PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrLAZCLUZE®

lazertinib tablets

80 mg and 240 mg lazertinib (as lazertinib mesylate), Oral

Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor

Janssen Inc*.
19 Green Belt Drive
Toronto, Ontario
M3C 1L9

Date of Initial Authorization:
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*a Johnson & Johnson company

Recent Major Label Changes

None at the time of the most recent authorization	

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Part 1: Healthcare Professional Information

1. Indications

- LAZCLUZE® (lazertinib) in combination with amivantamab is indicated for the first-line treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations (see 14 CLINICAL TRIALS)

When using LAZCLUZE in combination with amivantamab, consult the product monograph for amivantamab for further information on this drug.

1.1. Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics

Geriatrics (≥ 65 years of age): No adjustment of the starting dose is recommended based on age. Evidence from clinical studies suggests that use of LAZCLUZE in combination with amivantamab in the geriatric population is associated with differences in safety. Differences were seen in subgroup analyses for efficacy in geriatrics patients, however no formal statistical testing of efficacy was planned for subgroup analyses by age and interpretation of these differences is non-conclusive (see 7.1.4 Geriatrics, 14.1 Clinical Trials by Indication, and 10.3 Pharmacokinetics).

2. Contraindications

LAZCLUZE is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

3. Serious Warnings and Precautions Box

Serious Warnings and Precautions

- Interstitial lung disease (e.g., pneumonitis), including fatal cases (see 7 WARNINGS AND PRECAUTIONS, Respiratory and 8 ADVERSE REACTIONS)

4. Dosage and Administration

4.1. Dosing Considerations

- Before initiation of LAZCLUZE therapy, EGFR mutation-positive status must have been established using a validated test method.
- LAZCLUZE is to be used in combination with amivantamab. The recommended dosage of amivantamab is 1050 mg (if body weight < 80 kg) or 1400 mg (if body weight ≥80 kg) administered by intravenous (IV) infusion in 28-day cycles, once weekly for the first 4 weeks (with a split dose on days 1 and 2) and then once every 2 weeks at week 5 onwards. Refer to the amivantamab product monograph for further information on dosing considerations for amivantamab.

- Prophylactic anticoagulation is recommended to be used for the first four months of LAZCLUZE + amivantamab therapy (See 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

4.2. Recommended Dose and Dosage Adjustment

The recommended dosage of LAZCLUZE is 240 mg once daily, taken orally, in combination with amivantamab until disease progression or no longer tolerated by the patient. It is recommended to administer LAZCLUZE any time prior to amivantamab when given on the same day.

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

Table 1 - Recommended LAZCLUZE Dose Reductions for Adverse Reactions

Dose Reduction	Recommended Dosage
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.

Table 2 - Recommended LAZCLUZE and amivantamab Dose Modifications for Adverse Reactions

Adverse Reaction	Severity†	Dose Modification
Interstitial Lung Disease (ILD)/ pneumonitis (see 7 WARNINGS AND PRECAUTIONS, Respiratory and 8 ADVERSE REACTIONS)	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 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS)	Grade 2 or 3	• Withhold LAZCLUZE and amivantamab. • Administer anticoagulant treatment as clinically indicated. • Once anticoagulant treatment has been initiated LAZCLUZE and amivantamab can be resumed at the same dose level, at the discretion of the healthcare professional.

Adverse Reaction	Severity†	Dose Modification
	Grade 4 or recurrent Grade 2 or 3 despite therapeutic level of anticoagulation	• Withhold LAZCLUZE and permanently discontinue amivantamab. • Administer anticoagulant treatment as clinically indicated. • Once anticoagulant treatment has been initiated, treatment can continue with LAZCLUZE at the same dose level at the discretion of the healthcare professional.
Skin and Nail Reactions (including dermatitis acneiform, pruritus, dry skin) (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS)	Grade 2	• If there is no improvement after 2 weeks of supportive care, reduce amivantamab dose and continue LAZCLUZE. • Reassess every 2 weeks, if no improvement, reduce LAZCLUZE dose until ≤ Grade 1 (Table 1).
	Grade 3	• Withhold LAZCLUZE and amivantamab until the adverse reaction resolves to ≤ Grade 2. • Resume LAZCLUZE at the same dose or consider dose reduction. Resume amivantamab at a reduced dose. • If there is no improvement within 2 weeks, permanently discontinue both LAZCLUZE and amivantamab.
	Grade 4 (including severe bullous, blistering or exfoliating skin conditions)	• Permanently discontinue amivantamab. • Withhold LAZCLUZE until the adverse reaction resolves to ≤ Grade 2 or baseline. • Resume LAZCLUZE at the same dose or consider dose reduction.
Symptomatic congestive heart failure (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular and 8 ADVERSE REACTIONS)	Any Grade	• Permanently discontinue LAZCLUZE
Other Adverse Reactions (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS)	Grade 3-4	• Withhold LAZCLUZE and amivantamab until the adverse reaction resolves to ≤ Grade 1 or baseline.

Adverse Reaction	Severity†	Dose Modification
		• Resume one or both drugs at a reduced dose or LAZCLUZE alone. • Consider permanently discontinuing both LAZCLUZE and amivantamab if recovery does not occur within 4 weeks. • Permanently discontinue both LAZCLUZE and amivantamab for recurrent Grade 4 reactions.

† Severity criteria per CTCAE version 5.0

Refer to the amivantamab product monograph for information about dose modifications for infusion-related reactions (IRR).

4.4. Administration

This medicinal product is for oral use. Swallow tablets whole with or without food. Do not crush, split, or chew the tablet. If vomiting occurs any time after taking LAZCLUZE, instruct the patient to take the next dose at its next regularly scheduled time.

4.5. Missed Dose

If a 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, do **not** administer the missed dose and administer the next dose per the usual dosing schedule.

5. Overdose

The maximum tolerated dose of LAZCLUZE has not been determined. In clinical trials, daily doses of up to 320 mg once daily have been administered.

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.

For management of a suspected drug overdose, contact your regional poison control centre.

6. Dosage Forms, Strengths, Composition, and Packaging

Table 3 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet, 80 mg and 240 mg lazertinib (as lazertinib	LAZCLUZE 80 mg film-coated tablets: croscarmellose sodium, glyceryl monocaprylocaprate type I, hydrophobic

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
	mesylate)	colloidal silica, macrogol (PEG) polyvinyl alcohol graft copolymer, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl alcohol partially hydrolyzed, talc, titanium dioxide, yellow iron oxide. LAZCLUZE 240 mg film-coated tablets: black iron oxide, croscarmellose sodium, glyceryl monocaprylocaprate type I, hydrophobic colloidal silica, macrogol (PEG) polyvinyl alcohol graft copolymer, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl alcohol partially hydrolyzed, red iron oxide, talc, titanium dioxide

LAZCLUZE 80 mg tablets
Each tablet contains 80 mg of lazertinib (as mesylate monohydrate).
Yellow, oval film-coated tablet debossed with “LZ” on one side and “80” on the other side.
LAZCLUZE 80 mg tablets are available in HDPE bottles of 60 tablets.

LAZCLUZE 240 mg tablets
Each tablet contains 240 mg of lazertinib (as mesylate monohydrate).
Reddish purple, oval film-coated tablet, debossed with “LZ” on one side and “240” on the other side. LAZCLUZE 240 mg tablets are available in HDPE bottles of 30 tablets.

7. Warnings and Precautions

Cardiovascular

Left Ventricular Dysfunction and Cardiomyopathy

Left Ventricular Ejection Fraction (LVEF) reductions of >10 percentage points and a drop to below lower limit of normal occurred in 3.4% of patients treated with LAZCLUZE in combination with amivantamab and who had a baseline LVEF assessment. A total of 7.4% of patients treated with LAZCLUZE in combination with amivantamab reported cardiomyopathy events (defined as cardiac failure, chronic cardiac failure, congestive cardiac failure, pulmonary edema, ejection fraction decreased, left ventricular dysfunction).

Based on the available clinical trial data, a causal relationship between effects on changes in cardiac contractility and LAZCLUZE has not been established, however, causality cannot be completely ruled out. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered. Discontinuation of treatment with LAZCLUZE should be considered in patients who develop

congestive heart failure. See 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Test; 4.2 Recommended Dose and Dosage Adjustment

Venous Thromboembolic (VTE) Events

Venous thromboembolic (VTE) events, including deep venous thrombosis (DVT) and pulmonary embolism (PE), including fatal events, were reported in patients receiving LAZCLUZE in combination with amivantamab (see 8 ADVERSE REACTIONS). VTE events occurred predominantly in the first four months of therapy

Prophylactic anticoagulation is recommended to be used for the first four months of treatment to prevent VTE. Prophylactic anticoagulation beyond 4 months may be considered based on individual patient risk factors. Use of anticoagulants should align with clinical guidelines; use of Vitamin K antagonists is not recommended.

Monitor for signs and symptoms of VTE events. Treat patients with VTE events with anticoagulants as clinically indicated. For patients with Grade 4 or recurrent Grade 2 or 3 VTE events despite therapeutic levels of anticoagulation, withhold LAZCLUZE and permanently discontinue amivantamab. Administer anticoagulation treatment as clinically indicated. Once anticoagulation treatment has been initiated, treatment can continue with LAZCLUZE at the same dose level at the discretion of the healthcare professional (see 4.2 Recommended Dose and Dosage Adjustment).

Driving and Operating Machinery

No studies on the effects on the ability to drive and use machines have been performed. If patients experience visual impairment, dizziness or other symptoms affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

Monitoring and Laboratory Test

Electrolyte levels (calcium, potassium, and magnesium) should be assessed prior to initiating therapy with LAZCLUZE, and monitored periodically during treatment with LAZCLUZE, particularly in patients at risk for these electrolyte abnormalities. Hypocalcemia, hypokalemia, and hypomagnesemia should be corrected prior to LAZCLUZE administration (see 8 ADVERSE REACTIONS).

In patients with cardiac risk factors and those with conditions that can affect left ventricular ejection fraction (LVEF), cardiac monitoring, including an assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

Ophthalmologic

Keratitis occurred in patients receiving LAZCLUZE with amivantamab. Refer patients presenting with worsening eye symptoms promptly to an ophthalmologist and advise discontinuation of contact lenses until symptoms are evaluated. Withhold dose, reduce or permanently discontinue LAZCLUZE based on the severity of symptoms (see 4.2 Recommended Dose and Dosage Adjustment)

Reproductive Health

- **Fertility**

There are no data on the effect of LAZCLUZE on human fertility. Results from animal studies have shown that LAZCLUZE has effects on male and female reproductive organs and could impair fertility (see 16 NON-CLINICAL TOXICOLOGY)

- **Contraception**

Advise female patients of reproductive potential to use effective contraception during treatment and for 3 weeks after the final dose of LAZCLUZE. Advise male patients with female partners of reproductive potential to use effective contraception (e.g., condom) and not donate or store semen during treatment and for 3 weeks after the last dose of LAZCLUZE (see 7.1.1 Pregnancy). The recommended duration of contraception may need to be extended if amivantamab is co-administered. Refer to the product monograph for amivantamab for further information.

Respiratory

Interstitial lung disease (ILD)/pneumonitis, including fatal events, have been reported in patients receiving LAZCLUZE (see 8 ADVERSE REACTIONS). Monitor patients for symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). If symptoms develop, interrupt treatment with LAZCLUZE pending investigation of these symptoms. Evaluate suspected ILD and initiate appropriate treatment as necessary. Discontinue LAZCLUZE in patients with confirmed ILD (see 4.2 Recommended Dose and Dosage Adjustment)

Skin

Skin and nail reactions may occur when treated with LAZCLUZE.

Rash (including dermatitis acneiform), palmar-plantar erythrodysesthesia, pruritis and dry skin occurred in patients receiving LAZCLUZE with amivantamab (see 8 ADVERSE REACTIONS).

A prophylactic approach to rash prevention should be considered. Use of oral antibiotics may be considered for the first 8 weeks of treatment. Instruct patients to limit sun exposure during and for 2 months after LAZCLUZE therapy. Protective clothing and use of sunscreen is advisable. Alcohol-free emollient cream is recommended with the use of LAZCLUZE on a daily basis, starting at Day 1 of treatment. If skin or nail reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, administer oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue LAZCLUZE and amivantamab based on severity of symptoms (see 4.2 Recommended Dose and Dosage Adjustment)

7.1. Special Populations

7.1.1. Pregnancy

There are no data from the use of lazertinib in pregnant women. Studies in animals have shown reproductive toxicity (reduced embryo-fetal survival and decreases in fetal weight) (see 16 NON-CLINICAL TOXICOLOGY). Based on its mechanism of action and animal data, lazertinib may cause fetal harm when administered to a pregnant woman. LAZCLUZE should

not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh the potential risks to the fetus. Verify the pregnancy status of female patients of reproductive potential prior to initiating LAZCLUZE

7.1.2. Breastfeeding

It is not known 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, advise women not to breast-feed during treatment and for 3 weeks after the last dose of LAZCLUZE.

7.1.3. Pediatrics

Pediatrics (<18 years of age): The safety and efficacy of LAZCLUZE in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4. Geriatrics

Geriatrics (≥ 65 years of age): There are limited clinical data with lazertinib in patients 75 years or over. Older patients (≥ 65 years of age) reported more Grade 4 and Grade 5 adverse reactions compared to patients < 65 years of age (21% vs. 7%). The incidence of serious adverse reactions was 62% in patients ≥ 65 years of age and 38% in patients <65 years of age. While the rates of drug interruptions and dose reductions were similar, the rate of adverse reactions leading to any treatment discontinuation was higher in patients ≥ 65 years of age compared to patients < 65 years of age (47% vs. 25 %).

8. Adverse Reactions

8.1. Adverse Reaction Overview

The adverse reactions reported in ≥20% of patients who received LAZCLUZE in combination with amivantamab were paronychia, infusion related reaction (amivantamab-specific), rash, hypoalbuminemia (amivantamab-specific), alanine aminotransferase increased, edema peripheral, constipation, diarrhea, dermatitis acneiform, stomatitis, aspartate aminotransferase increased, COVID-19, decreased appetite, pruritus, anemia, nausea, and hypocalcemia.

Dose interruption of LAZCLUZE due to adverse reactions occurred in 71% patients. Adverse reactions requiring dose interruption of LAZCLUZE in ≥5% of patients included rash, paronychia, COVID-19, dermatitis acneiform, alanine aminotransferase increased, and aspartate aminotransferase increased.

Dose reduction of LAZCLUZE due to adverse reactions occurred in 42% patients. Adverse reactions requiring dose reduction of LAZCLUZE in ≥5% of patients included paronychia, rash and dermatitis acneiform.

Twenty percent of patients permanently discontinued LAZCLUZE due to adverse reactions. Adverse reactions leading to LAZCLUZE discontinuation in ≥1% of patients were ILD/pneumonitis, pneumonia, and pulmonary embolism.

Serious adverse reactions occurred in 49% of patients who received LAZCLUZE in combination with amivantamab. Serious adverse reactions in >2% of patients who received LAZCLUZE in combination with amivantamab included pulmonary embolism (6.2%), pneumonia (4.0%), deep vein thrombosis (2.9%), ILD/pneumonitis (2.9%), COVID-19 (2.4%) infusion related reaction (2.1%; amivantamab-specific), rash (2.1%) and pleural effusion

(2.1%).

Fatal adverse reactions occurred in 7% of patients who received LAZCLUZE in combination with amivantamab, which included death not otherwise specified (1.2%); sepsis and respiratory failure (1% each); pneumonia, myocardial infarction, and sudden death (0.7% each); cerebral infarction, pulmonary embolism (PE), and COVID-19 infection (0.5% each); and ILD/pneumonitis, acute respiratory distress syndrome (ARDS), and cardiopulmonary arrest (0.2% each).

8.2. Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety data described below reflect exposure to LAZCLUZE in combination with amivantamab in 421 treatment-naïve patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletion or exon 21 L858R substitution mutation in the MARIPOSA study. Patients in MARIPOSA received LAZCLUZE 240 mg orally once daily and amivantamab intravenously at 1,050 mg (for patients < 80 kg) or 1,400 mg (for patients ≥ 80 kg) once weekly for 4 weeks, then every 2 weeks thereafter starting at week 5. Patients in the osimertinib arm received 80 mg osimertinib once daily. The median treatment duration was 18.5 months (range 0.2 to 31.4 months) for the LAZCLUZE + amivantamab arm and the median treatment duration was 18.0 months (range: 0.2 to 32.7 months) for the osimertinib arm.

Among the 421 patients who received LAZCLUZE in combination with amivantamab, 83.6% were exposed to LAZCLUZE for ≥ 6 months and 73.2% were exposed to LAZCLUZE for > 1 year. For details on the study population, see 14 CLINICAL TRIALS.

Table 4 summarizes the adverse reactions (≥ 10%) in MARIPOSA.

Table 4 - Adverse Reactions (≥ 10%) in First-line Treatment of Patients with Locally Advanced or Metastatic NSCLC with EGFR Exon 19 Deletion or Exon 21 L858R Substitution Mutations in MARIPOSA

	LAZCLUZE + Amivantamab n=421		Osimertinib n=428	
System Organ Class Adverse Reaction	**All Grades (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Eye disorders				
Ocular infections, irritations and inflammations[a]	15	0.5	4	0
Gastrointestinal disorders				
Stomatitis[b]	43	2	26	0.5
Constipation	29	0	13	0
Diarrhea	29	2	44	0.7
Nausea	21	1	14	0.2
Vomiting	12	0.5	5	0
Haemorrhoids	10	0.2	2	0.2
General disorders and administration site conditions				

	LAZCLUZE + Amivantamab n=421		Osimertinib n=428	
System Organ Class Adverse Reaction	**All Grades (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Edema[c]	47	3	9	0
Fatigue[d]	32	4	20	2
Pyrexia	12	0	9	0
Infections and Infestations				
Paronychia	68	11	28	0.5
Injury, Poisoning and Procedural Complications				
Infusion related reaction[e]	63	6	0	0
Metabolism and nutrition disorders				
Decreased appetite	24	1	18	1
Musculoskeletal and connective tissue disorders				
Muscle spasms	17	0.5	7	0
Pain in extremity	15	0.2	5	0
Myalgia	13	0.7	4	0
Back pain	11	0.2	11	0
Nervous system disorders				
Paresthesia[f]	34	2	10	0.2
Headache	13	0.2	13	0
Dizziness	12	0	7	0
Skin and subcutaneous tissue disorders				
Rash[g]	88	26	47	0.7
Dry skin[h]	26	1	20	0.5
Pruritus	24	0.5	17	0.2
Vascular disorders				
Venous thromboembolism[i]	36	11	8	3

a Includes Blepharitis, Conjunctival hyperemia, Conjunctivitis, Episcleritis, Eye pruritus, Noninfective conjunctivitis, Ocular hyperemia
b Includes Angular cheilitis, Aphthous ulcer, Mouth ulceration, Mucosal inflammation, Stomatitis
c Includes Eye edema, Eyelid edema, Face edema, Generalized edema, Localized edema, Edema, Edema peripheral, Periorbital edema, Periorbital swelling, Peripheral swelling, Swelling face
d Includes Asthenia, Fatigue
e Amivantamab specific adverse reactions
f Includes Dysesthesia, Hypoesthesia, Neuropathy peripheral, Paresthesia, Peripheral motor neuropathy, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Polyneuropathy
g Includes Acne, Dermatitis, Dermatitis acneiform, Erythema, Folliculitis, Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash pruritic, Rash pustular, Skin lesion
h Includes Dry skin, Eczema, Eczema asteatotic, Skin fissures, Xeroderma, Xerosis
i Includes Axillary vein thrombosis, Deep vein thrombosis, Embolism, Embolism venous, Jugular vein thrombosis, Portal vein thrombosis, Pulmonary embolism, Pulmonary infarction, Sigmoid sinus thrombosis, Superior sagittal sinus thrombosis, Thrombosis, Vena cava thrombosis, Venous thrombosis, Venous thrombosis limb

8.3. Less Common Clinical Trial Adverse Reactions

Clinically relevant adverse reactions in <10% of patients who received LAZCLUZE in combination with amivantamab include:

Eye disorders: Dry eye (9%), vision blurred (3%), keratitis (3%), trichomegaly (1%), visual acuity reduced (1%), visual impairment (1%), eye disorders (1%), and growth of eyelashes (1%) (see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic)

Hepatobiliary disorders: hyperbilirubinemia (7%)

Gastrointestinal disorders*:* gingival bleeding (5%)

Metabolism and nutrition disorders: Hypomagnesemia (5%)

Skin and subcutaneous tissue disorders: nail toxicity (8%, including ingrowing nail, nail disorder, nail infection, nail toxicity, onychoclasis, onycholysis, onychomadesis); palmar-plantar erythrodysesthesia syndrome (6%); skin ulcer (5%); alopecia (4%); and urticaria (1%) (see 7 WARNINGS AND PRECAUTIONS, Skin)

Renal and urinary disorders: hematuria (5%)

Respiratory, thoracic and mediastinal disorders: epistaxis (8%), interstitial lung disease (ILD) / pneumonitis (3%) (see 7 WARNINGS AND PRECAUTIONS, Respiratory)

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

Table 5 summarizes the laboratory abnormalities in MARIPOSA.

Table 5 - Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in First-line Patients with Locally Advanced or Metastatic NSCLC with EGFR Exon 19 Deletion or Exon 21 L858R Substitution Mutations in MARIPOSA+

Laboratory Abnormality	LAZCLUZE + Amivantamab n=421		Osimertinib n=428	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Chemistry				
Decreased Albumin	89	8	22	<1
Increased Alanine Aminotransferase	65	7	29	3
Increased Aspartate Aminotransferase	52	4	36	2
Increased alkaline phosphatase	45	0.5	15	0.5
Decreased Calcium (Corrected)	41	1	27	1
Increased Gamma Glutamyl Transferase	39	3	24	2
Decreased Sodium	38	7	35	5
Decreased potassium	30	5	16	1.2
Increased Creatinine	26	1	35	1
Decreased magnesium	25	0.7	10	0.2
Increased Magnesium	12	3	20	5
Hematology				
Decreased Platelet Count	52	1	57	1

Laboratory Abnormality	LAZCLUZE + Amivantamab n=421		Osimertinib n=428	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Decreased Hemoglobin	47	4	56	2
Decreased White Blood Cell	38	1	66	1
Decreased Neutrophil Count	15	1	33	1

+ The denominator used to calculate the rate is the number of patients with a baseline value and at least one post-treatment value for the specific lab test.

9. Drug Interactions

9.1. Drug Interactions Overview

Lazertinib is primarily metabolized by glutathione conjugation, either enzymatic via glutathione S-transferase (GST) or non-enzymatic, as well as by CYP3A4 Clinical studies and physiological based PK models demonstrate that strong CYP3A4 inducers can decrease the exposure of lazertinib. Lazertinib is an inhibitor of CYP3A4 and may increase exposure of co-administered CYP3A4 substrates and the risk of exposure related toxicity. Lazertinib is an inhibitor of BCRP transporter and may increase exposure of co-administered BCRP substrates and the risk of exposure related toxicity.

9.2. Drug-Drug Interactions

Effect of Other Drugs on LAZCLUZE

CYP3A4 inducers

The co-administration of 240 mg lazertinib with rifampin (strong CYP3A4 inducer) decreased lazertinib plasma exposure. Lazertinib geometric mean ratios (90% CI) for C_{max} and $AUC_{0\text{-}120h}$ were 0.28 (0.23, 0.34) and 0.17 (0.14, 0.19) respectively, when co-administered with rifampin, relative to lazertinib alone. Based on physiological based PK model analysis, no clinically relevant decrease in lazertinib exposure is expected when LAZCLUZE is co-administered with weak or moderate CYP3A4 inducers. PBPK model simulations for co-administration of lazertinib with the moderate CYP3A4 inducer efavirenz (600 mg once daily) predicted an approximate 50% decrease in AUC. The co-administration of LAZCLUZE with moderate or strong CYP3A4 inducers should be avoided.

CYP3A4 inhibitors

The co-administration of 160 mg lazertinib with itraconazole (strong CYP3A4 inhibitor) increased lazertinib plasma exposure. The lazertinib geometric mean ratios (90% CI) for C_{max} and $AUC_{0\text{-}120h}$ were 1.19 (1.08, 1.30) and 1.46 (1.39, 1.53) respectively, when co-administered with itraconazole, relative to lazertinib alone.

The effect of the co-administration of strong CYP3A4 inhibitors with the recommended dose of 240 mg lazertinib has not been evaluated. The effect of moderate CYP3A4 inhibitors on lazertinib exposure has not been evaluated. No dose adjustments are required when LAZCLUZE is used with CYP3A4 inhibitors. However, close monitoring for LAZCLUZE related adverse reactions is recommended when co-administered with moderate or strong CYP3A4 inhibitors.

Gastric acid reducing agents

Results of a retrospective PK analysis from a patient population study suggest that there was no clinically relevant change in lazertinib plasma exposure when co-administered with gastric acid reducing agents. No dose adjustments are required when LAZCLUZE is used with gastric acid reducing agents.

Effect of LAZCLUZE on Other Drugs

CYP3A4 Substrates

The co-administration of midazolam (CYP3A4 substrate) with 160 mg lazertinib increased midazolam plasma exposure by less than 50%. The midazolam geometric mean ratios (90% CI) for C_{max} and $AUC_{0\text{-last}}$ were 1.39 (1.23, 1.58) and 1.47 (1.34, 1.60) respectively, when co-administered with lazertinib, relative to midazolam alone. Lazertinib is an inhibitor of CYP3A4 enzyme. For sensitive CYP3A4 substrates with narrow therapeutic index, monitor for adverse reactions as increased plasma exposure of co-administered CYP3A4 substrates may increase the risk of exposure-related toxicity.

BCRP substrate

The co-administration of rosuvastatin (BCRP substrate) with 160 mg lazertinib increased rosuvastatin plasma exposure by approximately 2-fold. The rosuvastatin geometric mean ratios (90% CI) for C_{max} and $AUC_{0\text{-last}}$ were 2.24 (1.82, 2.76) and 2.02 (1.70, 2.40) respectively, when co-administered with lazertinib, relative to rosuvastatin alone. Lazertinib is an inhibitor of BCRP transporter. For sensitive BCRP substrates with narrow therapeutic index, monitor for adverse reactions as increased plasma exposure of co-administered BCRP substrates may increase the risk of exposure-related toxicity.

OCT1 substrate

The co-administration of metformin (OCT1 substrate) with 160 mg lazertinib did not increase metformin plasma exposure. The metformin geometric mean ratios (90% CI) for C_{max} and $AUC_{0\text{-last}}$ were 0.81 (0.72, 0.91) and 0.94 (0.83, 1.06) respectively, when co-administered with lazertinib, relative to metformin alone. Lazertinib is not an inhibitor of OCT1 transporter.

In vitro findings suggest that lazertinib may inhibit UGT1A1; however, due to lack of effect on indirect bilirubin levels in clinical study and physiological based PK model analysis, no clinically relevant interaction is expected.

The drugs listed in Table 6 are based on drug interaction studies.

Table 6 - Established or Potential Drug-Drug Interactions

Common name	Source of Evidence	Effect	Clinical comment
CYP3A4 inducers	CT PBPK model	Co-administration of 240 mg lazertinib with rifampin (strong CYP3A4 inducer) or efavirenz (a moderated CYP3A4 inducer) decreased lazertinib plasma exposure.	Concomitant use with moderate or strong CYP3A4 inducers should be avoided.

Common name	Source of Evidence	Effect	Clinical comment
CYP3A4 Substrates (e.g., midazolam)	CT	Co-administration of midazolam (CYP3A4 substrate) with 160 mg lazertinib increased midazolam plasma exposure by less than 50%.	Use with caution and monitor for adverse reactions.
BCRP substrate (e.g., rosuvastatin)	CT	Co-administration of rosuvastatin (BCRP substrate) with 160 mg lazertinib increased rosuvastatin plasma exposure by approximately 2-fold.	Use with caution and monitor for adverse reactions.

Legend: CT = Clinical Trial

No formal drug-herb interaction studies have been conducted with LAZCLUZE.

9.5. Drug-Food Interactions

LAZCLUZE may be taken with or without food.

9.6. Drug-Herb Interactions

No formal drug-herb interaction studies have been conducted with LAZCLUZE.

9.7. Drug-Laboratory Test Interactions

No formal drug-laboratory test interaction studies have been conducted with LAZCLUZE.

10. Clinical Pharmacology

10.1. Mechanism of Action

Lazertinib is a third generation, EGFR tyrosine kinase inhibitor (TKI). It selectively inhibits both primary activating EGFR mutations (exon 19 deletions and exon 21 L858R substitution mutations) while having less activity against wild-type EGFR.

10.2. Pharmacodynamics

Based on the exposure-response analyses for efficacy, no apparent relationship between lazertinib exposure and progression-free survival was observed at the dose regimen of 240 mg once daily. A similar exposure-response analyses for safety, concluded that paresthesia and stomatitis appeared to show a trend of increasing occurrence with increase in lazertinib exposure.

Cardiac electrophysiology

A dedicated QT study was not performed with LAZCLUZE. As a substitute, an exposure-response analysis was performed with clinical data from a phase I/II study, which suggested no clinically relevant relationship between lazertinib plasma concentration and change in QTc interval. The 2-sided upper bound of the 90% CI of the change in QTc interval at steady state C_{max} in subjects administered either the recommended dose of 240 mg once daily or the highest tested clinical dose of 320 mg once daily was 5.83 and 7.23 msec respectively.

10.3. Pharmacokinetics

Following single and multiple once daily oral administration of LAZCLUZE, 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 the administration of 240 mg once daily administration and approximately 2-fold accumulation of lazertinib was observed.

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

Table 7 - Summary of lazertinib Pharmacokinetic Parameters Mean (%CV)

	C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	AUC_{0-24} (ng/h/mL)	CL/F (L/h)	Vd (L)
Single Dose	434 (29.0%)	1.99 (range 1.98-4.00)	64.7 (32.8%)	2866.24 (34.0%)	44.5 (29.5%)	4264 (43.2%)

Absorption: The median time to reach lazertinib C_{max} after a single dose or multiple once daily oral administration of LAZCLUZE was comparable and ranged from 2 to 4 hours.

Following administration of 240 mg lazertinib with a high-fat meal (800~1000 kcal, approximately 50% fat content), 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 L (43.2%) following a single 240 mg dose. Lazertinib mean (CV%) plasma protein binding was approximately 99.2% (0.13%) in humans.

Metabolism: Lazertinib is primarily metabolized by glutathione conjugation, either enzymatically via glutathione-S-transferase (GST) or non-enzymatically, as well as by CYP3A4 to a lesser extent. The most abundant metabolites are glutathione catabolites and considered clinically inactive. The plasma exposure of lazertinib was affected by GSTM1 mediated metabolism, leading to higher exposure (up to 2-fold difference) in null GSTM1 patients. No clinically significant differences in safety or efficacy were observed as a function of GSTM1 genotype in patients receiving LAZCLUZE in combination with amivantamab.

Elimination: The mean (CV%) apparent clearance and terminal elimination 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 radiolabeled lazertinib, approximately 86% of the dose was recovered in feces (<5% as unchanged) and 4% in urine (<0.2% as unchanged).

Special populations and conditions

Pediatrics (< 18 years of age): The pharmacokinetics of lazertinib in pediatric patients have not been investigated.

Geriatrics (≥ 65 years of age): Based on population PK analysis, no clinically meaningful age-based differences in pharmacokinetics of lazertinib were observed.

Sex, Body Weight, Race/Ethnicity: No clinically meaningful differences in lazertinib

pharmacokinetics were observed based on sex, body weight, race, ethnicity.

Hepatic Insufficiency: 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. Data in patients with moderate hepatic impairment are limited (n=2). Considering that hepatic CYP3A4 metabolism is one of the primary elimination pathways, close monitoring for adverse reactions is needed.

No data are available in patients with severe hepatic impairment (total bilirubin > 3×ULN and any AST).

Renal Insufficiency: Based on population PK analysis, no dose adjustment is required for patients with mild or moderate 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. No data are available in patients with end stage renal disease (eGFR < 15 mL/min).

11. Storage, Stability, and Disposal

Store at 15°C to 30°C. Keep out of the sight and reach of children.

12. Special Handling Instructions

Not applicable.

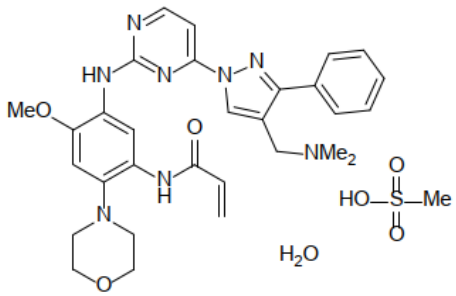
Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

Proper name / Common name:	lazertinib mesylate
Chemical name:	*N*-[5-[[4-[4-[(Dimethylamino)methyl]-3-phenyl-1*H*-pyrazol-1-yl] pyrimidin-2-yl]amino]-4-methoxy-2-(morpholin-4-yl)phenyl]acrylamide methanesulfonate hydrate (1:1:1).
Molecular formula:	C30H34N8O3·CH4O3S·H2O
Molecular mass:	The molecular weight of lazertinib mesylate monohydrate salt is 668.77 (554.66+96.10+18.02) grams/mole; the molecular weight of the free base is 554.66 grams/mole (JNJ-73841937-AAA)

Structure:



$pKa_1 = 2.5$ (basic oxazine moiety)

$pKa_2 = 8.2$ (basic amine moiety)

Physicochemical properties:	Lazertinib (as lazertinib mesylate monohydrate) is soluble below pH 3.9, practically insoluble at, or above, pH 3.9 in aqueous media.

14. Clinical Trials

14.1. Clinical Trials by Indication

First-Line Treatment of Adult Patients With Locally Advanced or Metastatic NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations

Trial Design and Study Demographics

Table 8 - Description of the MARIPOSA study in patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations.

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)
MARIPOSA 73841937NSC3003	A Phase 3 randomized multicenter study to compare the efficacy and safety of the combination of amivantamab and lazertinib (Arm A) versus osimertinib monotherapy (Arm B) and lazertinib monotherapy (Arm C) as first-line treatment in patients with EGFRm NSCLC.	**LAZCLUZE + amivantamab arm:** • LAZCLUZE (240 mg orally, once daily). • Amivantamab IV infusion (1050 mg for body weight <80 kg and 1400 mg for body weight ≥80 kg IV), once weekly for the first 4 weeks (split dose on Cycle 1 Days 1-2) and then once every 2 weeks). **Osimertinib arm:** • osimertinib (80 mg orally, once daily). **LAZCLUZE arm:** • lazertinib (240 mg orally, once daily).	**LAZCLUZE + amivantamab arm:** N=429 **osimertinib arm:** N=429 **LAZCLUZE arm:** N=216

The MARIPOSA study is a randomized, active-controlled, multicenter phase 3 study assessing the efficacy and safety of LAZCLUZE (lazertinib) in combination with amivantamab as compared to osimertinib monotherapy as first-line treatment in 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.

A total of 1074 patients were randomized (2:2:1) to receive open label treatment with LAZCLUZE in combination with amivantamab, and double-blinded treatment with osimertinib monotherapy, or LAZCLUZE monotherapy (an unapproved regimen for NSCLC) until disease progression or unacceptable toxicity. Randomization 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). Evaluation of efficacy relied upon comparison between the LAZCLUZE + amivantamab arm and the osimertinib arm.

Baseline demographics and disease characteristics were balanced across the treatment arms. The median age in the LAZCLUZE + amivantamab arm was 64 (range: 25–88) years, and 63.0 (range 28-88) years in the osimertinib arm. In the LAZCLUZE + amivantamab arm, 45% of patients were ≥ 65 years, 64% were female, 58% were Asian, and 38% were White. In the osimertinib arm, 45% of patients were ≥ 65 years, 59% were female, 59% were Asian and 38% were White. In the LAZCLUZE + amivantamab arm, baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (33%) or 1 (67%); 70% never smoked; 41% had prior brain metastases; and 97% had Stage IV cancer at screening. In the osimertinib arm, baseline ECOG performance status was 0 (35%) or 1 (65%); 69% never smoked; 40% had prior brain metastases, and 97% had Stage IV cancer at screening. With regard to EGFR mutation status, 60% were exon 19 deletions and 40% were exon 21 L858R substitution mutations for both treatment arms.

Study Results

The primary efficacy endpoint for the MARIPOSA study was progression-free survival (PFS), defined as the time from randomization until the date of objective disease progression or death, whichever came first, based on blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Key secondary endpoints were overall survival (OS), objective response rate (ORR) and duration of response (DOR).

LAZCLUZE in combination with amivantamab demonstrated a statistically significant and clinically meaningful improvement in PFS by BICR assessment, with a 30% reduction in the risk of progression compared with osimertinib (HR=0.70 [95% CI: 0.58, 0.85], p=0.0002). The corresponding median PFS was 23.7 months (95% CI: 19.12, 27.66) for the LAZCLUZE in combination with amivantamab arm and 16.6 months (95% CI: 14.78, 18.46) for the osimertinib arm.

While the ORR was comparable between the arms, the median DOR among confirmed responders was longer with LAZCLUZE in combination with amivantamab (25.8 vs 16.7 months).

Table 9 and Figure 1 summarize key efficacy results for LAZCLUZE in combination with amivantamab.

Table 9 - Efficacy Results in the MARIPOSA Study by BICR Assessment

	LAZCLUZE + amivantamab (N=429)	**Osimertinib (N=429)**
Progression-free survival (PFS)[a]		
Number of events	192	252
Median, months (95% CI)	23.7 (19.12, 27.66)	16.6 (14.78, 18.46)
HR (95% CI); p-value	0.70 (0.58, 0.85); p=0.0002	
Objective response rate (ORR)[a,b]		
ORR % (95% CI)	78% (71.4%, 82.1%)	73% (69.0%, 77.5%)
Complete response	5.4%	3.5%

	LAZCLUZE + amivantamab (N=429)	Osimertinib (N=429)
Partial response	73.0%	69.9%
Duration of response (DOR)[a,c]		
Median (95% CI), months	25.8 (20.14, NE)	16.7 (14.75, 18.53)

BICR – blinded independent central review; CI – confidence intervals
[a] BICR by RECIST v.1.1
[b] Confirmed responses in ITT population
[c] In confirmed responders

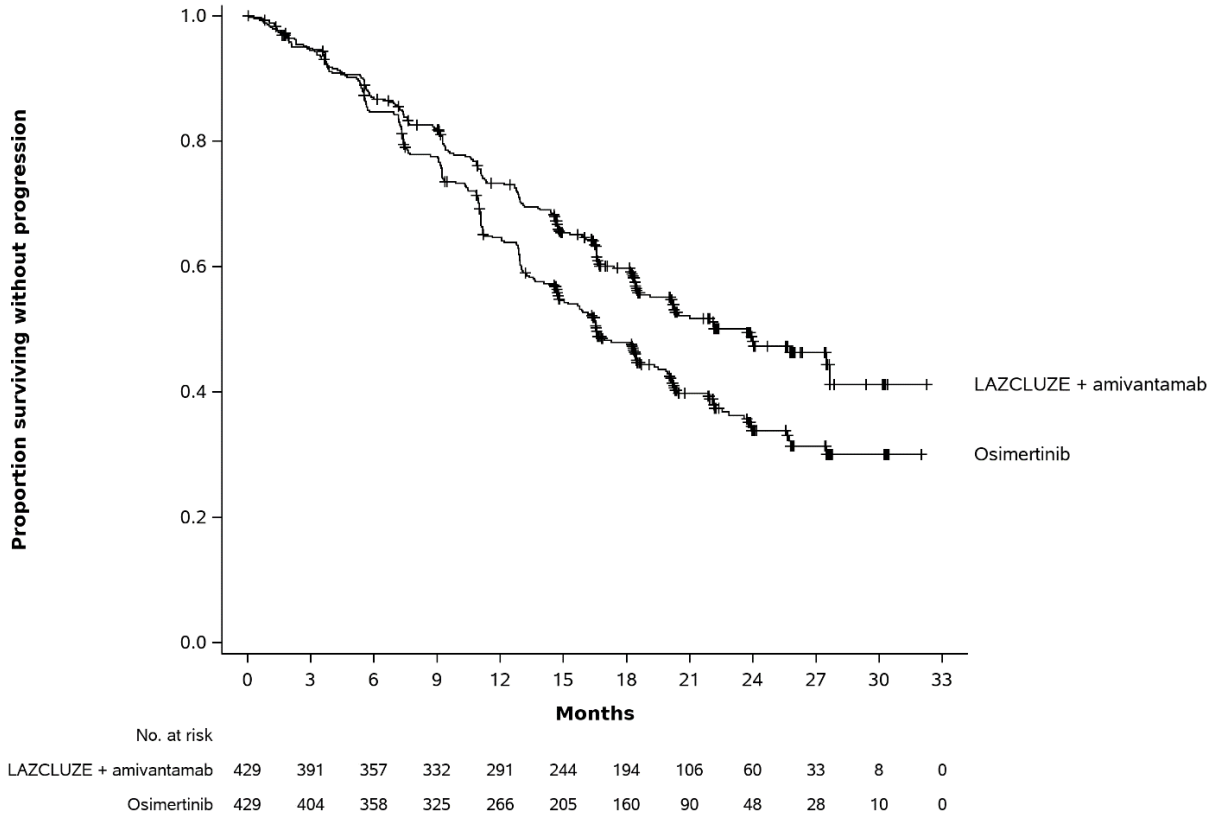


Figure 1 - Kaplan-Meier curve of PFS in previously untreated NSCLC patients by BICR assessment

The OS results were immature at the current analysis, with ~65% of pre-specified deaths for the final analysis reported. No trend towards a detriment was observed in the full analysis set.

Results of pre-specified exploratory analyses of central nervous system (CNS) ORR and DOR by BICR in the subset of patients with measurable intracranial lesions at baseline for 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 summarized in Table 10.

Table 10 - Intracranial ORR by BICR assessment in subjects with measurable intracranial lesions at baseline

	LAZCLUZE + amivantamab (N=180)	Osimertinib (N=187)
Intracranial Tumor Response Assessment		
Number of confirmed responders	122	129
Intracranial ORR (CR+PR), % (95% CI)	67.8 (60.4,74.5)	69.0 (61.8,75.5)
Complete response %	55.0	52.4

Subgroup Analyses

The outcomes of the subgroup analyses for PFS were generally consistent across the prespecified subgroups; however, differences were seen in subgroups of geriatric patients. No formal statistical testing was planned for subgroup analyses and the clinical interpretation of the subgroup analyses is therefore limited (see Table 11).

Table 11 - Progression-Free survival for pre-defined subgroups based on age in MARIPOSA study by BICR assessment

Subgroups	HR (95% CI)	Events / N LAZCLUZE + Amivantamab	Events / N Osimertinib
Age			
<65	0.50 (0.39, 0.65)	94/235	153/237
≥65	1.06 (0.80, 1.41)	98/194	99/192
<75	0.70 (0.57, 0.85)	165/378	220/376
≥75	0.77 (0.46, 1.30)	27/51	32/53

15. Microbiology

No microbiological information is required for this drug product.

16. Non-Clinical Toxicology

General Toxicity

In repeat-dose oral general toxicology studies up to 13-weeks duration in rats and dogs, lazertinib induced multi-organ histologic hyperplasia at exposures approximately equivalent or greater than the human exposure at the recommended dose of 240 mg. Hyperplasia was not reversible in the mandibular lymph node in the 4-week rat study.

In a 4-week toxicology study, lazertinib induced cardiac toxicity in two dogs characterized by histologic findings in the heart (degeneration/necrosis of the myocardium and vessels, fibrosis, hemorrhage, thrombus, mixed cell/vessel inflammation) at 20 mg/kg (approximately 4.8 times the clinical AUC at the 240 mg human dose). One of these dogs also exhibited increased cardiac troponin I and premature ventricular complexes. Myocardial degeneration, vessel inflammation, and fibrosis were not seen after a 2-week recovery period.

In the rat 4-week study, lazertinib induced renal toxicity characterized by histologic hyperplasia and inflammation in the kidney at doses ≥ 25 mg/kg (approximately 0.9 times the human exposure at the recommended dose of 240 mg/day based on AUC), along with increased urea nitrogen and histologic papillary necrosis, tubule degeneration/regeneration, and tubule dilatation at exposures approximately 4.4 times the human exposure at the recommended dose of 240 mg/day based on AUC. Increased urea nitrogen, papillary necrosis, and tubule dilatation showed evidence of recovery. In the 13-week toxicology study in dogs, one animal exhibited unilateral tubule cell renal carcinoma at 8 mg/kg/day (approximately 2 times the human exposure at the recommended dose of 240 mg/day based on AUC). Other renal findings in dogs included tubule degeneration/regeneration and infarct, which showed evidence of recovery.

In a 4-week study in rats, liver toxicity included increased single cell hepatocyte necrosis at ≥75 mg/kg/day with regenerative extramedullary hematopoiesis, and Kupffer cell hypertrophy (in males only at ≥50 mg/kg/day). At ≥75 mg/kg/day, Kupffer cell hypertrophy and single cell hepatocellular necrosis persisted and centrilobular hepatocellular vacuolation was observed in the recovery group. In a 13-week study in rats, liver enzyme increases (minimally to mildly increased ALT and AST in males at ≥12.5 mg/kg/day and a non-dose related, minimally increased AST in females at ≥25 mg/kg/day) correlated with microscopic findings of Kupffer cell hypertrophy/hyperplasia only at the high dose of 50 mg/kg/day, suggesting hepatocellular damage.

Lung inflammation and hyperplasia of alveolar type II cells were noted in both males and females in a 13-week study in dogs at 4 or 8 mg/kg/day and was resolved in males and partially recovered in females. In a 13-week study in rats, minimal to slight alveolar macrophage infiltrate was observed at 25 and 50 mg/kg/day in both sexes, with partial reversibility in males and full reversibility in females.

In a 13-week study in rats, in the 50 mg/kg/day group, corneal atrophy, corneal erosion/ulcer of the eyelids, epidermal erosion/ulcer with exudate or hyperplasia, and chronic/active inflammation in the eyelids were observed. In a 4-week study in dogs, epithelial atrophy in the cornea of the eye was present in both sexes at ≥5 mg/kg/day and showed evidence of recovery.

In a 4-week study in rats skin lesions including scabs, alopecia, hair follicle degeneration, acanthosis, erosion/ulcer, epidermal surface exudate, and mixed cell inflammation were observed at ≥50 mg/kg/day. Epidermal atrophy of the skin/subcutis was presented in a 4-week dog study at 20 mg/kg/day and showed evidence of recovery.

In a 4-week study in rats, villus blunting/fusion in duodenum was noted at ≥50 mg/kg/day and persisted in the 2-week recovery female group. In the 4- and 13-week studies in dog, esophageal epithelial atrophy was observed and showed evidence of recovery. In a 13-week study in dog, increased jejunum villi blunting/fusion and erosion/ulcer were observed in 1 female.

Carcinogenicity

No long-term animal studies have been performed to evaluate the carcinogenic potential of lazertinib.

Genotoxicity

No evidence of genotoxicity for lazertinib was observed in in vitro bacterial mutagenicity, in vitro chromosomal aberration, and in vivo micronucleus tests in rats.

Reproductive Toxicology

In a fertility and early embryonic development study in male and female rats, lazertinib induced an increase in post-implantation loss and a decrease in the number of live fetuses at 30 mg/kg/day (a dose level approximating the human clinical exposure at the recommended dose of 240 mg).

In the repeat-dose oral general toxicology studies, lazertinib induced histologic tubular degeneration in the testis; cellular lumen debris, degeneration/necrosis, and reduced sperm in the epididymis at exposures approximately equivalent to human exposure at the clinical dose. In female rats, decreased corpora lutea in the ovary and atrophy in the uterus and vagina were observed (at exposures approximately 2 times the human exposure at the recommended clinical dose). Findings in female reproductive organs were reversible. The tubular degeneration in the testis observed in rats at exposures approximately 4 times the human exposure at the recommended dose was not reversible within a 2-week recovery period.

In embryo-fetal development rat study adverse effects at 60 mg/kg/day included significant decreases in maternal body weight gain, overall body weight, food consumption and gravid uterine weight suggesting maternal toxicity at this dose. Decreases in fetal body weights in association with maternal toxicity were observed in rats at 60 mg/kg/day (exposure approximately 4 times higher than the human clinical exposure at 240 mg)

In an embryo-fetal development study in rabbits, lazertinib caused maternal toxicity (reduced body weight and food consumption leading to moribund condition and early termination) and misaligned caudal vertebra and unossified hyoid bone were observed in fetuses at 45 mg/kg/day, a maternal exposure approximating the human clinical exposure at 240 mg.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrLAZCLUZE®

lazertinib tablets

This Patient Medication Information is written for the person who will be taking **LAZCLUZE**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have questions about this medication or want more information about LAZCLUZE, talk to a healthcare professional.

Your cancer is treated with **LAZCLUZE** in combination with another medication called amivantamab. Read the Patient Medication Information for amivantamab as well as this one.

Serious warnings and precautions box

Interstitial Lung Disease and pneumonitis have been seen in patients taking LAZCLUZE. These conditions can cause the lungs to be inflamed and permanently scarred. They may lead to death in some cases.

What LAZCLUZE is used for:

LAZCLUZE is used in combination with another cancer medicine, 'amivantamab'. It is used to treat adults with a type of lung cancer called 'non-small cell lung cancer' that:

- has spread to other parts of the body or cannot be removed by surgery, and
- has changes (mutations) in a gene called EGFR (epidermal growth factor receptor). These changes are exon 19 deletions or exon 21 substitution mutations of the EGFR gene.

This will be checked with a test done by your healthcare professional before LAZCLUZE is used to make sure it is right for you.

How LAZCLUZE works:
LAZCLUZE works by blocking EGFR. It may help to slow or stop your lung cancer from growing. It may also help to reduce the size of the tumor.

The ingredients in LAZCLUZE are:
Medicinal ingredients: lazertinib mesylate

Non-medicinal ingredients: black iron oxide (240 mg tablet), croscarmellose sodium, glycerol monocaprylocaprate type I, hydrophobic colloidal silica, macrogol (PEG), magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl alcohol, red iron oxide (240 mg tablet), titanium dioxide, talc, yellow iron oxide (80 mg tablet)

LAZCLUZE comes in the following dosage forms:

Tablets, 80 mg, and 240 mg lazertinib (as lazertinib mesylate)

Do not use LAZCLUZE if:
- you are allergic to lazertinib or any of the other ingredients in LAZCLUZE or the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LAZCLUZE. Talk about any health conditions or problems you may have, including if you:

- have eye problems
- have or have ever had heart problems
- are over the age of 65

Other warnings you should know about:

Keratitis can happen in patients receiving LAZCLUZE. This is an eye condition where the coloured part of the eye is inflamed. If you have eye problems that are getting worse or eye pain, tell your healthcare professional right away. They may refer you to an eye specialist. If you use contact lenses and experience new eye problems, stop using the contact lenses until your heatlhcare professional checks your eyes.

Venous thromboembolic events can happen in patients treated with LAZCLUZE. This is a condition where a blood clot forms in a vein. These are more likely to happen in the first 4 months of treatment. Your healthcare professional will monitor you for signs of blood clots. They may give you medications to prevent and treat blood clots for at least the first 4 months of your treatment.

Skin and nail problems: While you are taking LAZCLUZE, you may get nail problems, rash, itching, dry skin and palms or soles of the feet that are red, swollen and painful. These are more likely to happen in areas exposed to the sun. While you are taking LAZCLUZE and for 2 months after your last dose limit your time in the sun, wear protective clothing and apply sunscreen. Consider also using moisturizers and anti-dandruff shampoo starting on the first day of treatment and continuing during your treatment. Your healthcare professional may also give you other medications to help prevent or treat these conditions. They may also recommend that you see a dermatologist.

Pregnancy, birth control and breastfeeding:

Female patients:
- If you are pregnant, think you might be pregnant, or are planning to have a baby, there are specific risks you should discuss with your healthcare professional.
- You should not take LAZCLUZE if you are pregnant unless the benefits to you outweigh the risks to your baby. LAZCLUZE may harm your unborn baby. Your healthcare professional will verify if you are pregnant before you start taking LAZCLUZE.
- Avoid becoming pregnant while you are taking LAZCLUZE. Use effective birth control during your treatment and for 3 weeks after your last dose.
- If you become pregnant or think you might be pregnant during your treatment, tell your healthcare professional right away. You and your healthcare professional will decide whether you should continue taking LAZCLUZE.
- Do not breast-feed while you are taking LAZCLUZE and for 3 weeks after your last dose.

Male patients:
- Avoid fathering a child while you are taking LAZCLUZE.
- During your treatment with LAZCLUZE and for 3 weeks after your last dose:

- Use a condom each time you have sex with a female partner.
- Do not donate or store sperm.

Fertility: Taking LAZCLUZE may make it more difficult for women to get pregnant and for men to father a child.

Driving and using machines: If you experience vision problems, dizziness, problems concentrating or in your ability to react, do not drive or use machines until your symptoms get better.

Tests:

- Your healthcare professional will do blood tests before you start LAZCLUZE. These will be repeated regularly during your treatment. They will tell your healthcare professional about the levels of potassium, calcium and magnesium in your blood.
- Before starting LAZCLUZE, patients who are at risk for heart problems will have other tests done to measure how their hearts are working. During treatment with LAZCLUZE, patients who have signs of heart problems may also have these tests done. The results will tell the healthcare professional if LAZCLUZE is affecting the hearts of these patients.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with LAZCLUZE:

- medicines used to treat seizures or fits called carbamazepine or phenytoin
- a medicine used to treat tuberculosis called rifampin
- a medicine used to treat fungal infections called itraconazole
- a herbal product used to treat mild depression and anxiety called St. John’s wort
- a medicine used to treat seizures or cause sleepiness before surgery called midazolam
- a medicine to lower cholesterol called rosuvastatin
- a medicine used in the treatment of HIV called efavirenz

How to take LAZCLUZE:

- Always take this medicine exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Take LAZCLUZE 1 time each day with or without food. Swallow LAZCLUZE tablets whole. Do not cut, crush, or chew the tablets.
- On the day amivantamab is also given, take LAZCLUZE before at any time before amivantamab.
- If you vomit after taking LAZCLUZE, do not take another dose. Wait until your next dose is due.

Usual dose:

Adults: 240 mg, once daily.

Your healthcare professional may temporarily or permanently stop your treatment or lower your dose. This may happen if you have side effects.

If you need a lower dose, your healthcare professional will tell you how much LAZCLUZE to take.

Overdose:

If you think you, or a person you are caring for, have taken too much LAZCLUZE contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:
If you miss a dose of LAZCLUZE and,

- there are less than 12 hours until your next dose is due, skip the missed dose. Take your next dose at its usual time.
- there are more than 12 hours until your next dose, take your dose as soon as you remember it.

Possible side effects from using LAZCLUZE:
These are not all the possible side effects you may feel when taking LAZCLUZE. If you experience any side effects not listed here, tell your healthcare professional.

- inflamed eye
- nosebleed
- bleeding gums
- constipation
- hemorrhoids
- nausea
- vomiting
- decreased appetite
- tingling, numbness, pain or loss of pain sensation
- headache
- dizziness
- feeling very tired
- muscle spasms and aches
- joint pain
- pain in the arms and legs
- back pain
- swelling
- fever
- hives
- hair loss
- blood in urine

LAZCLUZE can cause abnormal blood test results. Your healthcare professional will do blood tests during your treatment and will interpret the results.

Serious side effects and what to do about them

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Venous Thromboembolism (a blood clot in the veins, especially in the lungs or legs): sharp chest pain, shortness of breath, rapid breathing, leg pain, and swelling of your arms or legs. Can be fatal.		✓	
Skin and nail problems: rash (including acne), dry skin, itching, pain, and redness, nail infection (red, hot and painful pus-filled blisters around the nail, with swelling. Detached, discoloured or abnormally shaped nails), palms or soles of feet that are red, swollen and painful		✓	
COMMON			
Lung Problems (interstitial lung disease and pneumonitis pneumonia): serious or suddenly worse shortness of breath, tiredness possibly with a cough or fever, painful breathing. May be fatal			✓
Eye Problems: eye redness, eye pain, vision problems, sensitivity to light, dry eye, blurred vision, growth of eyelashes.		✓	
Heart problems (left ventricular dysfunction, cardiomyopathy and congestive heart failure): tiredness along with swollen ankles, shortness of breath especially when lying down			✓
Stomatitis (inflammation of the mouth and lips): ulcers, sore red and inflamed lips or inside the mouth	✓		

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Diarrhea: loose bowel movements that come and go, at least 3 loose liquid bowel movements a day	✓		
Jaundice: yellowing of the skin or eyes		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting canada.ca/drug-device-reporting for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 15°C to 30°C. Keep out of the sight and reach of children.

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

If you want more information about LAZCLUZE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (innovativemedicine.jnj.com/canada), or by calling 1-800-567-3331 or 1-800-387-8781.

This leaflet was prepared by: Janssen Inc., a Johnson & Johnson company, Toronto, Ontario, M3C 1L9

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