthy subjects. The co-administration of Lazcluze with strong CYP3A4 inducers (e.g. carbamazepine, phenytoin, rifampicin, St. John's wort) should be avoided. The co-administration of Lazcluze with moderate CYP3A4 inducers may also decrease lazertinib plasma concentrations and hence moderate CYP3A4 inducers (e.g. bosentan, efavirenz, modafinil) should be used with caution.

CYP3A4 inhibitors

The co-administration of multiple doses of itraconazole (strong CYP3A4 inhibitor) increased lazertinib C_{max} by 1.19-fold and AUC by 1.46-fold in healthy subjects. No initial dose adjustment is required when Lazcluze is co-administered with CYP3A4 inhibitors.

Gastric acid reducing agents

No clinically relevant differences in lazertinib pharmacokinetics were observed when co-administered with gastric acid reducing agents (proton pump inhibitors and H2-receptor antagonists). No dose adjustments are required when Lazcluze is used with gastric acid reducing agents.

Agents that may have their plasma concentrations altered by Lazcluze

CYP3A4 substrates

The co-administration of multiple doses of 160 mg Lazcluze once daily increased midazolam (CYP3A4 substrate) C_{max} by 1.39-fold and AUC by 1.47-fold. Narrow therapeutic index medicinal products that are CYP3A4 substrates (e.g., cyclosporine, everolimus, pimozide, quinidine, sirolimus, tacrolimus) should be used with caution, as lazertinib may increase the plasma concentrations of these medicinal products.

BCRP substrates

The co-administration of multiple doses of 160 mg Lazcluze once daily increased rosuvastatin (BCRP substrate) C_{max} by 2.24-fold and AUC by 2.02-fold. Narrow therapeutic index medicinal products that are BCRP substrates (e.g., sunitinib) should be used with caution, as lazertinib may increase the plasma concentrations of these medicinal products.

CYP1A2 substrates

Induction of CYP1A2 cannot be excluded. Therefore, caution is advised when co-administering with substrates of CYP1A2 (e.g., tizanidine).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should be advised to use effective contraception during treatment and up to 3 weeks after treatment.

Male patients with female partners of reproductive potential should be advised to use effective contraception (e.g., condom) and not donate or store semen during treatment and for 3 weeks after the last dose of lazertinib.

Pregnancy

There are no data from the use of lazertinib in pregnant women. Studies in animals have shown reproductive toxicity (reduced embryo-foetal survival and foetal body weight) (see section 5.3). Based on its mechanism of action and animal data, lazertinib may cause foetal harm when administered to a pregnant woman. Lazertinib should not be used during pregnancy unless the benefit of treatment of the woman is considered to outweigh potential risks to the foetus. If the patient becomes pregnant while taking this medicinal product the patient should be informed of the potential risk to the foetus.

Breast-feeding

It is unknown whether lazertinib or its metabolites are excreted in human milk or affects milk production. Because the risk to the breast-feeding child cannot be excluded, female patients should be advised not to breast-feed during treatment and for 3 weeks after the last dose of lazertinib.

Fertility

There are no data on the effect of Lazcluze on human fertility. Studies in animals have shown that lazertinib has effects on reproductive organs in females (decreased numbers of oestrus cycles and corpora lutea) and males (degenerative changes in the testis) and may impair female and male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Lazcluze has minor influence on the ability to drive and use machines. If patients experience treatment-related symptoms (such as fatigue) affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions in all grades were rash (89%), nail toxicity (71%), infusion-related reaction (amivantamab) (63%), hypoalbuminaemia (amivantamab) (48%), hepatotoxicity (47%), oedema (amivantamab) (47%), stomatitis (43%), venous thromboembolism (37%), paraesthesia (34%), fatigue (32%), constipation (29%), diarrhoea (29%), dry skin (26%), decreased appetite (24%), pruritus (24%), hypocalcaemia (21%), other eye disorders (21%) and nausea (21%).

The most frequent serious adverse reactions included venous thromboembolism (11%), pneumonia (4.0%), rash (3.1%), interstitial lung disease/pneumonitis (2.9%), COVID-19 (2.4%), hepatotoxicity (2.4%), pleural effusion (2.1%), infusion-related reaction (amivantamab) (2.1%), respiratory failure (1.4%), fatigue (1.2%), oedema (amivantamab) (1.2%), hypoalbuminaemia (amivantamab) (1.2%), and hyponatraemia (1.2%).

The most frequent adverse reactions leading to any treatment discontinuation in patients receiving Lazcluze in combination with amivantamab were rash (6%), infusion-related reaction (amivantamab) (4.5%), nail toxicity (3.6%), interstitial lung disease/pneumonitis (2.9%), venous thromboembolism (2.9%), pneumonia (1.9%) and oedema (amivantamab) (1.7%).

Tabulated list of adverse reactions

Table 3 summarises the adverse reactions that occurred in patients receiving lazertinib in combination with amivantamab.

The data reflects exposure to lazertinib in 421 patients who received lazertinib in combination with amivantamab in MARIPOSA. The median exposure to lazertinib was 18.5 months (range: 0.2 to 31.4 months).

Adverse reactions observed during clinical studies are listed below by frequency category. Frequency categories are defined as follows: 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 (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse reactions in patients receiving lazertinib in combination with amivantamab

System organ class Adverse reaction	**Frequency category**	**Any grade (%)**	**Grade 3-4 (%)**
Metabolism and nutrition disorders			
Hypoalbuminaemia[a, b]	Very common	48	5
Decreased appetite		24	1.0
Hypocalcaemia		21	2.1
Hypokalaemia		14	3.1
Hypomagnesaemia	Common	5	0
Nervous system disorders			
Paraesthesia[a]	Very common	34	1.7
Dizziness[a]		13	0

Eye disorders			
Other eye disorders[a]	Very common	21	0.5
Visual impairment[a]	Common	4.5	0
Keratitis		2.6	0.5
Growth of eyelashes[a]		1.9	0
Vascular disorders			
Venous thromboembolism[a]	Very common	37	11
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease/pneumonitis[a]	Common	3.1	1.2
Gastrointestinal disorders			
Stomatitis[a]	Very common	43	2.4
Diarrhoea		29	2.1
Constipation		29	0
Nausea		21	1.2
Vomiting		12	0.5
Abdominal pain[a]		11	0
Haemorrhoids	Common	10	0.2
Hepatobiliary disorders			
Hepatotoxicity[a]	Very common	47	9
Skin and subcutaneous tissue disorders			
Rash[a]	Very common	89	27
Nail toxicity[a]		71	11
Dry skin[a]		26	1.0
Pruritus		24	0.5
Palmar-plantar erythrodysaesthesia syndrome	Common	6	0.2
Urticaria		1.2	0
Musculoskeletal and connective tissue disorders			
Muscle spasms	Very common	17	0.5
Myalgia		13	0.7
General disorders and administration site conditions			
Oedema[a, b]	Very common	47	2.9
Fatigue[a]		32	3.8
Pyrexia		12	0
Injury, poisoning and procedural complications			
Infusion-related reaction[b]	Very common	63	6

[a] grouped terms

[b] applicable only to amivantamab.

Description of selected adverse reactions

Venous thromboembolism

Venous thromboembolic (VTE) events, including deep vein thrombosis (14.5%) and pulmonary embolism (PE) (17.3%), were reported in 37% of patients receiving lazertinib in combination with amivantamab. Most cases were Grade 1 or 2, with Grade 3-4 events occurring in 11% and deaths occurring in 0.5% of patients receiving lazertinib in combination with amivantamab. For information on prophylactic anticoagulants and management of VTE events, see sections 4.2 and 4.4.

In patients receiving lazertinib in combination with amivantamab, the median time to first onset of a VTE event was 84 days. VTE events led to any treatment discontinuation in 2.9% of patients.

Interstitial lung disease (ILD)/pneumonitis

Interstitial lung disease or ILD-like adverse reactions (e.g., pneumonitis) have been reported with the use of lazertinib in combination with amivantamab as well as with other EGFR inhibitors. ILD or pneumonitis was reported in 3.1% of patients treated with lazertinib in combination with

amivantamab, including 0.2% fatal cases. Patients with a medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD were excluded from the clinical study (see section 4.4).

Skin and nail reactions

Rash (including dermatitis acneiform), pruritus and dry skin has occurred. Rash occurred in 89% of patients treated with lazertinib in combination with amivantamab. Most cases were Grade 1 or 2, with Grade 3 events occurring in 27% of patients. Rash leading to any treatment discontinuation occurred in 6% of patients. Rash usually developed within the first 4 weeks of therapy, with a median time to onset of 14 days. Nail toxicity occurred in patients treated with lazertinib in combination with amivantamab. Most events were Grade 1 or 2, with Grade 3 nail toxicity occurring in 11% of patients (see section 4.4).

Eye disorders

Eye disorders, including keratitis (2.6%), occurred in patients treated with lazertinib in combination with amivantamab. Other reported adverse reactions included growth of eyelashes, visual impairment, and other eye disorders. Most events were Grade 1-2 (see section 4.4).

Hepatotoxicity

Hepatotoxicity-related reactions occurred in 47% of patients treated with lazertinib in combination with amivantamab. Most events were Grade 1-2, with Grade 3-4 hepatotoxicity occurring in 9% of patients. Most events were related to elevations of serum transaminases (36% alanine aminotransferase increased and 29% aspartate aminotransferase increased). Most patients with elevations of transaminases were able to continue study treatment without modification of study treatment while a small number were managed with a dose interruption or with a dose reduction. There were no cases of liver failure or fatal cases of hepatotoxicity in clinical studies.

Paraesthesia

Paraesthesia occurred in 34% of patients treated with lazertinib in combination with amivantamab. Most events were Grade 1-2, with Grade 3 paraesthesia occurring in 1.7% of patients. Most patients with paraesthesia had resolution with dose interruption or dose reduction.

Stomatitis

Stomatitis occurred in 43% of patients treated with lazertinib in combination with amivantamab. Most events were Grade 1-2, with Grade 3 stomatitis occurring in 2.4% of patients.

Diarrhoea

Diarrhoea occurred in 29% of patients treated with lazertinib in combination with amivantamab. Most events were Grade 1-2, with Grade 3 diarrhoea occurring in 2.1% of patients.

Special populations

Elderly

There are limited clinical data with lazertinib in patients 75 years of age or over (see section 5.1). Older patients (≥ 65 years of age) reported more Grade 3 or higher adverse events compared to patients < 65 years of age (81% vs. 70%). While the rates of drug interruptions and dose reductions were similar, the rate of adverse events leading to any treatment discontinuation was higher in patients ≥ 65 years of age compared to patients < 65 years of age (47% vs. 25%).

Reporting of suspected adverse reactions

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

4.9 Overdose

There is no known specific antidote for Lazcluze overdose. In the event of an overdose, stop Lazcluze and undertake general supportive measures. Patients should be closely monitored for signs or symptoms of adverse reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EB09.

Mechanism of action

Lazertinib is an irreversible EGFR tyrosine kinase inhibitor (TKI). It selectively inhibits both primary activating EGFR mutations (exon 19 deletions and exon 21 L858R substitution mutations) and the EGFR T790M resistance mutation, while having less activity against wild-type EGFR.

Pharmacodynamic effects

Based on the exposure-response analyses for safety, paraesthesia and stomatitis appeared to show a trend of increasing occurrence with increase in lazertinib exposure.

Cardiac electrophysiology

The QTc interval prolongation potential of lazertinib was evaluated by exposure-response (E-R) analysis conducted with clinical data from 243 NSCLC patients who received 20, 40, 80, 120, 160, 240 or 320 mg lazertinib once daily in a phase 1/II study. The E-R analysis revealed no clinically relevant relationship between lazertinib plasma concentration and change in QTc interval.

Clinical efficacy and safety

MARIPOSA is a randomised, open-label, active-controlled, multicentre phase 3 study assessing the efficacy and safety of Lazcluze in combination with amivantamab as compared to osimertinib monotherapy in the first-line treatment of patients with EGFR-mutated locally advanced or metastatic NSCLC not amenable to curative therapy. Patient samples were required to have one of the two common EGFR mutations (exon 19 deletion or exon 21 L858R substitution mutation), as identified by local testing. Tumour tissue (94%) and/or plasma (6%) samples for all patients were tested locally to determine EGFR exon 19 deletion and/or exon 21 L858R substitution mutation status using polymerase chain reaction (PCR) in 65% and next generation sequencing (NGS) in 35% of patients.

A total of 1074 patients were randomised (2:2:1) to receive Lazcluze in combination with amivantamab, osimertinib monotherapy, or Lazcluze monotherapy until disease progression or unacceptable toxicity. Lazcluze was administered at 240 mg orally once daily. Amivantamab was administered intravenously at 1050 mg (for patients < 80 kg) or 1400 mg (for patients ≥ 80 kg) once weekly for 4 weeks, then every 2 weeks thereafter starting at week 5. Osimertinib was administered at a dose of 80 mg orally once daily. Randomisation was stratified by EGFR mutation type (exon 19 deletion or exon 21 L858R substitution mutation), race (Asian or non-Asian), and history of brain metastasis (yes or no).

Baseline demographics and disease characteristics were balanced across the treatment arms. The median age was 63 (range: 25–88) years with 45% of patients ≥ 65 years and 11% ≥ 75 years; 62% were female; and 59% were Asian, and 38% were White. Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (34%) or 1 (66%); 69% never smoked; 41% had prior brain metastases; and 90% had Stage IV cancer at initial diagnosis. With regard to EGFR mutation status, 60% were exon 19 deletions and 40% were exon 21 L858R substitution mutations.

Lazcluze in combination with amivantamab demonstrated a statistically significant improvement in progression-free survival (PFS) by BICR assessment.

Table 4, Figure 1 and Figure 2 summarise efficacy results for Lazcluze in combination with amivantamab.

Table 4: Efficacy results in MARIPOSA

	Lazcluze + amivantamab (N=429)	**Osimertinib (N=429)**
Progression-free survival (PFS)[a]		
Number of events	192 (45%)	252 (59%)
Median, months (95% CI)	23.7 (19.1, 27.7)	16.6 (14.8, 18.5)
HR (95% CI); p-value	0.70 (0.58, 0.85); p=0.0002	
Overall survival (OS)		
Number of events	142 (33%)	177 (41%)
Median, months (95% CI)	NE (NE, NE)	37.3 (32.5, NE)
HR (95% CI); p-value[b]	0.77 (0.61, 0.96); p=0.0185	
Objective response rate (ORR)[a, c]		
ORR % (95% CI)	80% (76%, 84%)	77% (72%, 81%)
Duration of response (DOR)[a, c]		
Median, months (95% CI)	25.8 (20.3, 33.9)	18.1 (14.8, 20.1)

BICR = blinded independent central review; CI = confidence interval; NE = not estimable.

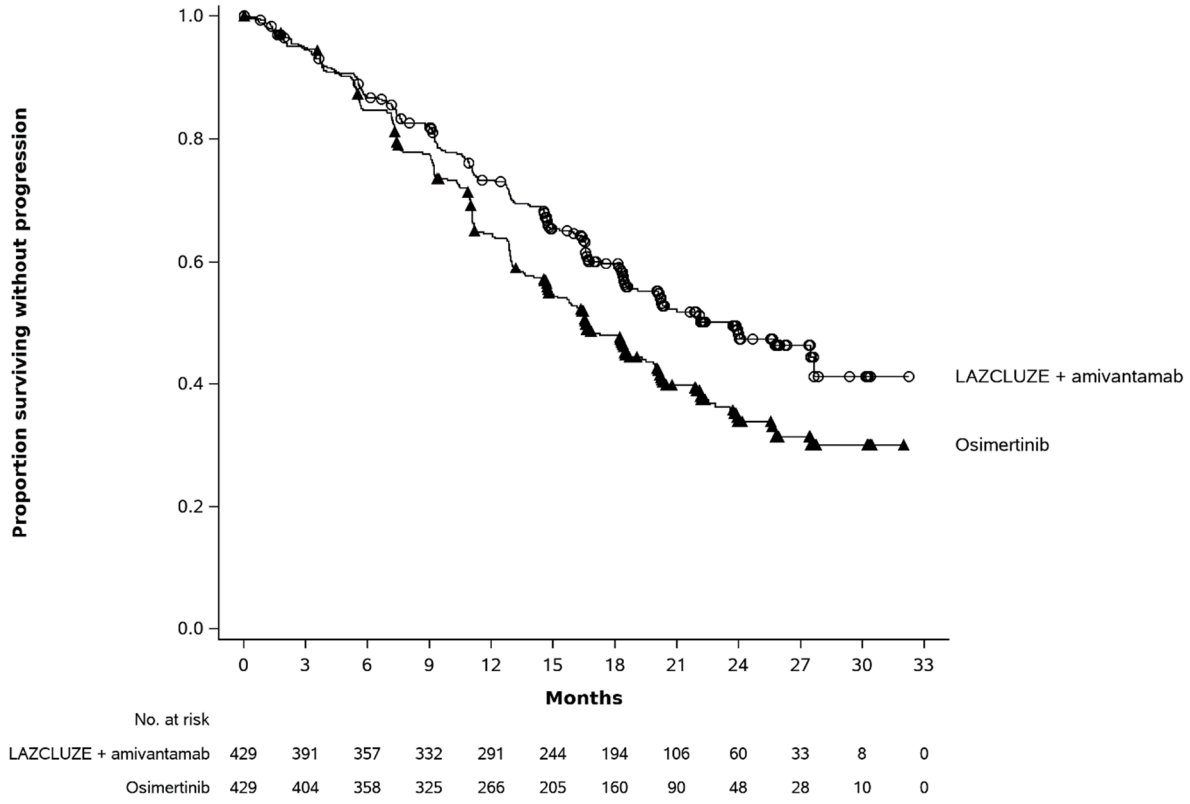
PFS results are from data cut-off 11 August 2023 with median follow-up of 22.0 months. OS, ORR, and DOR results are from data cut-off 13 May 2024 with median follow-up of 31.3 months.

[a] BICR by RECIST v1.1.

[b] The p-value is compared to a 2-sided significance level of 0.00001. Thus the OS results are not statistically significant as of the latest interim analysis.

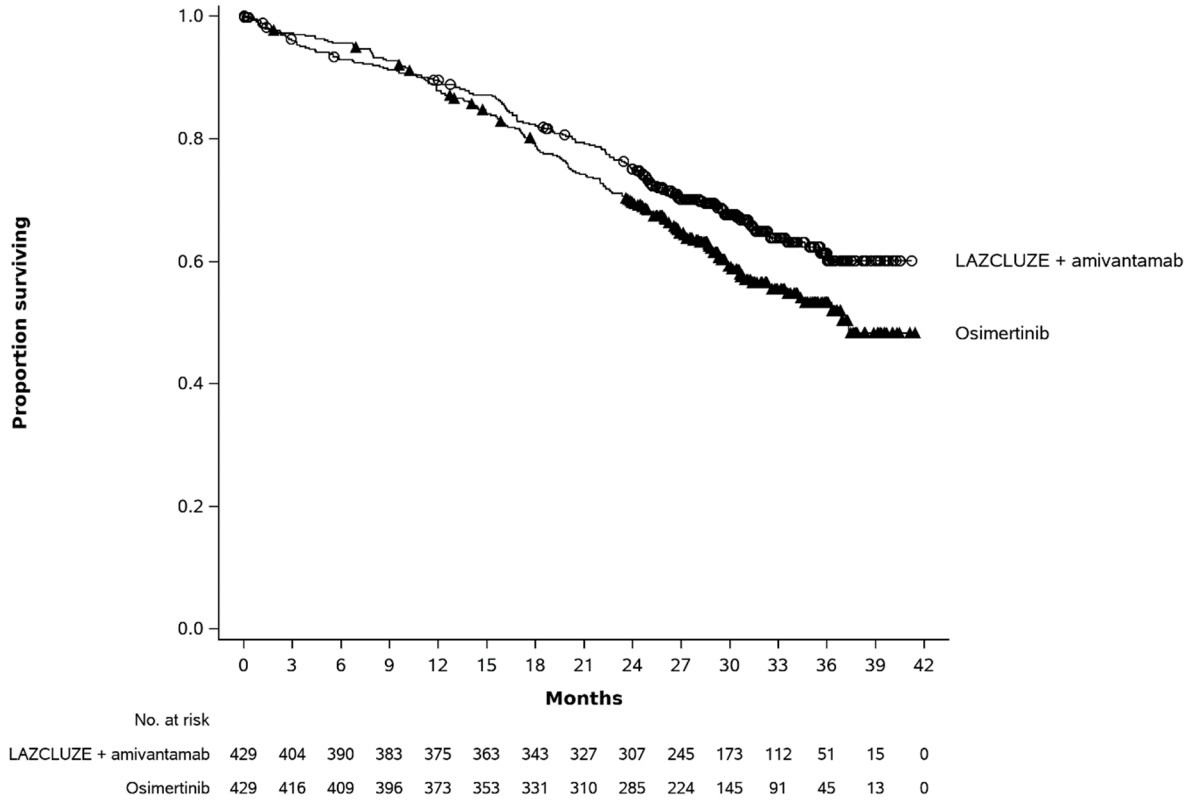
[c] Based on confirmed responders.

Figure 1: Kaplan-Meier curve of PFS in previously untreated NSCLC patients by BICR assessment



With a median follow up of approximately 31 months, the updated OS HR was 0.77 (95% CI: 0.61, 0.96; p=0.0185). This was not statistically significant as compared to a 2-sided significance level of 0.00001.

Figure 2: Kaplan-Meier curve of OS in previously untreated NSCLC patients



Intracranial ORR and DOR by BICR were pre-specified endpoints in MARIPOSA. In the subset of patients with intracranial lesions at baseline, the combination of Lazcluze and amivantamab demonstrated similar intracranial ORR to the control. Per protocol, all patients in MARIPOSA had serial brain MRIs to assess intracranial response and duration. Results are summarised in Table 5.

Table 5: Intracranial ORR and DOR by BICR assessment in subjects with intracranial lesions at baseline

	Lazcluze + amivantamab (N=180)	**Osimertinib (N=186)**
Intracranial tumour response assessment		
Intracranial ORR (CR+PR), % (95% CI)	77% (70%, 83%)	77% (71%, 83%)
Complete response	63%	59%
Intracranial DOR		
Median, months (95% CI)	NE (21.4, NE)	24.4 (22.1, 31.2)

CI = confidence interval; NE = not estimable

Intracranial ORR and DOR results are from data cut-off 13 May 2024 with median follow-up of 31.3 months.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Lazcluze in all subsets of the paediatric population in non-small cell lung cancer.

5.2 Pharmacokinetic properties

Following single and multiple once daily oral administration, lazertinib maximum plasma concentration (C_{max}) and area under plasma concentration time curve (AUC) increased approximately dose proportionally across 20 to 320 mg dose range.

The steady state plasma exposure was achieved by day 15 of once daily administration and approximately 2-fold accumulation was observed at steady state with 240 mg once daily dose.

The lazertinib plasma exposure was comparable when lazertinib was administered either in combination with amivantamab or as a monotherapy.

Absorption

The median time to reach single dose and steady state C_{max} was comparable and ranged from 2 to 4 hours.

Following administration of 240 mg lazertinib with a high-fat meal (800~1000 kcal, fat content approximately 50%), the C_{max} and AUC of lazertinib were comparable to that under fasting conditions suggesting lazertinib can be taken with or without food.

Distribution

Lazertinib was extensively distributed, with mean (CV%) apparent volume of distribution of 4264 (43.2%) L at 240 mg dose. Lazertinib mean (CV%) plasma protein binding was approximately 99.2% (0.13%) in humans. Lazertinib demonstrated covalent binding to human blood and plasma proteins after oral dosing, and during in vitro incubations.

Metabolism

Lazertinib is primarily metabolised by glutathione conjugation, either enzymatic via glutathione-S-transferase (GST) or non-enzymatic, as well as by CYP3A4. The most abundant metabolites are glutathione catabolites and considered clinically inactive. The plasma exposure of

lazertinib was affected by GSTM1 mediated metabolism, leading to lower exposure (less than 2-fold difference) in Non-null GSTM1 patients. No dose adjustment is required based on GSTM1 status.

Elimination

The mean (CV%) apparent clearance and terminal half-life of lazertinib at 240 mg dose were 44.5 (29.5%) L/h and 64.7 (32.8%) hours, respectively.

Excretion

Following a single oral dose of radiolabelled lazertinib, approximately 86% of the dose was recovered in faeces (< 5% as unchanged) and 4% in urine (< 0.5% as unchanged).

Co-administration with OCT1 and UGT1A1 substrates

The co-administration of multiple doses of Lazcluze did not increase metformin (OCT1 substrate) C_{max} and AUC. Lazcluze does not inhibit OCT1.

Based on *in vitro* studies, Lazcluze may inhibit UGT1A1. However, due to lack of effect on indirect bilirubin levels in clinical study, no clinically relevant interaction is expected with UGT1A1 substrates.

Special populations

Elderly

Based on population PK analysis, no clinically meaningful age-based differences in pharmacokinetics of lazertinib were observed.

Renal impairment

Based on population PK analysis, no dose adjustment is required for patients with mild, moderate or severe renal impairment with estimated glomerular filtration rate (eGFR) of 15 to 89 mL/min. Data in patients with severe renal impairment (eGFR of 15 to 29 mL/min) are limited (n=3), but there is no evidence to suggest that dose adjustment is required in these patients. No data are available in patients with end stage renal disease (eGFR < 15 mL/min).

Hepatic impairment

Based on findings from clinical pharmacology study, moderate hepatic impairment (Child-Pugh Class B) had no clinically meaningful effect on lazertinib single dose PK. Based on population PK analysis, no dose adjustment is required for patients with mild (total bilirubin ≤ ULN and AST > ULN or ULN < total bilirubin ≤ 1.5×ULN and any AST) or moderate (1.5×ULN < total bilirubin ≤ 3×ULN and any AST) hepatic impairment. No data are available in patients with severe hepatic impairment (total bilirubin > 3×ULN and any AST).

Paediatric population

The pharmacokinetics of lazertinib in paediatric patients have not been investigated.

Other populations

No clinically meaningful differences in lazertinib PK were observed based on sex, body weight, race, ethnicity, baseline laboratory assessments (creatinine clearance, albumin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase), ECOG performance status, EGFR mutation type, initial diagnosis cancer stage, prior therapies, brain metastasis, and history of smoking.

5.3 Preclinical safety data

The main findings observed in repeat-dose toxicity studies with lazertinib in rats and dogs comprised mild epithelial atrophy to degenerative erosions, inflammation, and necrosis affecting the eye (corneal atrophy) skin (thin and rough hair coat, hair follicle degeneration, alopecia, ulcer), liver (increased liver enzymes, Kupffer cell hypertrophy and hepatocellular necrosis), lungs (alveolar macrophage infiltrate, lung inflammation and hyperplasia of alveolar type II cells), kidney (tubular dilatation, papillary necrosis, higher urea nitrogen, creatinine (females only), inorganic phosphorus, and potassium), GI (oesophageal epithelial atrophy, villus blunting/fusion in duodenum, and jejunum, liquid faeces), reproductive system (testis tubular degeneration, hypospermia, decreased oestrous cycles and corpora lutea, atrophy in uterus and vagina) These findings were observed in animals in exposures ranges of 0.9-3.4x than estimated exposures of patients administered with the recommended dose (240 mg) and were fully or partially resolved during the recovery phases. The heart was considered a target organ in dog alone and occurred at exposure levels 7x to that of exposure levels expected at the human recommended dose.

Carcinogenicity and mutagenicity

No evidence of genotoxicity for lazertinib was observed in *in vitro* bacterial mutagenicity, *in vitro* chromosomal aberration, and *in vivo* micronucleus tests in rats. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of lazertinib.

Reproductive toxicology

Based on studies in animals, male and female fertility may be impaired by treatment with lazertinib. Degenerative changes were present in the testes of rats and dogs resulting in reduced luminal sperm in dogs following exposure to lazertinib for 1 month at clinically relevant exposure levels. Decreased numbers of corpora lutea were noted in the ovaries of rats exposed to lazertinib for ≥ 1 month at clinically relevant exposure levels. In a fertility and early embryonic development study in male and female rats, lazertinib induced a decrease in the number of oestrus cycles, an increase in post-implantation loss and decreased live litter size at or below the dose level that approximated the human clinical exposure at the recommended dose of 240 mg.

Developmental toxicity was observed in embryo-foetal development studies in rats and rabbits. In rats, decreases in foetal body weights in association with maternal toxicity were observed at a maternal exposure approximately 4 times higher than the human clinical exposure at 240 mg. In rabbits, an increased incidence of a foetal skull bone fusion (zygomatic arch fused to the maxillary process) was observed at maternal exposures well below the human clinical exposure at 240 mg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Silica, hydrophobic colloidal
Croscarmellose sodium (E468)
Cellulose, microcrystalline (E460 (i))
Mannitol (E421)
Magnesium stearate (E572)

Film coating

Lazcluze 80 mg film-coated tablets

Macrogol poly(vinyl alcohol) grafted copolymer (E1209)

Polyvinyl alcohol (E1203)
Glycerol monocaprylocaprate type I (E471)
Titanium dioxide (E171)
Talc (E553b)
Yellow iron oxide (E172)

Lazcluze 240 mg film-coated tablets

Macrogol poly(vinyl alcohol) grafted copolymer (E1209)
Polyvinyl alcohol (E1203)
Glycerol monocaprylocaprate type I (E471)
Titanium dioxide (E171)
Talc (E553b)
Red iron oxide (E172)
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Lazcluze 80 mg film-coated tablets

Blister pack

Polyvinyl chloride – polychlorotrifluoroethylene (PVC-PCTFE) film and aluminium push-through foil.

- One carton contains 56 film-coated tablets (2 wallet packs containing 28 tablets each).

Bottle

White opaque high-density polyethylene (HDPE) bottle with polypropylene child-resistant closure containing either 60 or 90 tablets. Each carton contains one bottle.

Lazcluze 240 mg film-coated tablets

Blister pack

Polyvinyl chloride – polychlorotrifluoroethylene (PVC-PCTFE) film and aluminium push-through foil.

- One carton contains 14 film-coated tablets (1 wallet pack containing 14 tablets).
- One carton contains 28 film-coated tablets (2 wallet packs containing 14 tablets each).

Bottle

White opaque high-density polyethylene (HDPE) bottle with polypropylene child-resistant closure containing 30 film-coated tablets. Each carton contains one bottle.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1886/001
EU/1/24/1886/002
EU/1/24/1886/003
EU/1/24/1886/004
EU/1/24/1886/005
EU/1/24/1886/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Janssen Cilag SpA
Via C. Janssen
Borgo San Michele
Latina 04100
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

- **Risk management plan (RMP)**

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

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR WALLET 80 MG

1. NAME OF THE MEDICINAL PRODUCT

Lazcluze 80 mg film-coated tablets
lazertinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 80 mg lazertinib (as mesylate monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

56 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Swallow the tablets whole.
Do not crush, split or chew the tablet.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1886/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lazcluze 80 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

OUTER WALLET 80 MG

1. NAME OF THE MEDICINAL PRODUCT

Lazcluze 80 mg film-coated tablets
lazertinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 80 mg lazertinib (as mesylate monohydrate).

3. LIST OF EXCIPIENTS

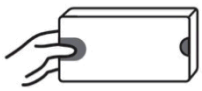
4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Swallow the tablets whole.
Do not crush, split or chew the tablet.
Read the package leaflet before use.

(1) Press and hold



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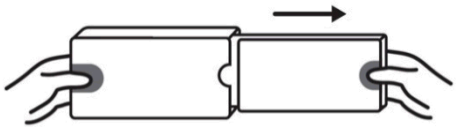


6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1886/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lazcluze 80 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INNER WALLET 80 MG

1. NAME OF THE MEDICINAL PRODUCT

Lazcluze 80 mg film-coated tablets
lazertinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV

3. EXPIRY DATE

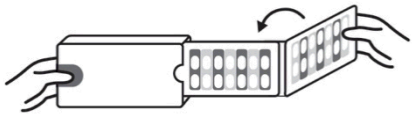
EXP

4. BATCH NUMBER

Lot

5. OTHER

Fold over to close



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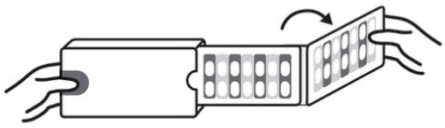


MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER 80 MG

1. NAME OF THE MEDICINAL PRODUCT

Lazcluze 80 mg film-coated tablets
lazertinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR WALLET 240 MG

1. NAME OF THE MEDICINAL PRODUCT

Lazcluze 240 mg film-coated tablets
lazertinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 240 mg lazertinib (as mesylate monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

14 film-coated tablets
28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Swallow the tablets whole.
Do not crush, split or chew the tablet.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1886/004 (14 film-coated tablets)
EU/1/24/1886/005 (28 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lazcluze 240 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

OUTER WALLET 240 MG

1. NAME OF THE MEDICINAL PRODUCT

Lazcluze 240 mg film-coated tablets
lazertinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 240 mg lazertinib (as mesylate monohydrate).

3. LIST OF EXCIPIENTS

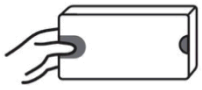
4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets

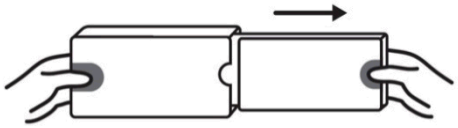
5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Swallow the tablets whole.
Do not crush, split or chew the tablet.
Read the package leaflet before use.

(1) Press and hold



(2) Pull out



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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1886/004 (14 film-coated tablets)
EU/1/24/1886/005 (28 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lazcluze 240 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INNER WALLET 240 MG

1. NAME OF THE MEDICINAL PRODUCT

Lazcluze 240 mg film-coated tablets
lazertinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV

3. EXPIRY DATE

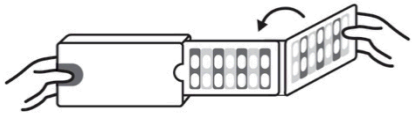
EXP

4. BATCH NUMBER

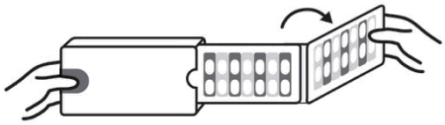
Lot

5. OTHER

Fold over to close



Flip open



MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER 240 MG

1. NAME OF THE MEDICINAL PRODUCT

Lazcluze 240 mg film-coated tablets
lazertinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BOTTLE 80 MG

1. NAME OF THE MEDICINAL PRODUCT

Lazcluze 80 mg film-coated tablets
lazertinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 80 mg lazertinib (as mesylate monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

60 film-coated tablets
90 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Swallow the tablets whole.
Do not crush, split or chew the tablet.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1886/002 (60 film-coated tablets)
EU/1/24/1886/003 (90 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lazcluze 80 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOTTLE LABEL 80 MG

1. NAME OF THE MEDICINAL PRODUCT

Lazcluze 80 mg film-coated tablets
lazertinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 80 mg lazertinib (as mesylate monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

60 tablets
90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Swallow the tablets whole.
Do not crush, split or chew the tablet.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

Dispose as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1886/002 (60 film-coated tablets)
EU/1/24/1886/003 (90 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BOTTLE 240 MG

1. NAME OF THE MEDICINAL PRODUCT

Lazcluze 240 mg film-coated tablets
lazertinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 240 mg lazertinib (as mesylate monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Swallow the tablets whole.
Do not crush, split or chew the tablet.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

Dispose of unused medicines as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1886/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lazcluze 240 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOTTLE LABEL 240 MG

1. NAME OF THE MEDICINAL PRODUCT

Lazcluze 240 mg film-coated tablets
lazertinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 240 mg lazertinib (as mesylate monohydrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Swallow the tablets whole.
Do not crush, split or chew the tablet.
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

Dispose as per local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV

12. MARKETING AUTHORISATION NUMBER(S)

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13. BATCH NUMBER

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14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Lazcluze 80 mg film-coated tablets
Lazcluze 240 mg film-coated tablets
lazertinib

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

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Lazcluze is and what it is used for

Lazcluze is a cancer medicine that contains the active substance lazertinib. It belongs to a group of medicines called protein kinase inhibitors.

Lazcluze is used with amivantamab, another cancer medicine, to treat adults with a type of lung cancer called non-small cell lung cancer. It is used when the cancer is advanced (unlikely to be cured) and has gone through certain changes (exon 19 deletion or exon 21 substitution mutation) in a gene called *EGFR*.

A separate patient information leaflet is available for amivantamab. Please read it before you start treatment.

The *EGFR* gene makes a protein, EGFR, that is involved in cell growth and survival. Mutations (changes) in the *EGFR* gene change the shape of this protein, which may cause cancer cells to grow and spread in the body. The active substance in Lazcluze, lazertinib, works by blocking the faulty protein and may help to slow or stop your lung cancer from growing. It may also help to reduce the size of the tumour. Lazertinib targets mutations in EGFR proteins that are known to cause cancer, while having less effect on normal EGFR proteins.

2. What you need to know before you take Lazcluze

Do not take Lazcluze
- if you are allergic to lazertinib or any of the other ingredients of this medicine (listed in section 6).

If you are not sure, talk to your doctor, pharmacist, or nurse before taking Lazcluze.

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before taking Lazcluze:
- if you have suffered from inflammation of your lungs (a condition called 'interstitial lung disease' or 'pneumonitis').

Tell your doctor straight away if you have any of the following (see 'Serious side effects' in section 4 for more information):
- Skin problems. To reduce the risk of skin problems, keep out of the sun, wear protective clothing, apply sunscreen, use moisturisers regularly on your skin and nails, and use anti-dandruff shampoo while taking this medicine. You will need to continue doing this for 2 months after you stop treatment. Your doctor may recommend that you start a medicine(s) to prevent skin problems, may treat you with a medicine(s), or send you to see a skin specialist (dermatologist) if you get skin reactions during treatment.
- Sudden difficulty in breathing, cough, or fever that may suggest inflammation of the lungs. The condition may be life-threatening, therefore healthcare professionals will monitor you for potential symptoms.
- When used with another drug called amivantamab; life-threatening side effects (due to blood clots in the veins) may occur. Your doctor will give you additional medicines to help prevent blood clots during the course of your treatment and will monitor you for potential symptoms.
- Eye problems. If you have vision problems or eye pain, contact your doctor or nurse straight away. If you use contact lenses and have any new eye symptoms, stop using contact lenses and tell your doctor straight away.

Children and adolescents
Lazcluze has not been studied in children or adolescents. Do not give this medicine to children or adolescents under the age of 18 years.

Other medicines and Lazcluze
Tell your doctor, or pharmacist if you are taking, have recently taken, or might take any other medicines. This is because Lazcluze can affect the way some medicines work. Also, some other medicines can affect the way Lazcluze works.

The following medicines may reduce how well Lazcluze works:
- **Carbamazepine or phenytoin** (anti-epileptic used to treat seizures or fits)
- **Rifampicin** (used to treat tuberculosis)
- **St. John's wort** (a herbal product used to treat mild depression and anxiety)
- **Bosentan** (used to treat pulmonary arterial hypertension)
- **Efavirenz** (used for treatment and prevention of HIV-1 infection)
- **Modafinil** (used for sleep disorders).

Lazcluze may affect how well other medicines work and/or increase the risk of side effects of these medicines:
- **Tizanidine** (used to relax muscles)
- **Cyclosporine or sirolimus or tacrolimus** (used to suppress the immune system)
- **Everolimus** (used to treat hormone receptor-positive advanced breast cancer, neuroendocrine tumours of pancreatic, gastrointestinal or lung origin and renal cell carcinoma)
- **Pimozide** (used in patients with Tourette's Disorder)
- **Quinidine** (used to treat malaria)
- **Sunitinib** (used to treat gastrointestinal stromal tumour, renal cell carcinoma and pancreatic neuroendocrine tumours).

This is not a complete list of medicines. Tell your healthcare provider about all medicines that you are taking. Your doctor will talk to you about the best treatment for you.

Pregnancy
- Tell your doctor before you are given this medicine if you are pregnant, think you might be pregnant, or are planning to have a baby.
- It is possible that this medicine may harm an unborn baby. If you become pregnant during treatment, tell your doctor straight away. You and your doctor will decide whether you should continue taking Lazcluze.
- If you can become pregnant, you should use effective birth control (contraception) during treatment and up to 3 weeks after treatment.
- Male patients with a partner who can become pregnant must use effective contraception, such as a condom, and not donate sperm during treatment with Lazcluze and for 3 weeks after completing treatment.

Breast-feeding
Do not breast-feed during treatment with Lazcluze and for 3 weeks after stopping treatment. This is because it is not known if there is a risk to your baby.

Driving and using machines
Lazcluze has minor influence on the ability to drive and use machines. If you feel tired after taking Lazcluze, do not drive or use machines.

Lazcluze contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

3. How to take Lazcluze

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
- The recommended dose is 240 mg each day with amivantamab.
- If you experience certain side effects, your doctor may reduce your dose to 160 mg or 80 mg each day.

How to take
- Lazcluze is taken by mouth.
- Swallow the tablet whole. Do not crush, split, or chew the tablet.
- You can take this medicine with or without food.
- Do not take an additional dose if you vomit after taking Lazcluze. Wait until your next dose is due.

If you take more Lazcluze than you should
If you take more than the normal dose, contact your doctor. You may have an increased risk of side effects.

If you forget to take Lazcluze
If you forget a dose, take it as soon as you remember it. However, if it is less than 12 hours until your next dose is due, skip the missed dose. Take your next normal dose at its scheduled time.

If you stop taking Lazcluze
Do not stop taking this medicine unless your doctor tells you to.

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

4. Possible side effects

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

Serious side effects
The following side effects have been reported in clinical studies with Lazcluze in combination with amivantamab. Tell your doctor straight away if you notice the following serious side effects:

Very common (may affect more than 1 in 10 people):
- Skin problems - such as rash (including acne), dry skin, itching, pain, and redness. Tell your doctor if your skin problems get worse.
- Blood clots in the veins, especially in the lungs or legs. Symptoms may include sharp chest pain, shortness of breath, rapid breathing, leg pain, and swelling of your arms or legs.

Common (may affect up to 1 in 10 people):
- Signs of inflammation and scarring in the lungs - such as sudden difficulty in breathing, shortness of breath, cough, or fever. This could lead to permanent damage. Your doctor may wish to stop treatment with Lazcluze if you develop this side effect.
- Signs of inflamed cornea (front part of your eye) - such as eye redness, eye pain, problems with vision, or sensitivity to light.
- Eye problems - such as problems with vision or growth of eyelashes.

Tell your doctor straight away if you notice the serious side effects listed above.

Other side effects
Talk to your doctor if you get any other side effects. These can include:

Very common (may affect more than 1 in 10 people):
- nail problems
- signs of a reaction to the infusion of amivantamab
- low level of the protein ‘albumin’ in the blood
- liver toxicity
- swelling caused by fluid build up in the body
- sores in the mouth
- nerve damage that may cause tingling, numbness, pain or loss of pain sensation
- feeling very tired
- diarrhoea
- constipation
- decreased appetite
- low level of calcium in the blood
- feeling sick
- muscle spasms
- low level of potassium in the blood
- feeling dizzy
- muscle aches
- vomiting
- fever
- stomach pain.

Common (may affect up to 1 in 10 people):
- haemorrhoids
- redness, swelling, peeling or tenderness, mainly on the hands or feet
- low level of magnesium in the blood
- itchy rash (hives).

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

5. How to store Lazcluze

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

Do not use this medicine after the expiry date which is stated on the container (blister foil, inner wallet, outer wallet, bottle, and carton) after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

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

6. Contents of the pack and other information

What Lazcluze contains
- The active substance is lazertinib (as mesylate monohydrate). Each 80 mg film-coated tablet contains 80 mg of lazertinib. Each 240 mg film-coated tablet contains 240 mg of lazertinib.
- The other ingredients are:
  Tablet core: hydrophobic colloidal silica, croscarmellose sodium (E468), microcrystalline cellulose (E460 (i)), mannitol (E421), and magnesium stearate (E572). See section 2 “Lazcluze contains sodium”.
  Film coating: macrogol poly(vinyl alcohol) grafted copolymer (E1209), polyvinyl alcohol (E1203), glycerol monocaprylocaprate type I (E471), titanium dioxide (E171), and talc (E553b). Each 80 mg tablet also contains yellow iron oxide (E172). Each 240 mg tablet also contains red iron oxide (E172) and black iron oxide (E172).

What Lazcluze looks like and contents of the pack
Lazcluze 80 mg is supplied as yellow, 14-mm long, oval, film-coated tablets, debossed with “LZ” on one side and “80” on the other side. Lazcluze 80 mg is available in cartons of 56 film-coated tablets (two cardboard wallet packs of 28 tablets each) or bottles of 60 or 90 tablets.

Lazcluze 240 mg is supplied as reddish purple, 20-mm long, oval, film-coated tablets, debossed with “LZ” on one side and “240” on the other side. Lazcluze 240 mg is available in cartons of 14 film-coated tablets (one cardboard wallet pack of 14 tablets), cartons of 28 film-coated tablets (two cardboard wallet packs of 14 tablets each), or bottles of 30 tablets.

Not all pack sizes may be marketed.

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Manufacturer
Janssen Cilag SpA
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Italy

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.