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

AUSTRALIAN PRODUCT INFORMATION

LAZCLUZE® (lazertinib)

Film-coated tablets

1. NAME OF THE MEDICINE

Lazertinib (as mesilate monohydrate)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 80 mg or 240 mg of lazertinib (as mesilate monohydrate).

For the full list of excipients, see section 6.1 List of Excipients.

3. PHARMACEUTICAL FORM

80 mg tablets
Yellow, oval film-coated tablet, debossed with “LZ” on one side and “80” on the other side.

240 mg tablets
Reddish purple, oval film-coated 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 locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Dosage – adults (≥18 years)

The recommended dosage of LAZCLUZE is 240 mg orally once daily 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. Refer to the amivantamab product information for recommended amivantamab dosing information.

Prior to the use of LAZCLUZE, the presence of the relevant EGFR mutation (exon 19 deletion or exon 21 L858R substitution) must be established (see Section 5.1 Clinical trials).

When initiating treatment with LAZCLUZE in combination with amivantamab, it is recommended to administer anticoagulant prophylaxis to prevent venous thromboembolic (VTE) events for the first four months of treatment. Ongoing anticoagulation beyond four months is at clinician's discretion. Anticoagulants use should align with clinical guidelines, use of Vitamin K antagonists is not recommended (See Section 4.4 Special warnings and precautions for use).

Missed dose(s)

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.

Dose modifications

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

Table 1: Recommended 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 dose modifications for adverse reactions,

Adverse reaction	Severity	Dose modification
Interstitial Lung Disease (ILD) / pneumonitis (see section 4.4)	Any grade	• Withhold LAZCLUZE if ILD/pneumonitis is suspected. • Permanently discontinue LAZCLUZE if ILD/pneumonitis is confirmed.
Venous Thromboembolic (VTE) Events (see section 4.4)	Grade 2 or 3	• Withhold LAZCLUZE and amivantamab until the patient is clinically stable. Thereafter, both drugs can be resumed at the same dose, at the discretion of the treating physician.
	Grade 4 or recurrent grade 2 or 3 despite therapeutic level anticoagulation	• Permanently discontinue amivantamab. Treatment can resume with LAZCLUZE at the same dose, if clinically warranted.
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	• Initiate supportive care management. Withhold LAZCLUZE and amivantamab. • Upon recovery to ≤ Grade 2, resume both drugs 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)	• Permanently discontinue amivantamab. • Withhold LAZCLUZE until ≤ Grade 2 or baseline. • Upon recovery to ≤ Grade 2, resume LAZCLUZE at the same dose or consider dose reduction.
Hepatotoxicity	Grade 3-4	• Withhold LAZCLUZE and amivantamab.

		• Upon recovery to ≤ Grade 1, resume both drugs at the same dose or consider dose reduction, preferentially reducing the dose of amivantamab first.
Other adverse reactions	Grade 3-4	• Withhold both LAZCLUZE and amivantamab until the adverse reaction resolves to ≤ Grade 1 or baseline. • Resume one or both drugs, 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 the amivantamab product information for information about dose modifications for amivantamab.

Special populations

Paediatrics (17 years of age and younger)

The safety and efficacy of LAZCLUZE have not been established in paediatric patients.

Elderly (65 years of age and older)

Among 421 patients with non-small cell lung cancer treated with LAZCLUZE in combination with amivantamab in NSC3003 (MARIPOSA), 44.7% were 65 years and older and 11.6% were 75 years and older. 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%). No dose adjustment based on age is required (see Section 5.2 Pharmacokinetic properties).

Renal impairment

No dose adjustment is recommended in patients with mild or moderate renal impairment. Lazcluze has not been studied in patients with severe renal impairment or end-stage renal disease (eGFR < 30mL/min). (see Section 5.2 Pharmacokinetic properties).

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 Pharmacokinetic properties).

Administration

This 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, take the next dose the next day.

4.3 CONTRAINDICATIONS

Hypersensitivity to lazertinib or to any of the excipients listed in section 6.1 List of Excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Interstitial lung disease (ILD)/pneumonitis

Interstitial lung disease (ILD)/pneumonitis, including fatal events, have been reported in patients receiving LAZCLUZE (see section 4.8 Adverse Effects (Undesirable Effects)). 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.

Monitor patients for symptoms indicative of ILD/pneumonitis (e.g., dyspnoea, 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 Section 4.2 Dose and method of administration, Table 2).

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 with amivantamab. VTE events occurred predominantly in the first four months of therapy (see section 4.8 Adverse Effects (Undesirable Effects)).

Prophylactic anticoagulants are recommended to be used for the first four months of treatment. Ongoing anticoagulation beyond four months is at clinician's discretion. 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 VTE events associated with clinical instability, treatment should be held until the patient is clinically stable. Thereafter, both LAZCLUZE and amivantamab can be resumed at the discretion of the treating physician.

In the event of recurrence despite appropriate anticoagulation, permanently discontinue amivantamab. Treatment can continue with LAZCLUZE at the same dose, if clinically warranted (see Section 4.2 Dose and method of administration, Table 2).

Skin and nail reactions

Skin and nail reactions may occur when treated with LAZCLUZE.

Rash (including dermatitis acneiform), pruritus and dry skin occurred in patients receiving LAZCLUZE with amivantamab therapy (see section 4.8 Adverse Effects (Undesirable Effects)). Instruct patients to limit sun exposure during and for 2 months after LAZCLUZE therapy.

A prophylactic approach to rash prevention should be considered. 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 for dry areas with the use of LAZCLUZE. If skin or nail reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 or poorly-tolerated Grade 2 events, add systemic antibiotics and oral steroids and consider dermatologic consultation. Withhold, reduce dose, or permanently discontinue LAZCLUZE based on severity (see Section 4.2 Dose and method of administration, Table 2).

Eye disorders

Keratitis occurred in patients receiving LAZCLUZE with amivantamab (see section 4.8 Adverse Effects (Undesirable Effects)). Refer patients presenting with worsening eye symptoms promptly to an ophthalmologist and advise discontinuation of contact lenses until symptoms are evaluated.

Use in the elderly

See section 4.2 Dose and method of administration.

Paediatric use

The safety and efficacy of LAZCLUZE have not been established in paediatric patients.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of other drugs on lazertinib

Strong 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 CYP3A4 inducers. Avoid concomitant use of LAZCLUZE with strong and moderate CYP3A4 inducers.

Strong CYP3A4 inhibitors

The co-administration of 160 mg lazertinib with itraconazole (strong CYP3A4 inhibitor) increased lazertinib plasma exposure by less than 50%. 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. No dose adjustments are required when LAZCLUZE is used with 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 Lazertinib on other drugs

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.

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.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effect of LAZCLUZE on human fertility. Studies in animals have shown that lazertinib may impair male and female fertility. In a rat fertility and early embryonic development study in treated male and female, lazertinib did not affect oestrous cyclicity, mating, fertility or sperm parameters, but induced an increase post-implantation loss and decreased live litter size at 30 mg/kg/day, a dose level approximating the human clinical exposure at the recommended dose of 240 mg. As well, histological changes (e.g. tubular degeneration in the testis, cellular lumen debris, degeneration/necrosis, and reduced sperm in the epididymis; decreased corpora lutea in the ovary and atrophy of the uterus and vagina) observed in the reproductive organs of male and females from rat and dog repeat dose toxicity studies were suggestive of possible impairments to fertility.

Use in pregnancy – Pregnancy Category D

There are no data from the use of lazertinib in pregnant women. In rat embryo-fetal development studies, increased post-implantation losses were observed in a dose-range finding study at 75 mg/kg/day (equivalent to 2.8 times the clinical dose based on body surface area), and decreases in fetal body weights in association with maternal toxicity in the main study at 60 mg/kg/day, which achieved maternal exposures 3.6 times above human clinical exposure at 240 mg. In rabbits there was an increased incidence of skeletal malformations and variations (skull fused maxillary process/zygomatic arch, misaligned vertebra caudal) at 45 mg/kg/day (maternal exposure 0.4 times the human clinical exposure at 240 mg).

Based on its mechanism of action and animal data, lazertinib may cause fetal harm when administered to a pregnant woman. Lazertinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with lazertinib.

Verify the pregnancy status of females of reproductive potential prior to initiating LAZCLUZE.

Advise females 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.

Use in lactation

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.

4.7 EFFECTS OF ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial data

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the

clinical trials of another drug and may not reflect the rates observed in practice.First-line treatment of NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutation

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 tumours have EGFR exon 19 deletion or exon 21 L858R substitution mutation in MARIPOSA.

Table 3 summarises the adverse reactions (≥ 10%) in MARIPOSA.

Table 3: Adverse Reactions (≥ 10%) in Patients with NSCLC with Exon 19 Deletion or Exon 21 L858R Substitution Mutations in MARIPOSA

Adverse Reaction	LAZCLUZE in combination with amivantamab (N=421)		Osimertinib (N=428)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders				
Rash*	86	26	48	1.2
Nail toxicity*	71	11	34	0.7
Dry skin*	25	1	18	0.2
Pruritus	24	0.5	17	0.2
Injury, poisoning and procedural complications				
Infusion-related reaction†	63	6	0	0
Hepatobiliary disorders				
Hepatotoxicity	47	9	25	4.4
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	47	2.1	39	1.9
Gastrointestinal disorders				
Stomatitis*	43	2.4	27	0.5
Diarrhoea*	31	2.6	45	0.9
Constipation	29	0	13	0
Nausea	21	1.2	14	0.2
Vomiting	12	0.5	5	0
Abdominal pain*	11	0	10	0
Haemorrhoids	10	0.2	2.1	0.2
General disorders and administration site conditions				
Oedema*	43	2.6	8	0
Fatigue*	32	3.8	20	1.9
Pyrexia	12	0	9	0
Vascular disorders				
Venous thromboembolism*	36	11	8	2.8
Haemorrhage*	25	1	13	1.2
Nervous system disorders				
Paraesthesia*	35	1.7	10	0.2
Dizziness*	14	0	10	0
Headache*	13	0.2	13	0
Infections and infestations				
COVID-19	26	1.7	24	1.4
Conjunctivitis	11	0.2	1.6	0
Metabolism and nutrition disorders				
Decreased appetite	24	1	18	1.4
Respiratory, thoracic and mediastinal disorders				
Cough*	19	0	23	0
Dyspnoea*	14	1.7	17	3.5
Eye disorders				
Ocular toxicity*	16	0.7	7	0
Psychiatric disorders				
Insomnia	10	0	11	0

* Grouped terms

† Applicable only to amivantamab

Clinically relevant adverse reactions occurring in < 10% of patients who received LAZCLUZE in combination with amivantamab included ILD/pneumonitis (3.1%).

Table 4 summarises the laboratory abnormalities in MARIPOSA.

Table 4: Select laboratory abnormalities (≥ 20%) that worsened from baseline in first-line patients with 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	<1	15	<1
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	15	1
Increased creatinine	26	1	35	1
Decreased magnesium	25	1	10	<1
Increased magnesium	12	3	20	5
Haematology				
Decreased platelet count	52	1	57	1
Decreased haemoglobin	47	4	56	2
Decreased white blood dell	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.

Description of selected adverse reactions

Venous thromboembolism

Venous thromboembolic (VTE) events, including deep vein thrombosis and pulmonary embolism (PE), were reported in 36% 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 lazertinib discontinuation in 1.9% 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 86% of patients treated with lazertinib in combination with amivantamab. Most cases were Grade 1 or 2, with Grade 3 events occurring in 26% of patients. Rash leading to lazertinib discontinuation occurred in 1.7% 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 35% 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 31% of patients treated with lazertinib in combination with amivantamab. Most events were Grade 1-2, with Grade 3 diarrhoea occurring in 2.6% of patients.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms and signs

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.

Treatment

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 information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, ATC code: L01EB09

Mechanism of action

Lazertinib is a third generation, EGFR tyrosine kinase inhibitor (TKI) that 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. Lazertinib demonstrated anti-tumour activity in human NSCLC cells and mouse xenograft models of EGFR exon 19 deletions or L858R substitution mutations. Treatment with lazertinib in combination with amivantamab increased *in vivo* anti-tumour activity compared to either agent alone in mouse xenograft models of human NSCLC with an EGFR L858R mutation.

Pharmacodynamic effects

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.

Effect on QT/QTc interval and cardiac electrophysiology

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 I/II study. The E-R analysis revealed no clinically relevant relationship between lazertinib plasma concentration and change in QTc interval. The 2-sided upper bound of 90% CI at steady state C_{max} from the recommended dose of 240 mg once daily and highest tested clinical dose of 320 mg once daily was 5.83 and 7.23 msec respectively.

Clinical trials

NSC3003 (MARIPOSA) is a randomised, active-controlled, multicentre phase 3 study assessing the efficacy and safety of LAZCLUZE 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. Central cobas tissue testing (using the cobas® EGFR Mutation Test v2) was concordant with local testing in 96.3% of the samples with a valid cobas tissue test result.

A total of 1074 patients were randomised (2:2:1) to receive LAZCLUZE in combination with amivantamab, osimertinib monotherapy, or LAZCLUZE monotherapy (an unapproved regimen for NSCLC) 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; 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 and clinically meaningful improvement in progression-free survival (PFS) by BICR assessment, with a 30% reduction in the risk of progression or death compared with osimertinib (HR=0.70 [95% CI: 0.58, 0.85], p=0.0002). The corresponding median PFS was 23.72 months (95% CI: 19.12, 27.66) for

the LAZCLUZE in combination with amivantamab arm and 16.59 months (95% CI: 14.78, 18.46) for the osimertinib arm.

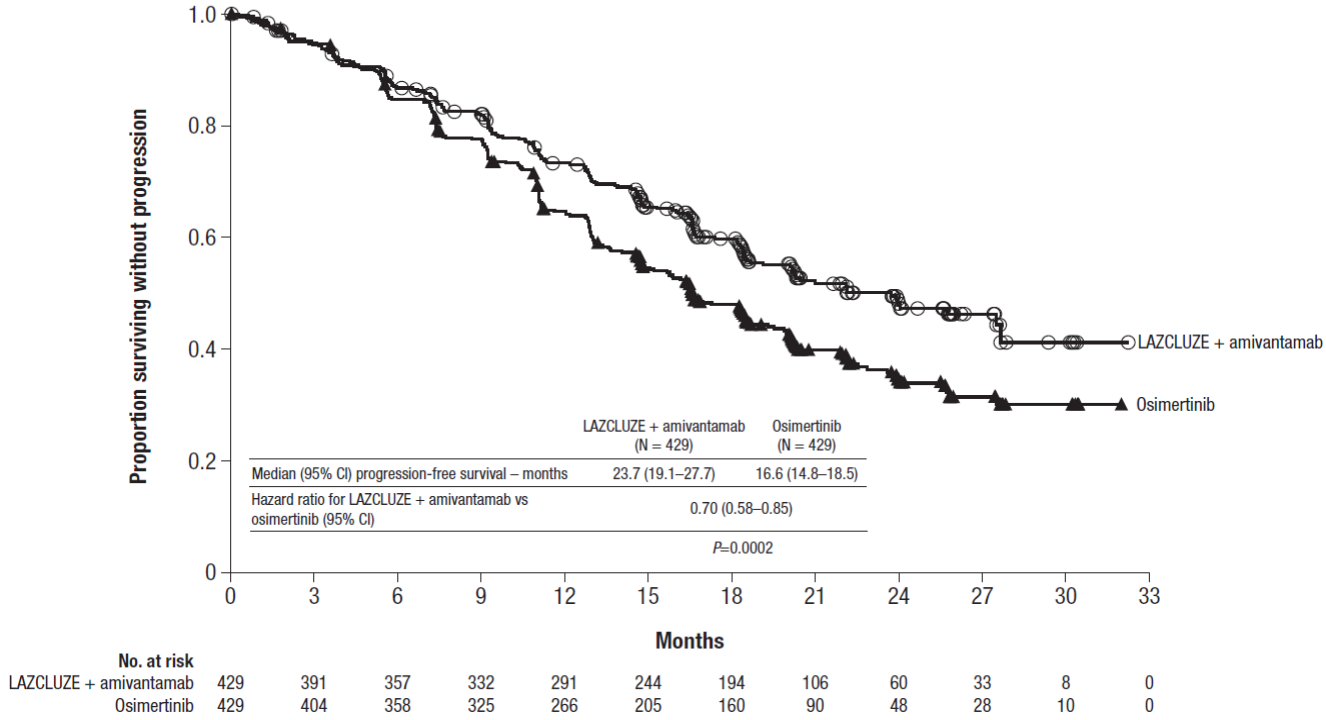
While OS results were immature at the current analysis, with 55% of pre-specified deaths for the final analysis reported, no trend towards a detriment was observed.

Table 5: Efficacy Results in MARIPOSA by BICR Assessment

	LAZCLUZE in combination with amivantamab (N=429)	**Osimertinib (N=429)**
Progression-free survival (PFS)		
Number of events (%)	192 (45)	252 (59)
Median, months (95% CI)	23.7 (19.1, 27.7)	16.6 (14.8, 18.5)
HR[1,2] (95% CI); p-value[1,3]	0.70 (0.58, 0.85); p=0.0002	
Overall response rate (ORR)[4]		
ORR, % (95% CI)	78 (74, 82)	73 (69, 78)
Complete response, %	5	3.5
Partial response, %	73	70
Duration of response (DOR)[5]		
Median (95% CI), months	25.8 (20.1, NE)	16.7 (14.8, 18.5)
Patients with DOR ≥ 6 months[6], %	86	85
Patients with DOR ≥ 12 months[6], %	68	57

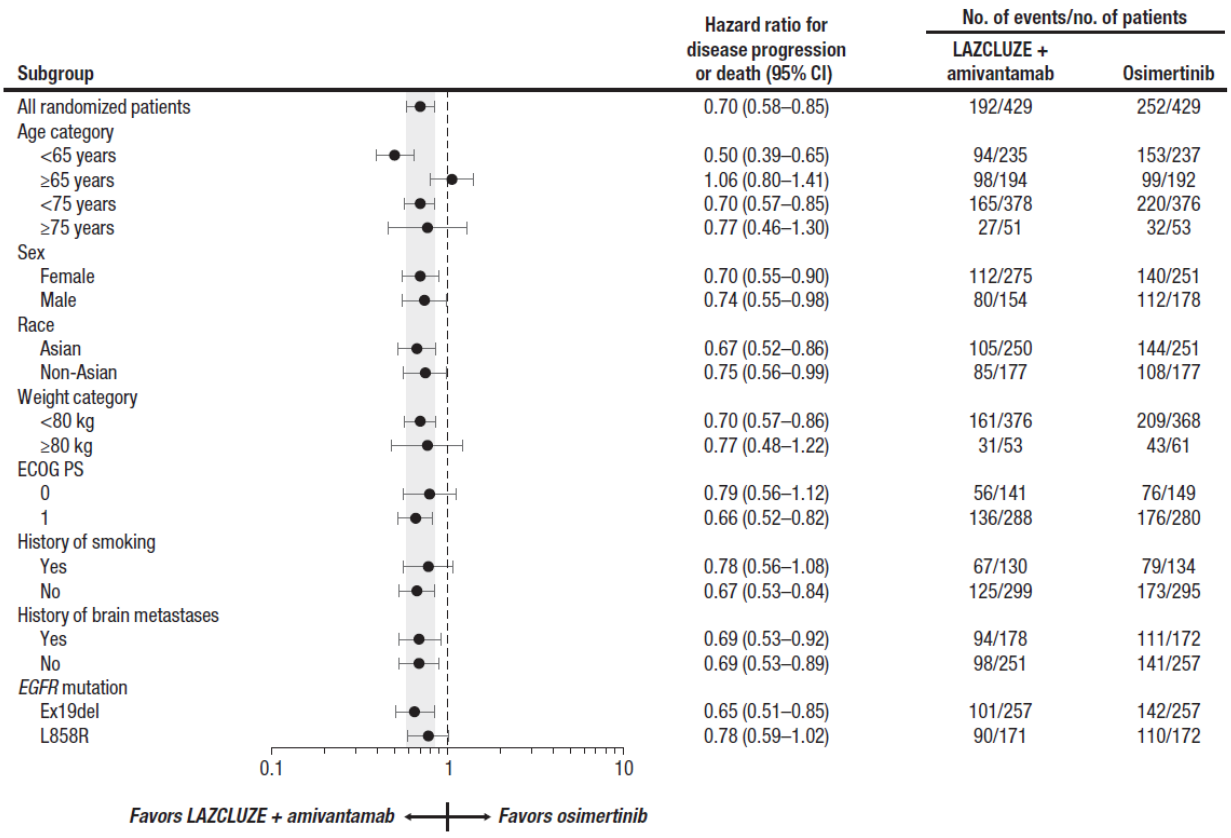
CI = confidence interval; NE = not estimable
[1]Stratified by mutation type (Exon 19del or Exon 21 L858R), prior brain metastases (yes or no), and Asian race (yes or no).
[2]Stratified Cox proportional hazards regression.
[3]Stratified log-rank test.
[4]Confirmed responses based on the ITT population.
[5]In confirmed responders.
[6]Based on observed rates.

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



The PFS benefit of LAZCLUZE in combination with amivantamab as compared to osimertinib was generally consistent across prespecified, clinically relevant subgroups, including age group, sex, race, weight, mutation type, ECOG performance status, history of smoking, and history of brain metastasis at study entry (See Figure 2).

Figure 2: Forest plot of PFS in previously untreated NSCLC patients by BICR assessment



The MARIPOSA study included protocol-mandated brain magnetic resonance imaging (MRIs), which have historically not been used in trials evaluating EGFR-mutated NSCLC. This may have led to earlier detection of recurrences and associated shorter median values for PFS. To account for this, a sensitivity analysis was done whereby patients with brain-only progression as the site of first progression were censored. Extracranial PFS based on BICR assessment was consistent with the treatment benefit observed in the primary analysis. The median extracranial PFS was 27.5 months with LAZCLUZE in combination with amivantamab, as compared to 18.37 months with osimertinib (HR=0.68 [95% CI: 0.55, 0.83], nominal p=0.0001).

The stratified analysis of investigator-assessed PFS shows that the improved treatment effect of the combination of LAZCLUZE and amivantamab relative to osimertinib was also observed (median PFS of 23.92 months in the RYBREVANT in combination with lazertinib arm, compared to median of 19.94 months in the osimertinib arm (HR of 0.79 [95% CI: 0.65, 0.95, nominal p=0.0139])) when assessed by investigator. Results for the analysis of ORR based on investigator assessment for comparison of the LAZCLUZE in combination with amivantamab arm versus the osimertinib arm were consistent with results for ORR based on BICR assessment.

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 summarised in Table 6.

Table 6: Intracranial ORR and DOR by BICR Assessment in Subjects with Measurable Intracranial Lesions at Baseline

	LAZCLUZE + amivantamab (N=180)	Osimertinib (N=187)	LAZCLUZE (N=93)
Intracranial Tumour Response Assessment			
Intracranial ORR (CR+PR), % (95% CI)	76.7 (69.8, 82.6)	76.5 (69.7, 82.4)	74.2 (64.1, 82.7)
Complete response %	62.2	57.8	54.8
Intracranial DOR			
Number or responders	138	143	69
Response duration ≥6 months, %	77.5	77.6	79.7
Response duration ≥12 months, %	58.0	53.8	52.2
Response duration ≥18 months, %	31.2	21.0	18.8

CI = confidence interval

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.

Metabolism

Lazertinib is primarily metabolised by glutathione conjugation, either enzymatic via glutathione-S-transferase (GST) or non-enzymatic, as well as by CYP3A4-mediated oxidative metabolism. The most abundant metabolites are glutathione catabolites and considered clinically inactive. The plasma exposure of lazertinib was affected by GST mu 1 (GSTM1) genotype, leading to lower exposure (less than 2-fold difference) in Non-null GSTM1 patients. No dose adjustment is required based on GSTM1 status.

Excretion

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.

Following a single oral dose of radiolabeled lazertinib, approximately 86% of the dose was recovered in faeces (<5% as unchanged) and 4% in urine (<0.2% as unchanged).

Special populations

Paediatrics (17 years of age and younger)

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

Elderly (65 years of age and older)

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).

Other populations

No clinically meaningful differences in lazertinib PK were observed based on age, sex, body weight, race, ethnicity, hepatic function, renal function, 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

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.

Carcinogenicity

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of lazertinib.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core:
hydrophobic colloidal silica anhydrous
microcrystalline cellulose
mannitol
croscarmellose sodium
magnesium stearate

80 mg tablet film coating:
OPADRY QX Quick and FleXible Film Coating System 321A220024-CN Yellow (PI 147702)

240 mg tablet film coating:
OPADRY QX Quick and FleXible Film Coating System 321A200022-CN Purple (PI 147703)

6.2 INCOMPATIBILITIES

See section 4.5 Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Blister pack

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

- 80 mg tablets packaged in 56-count blister pack (2 dosepaks containing 28 tablets each).
- 240 mg tablets packaged in 14-count blister pack (1 dosepak containing 14 tablets) or 28-count blister pack (2 dosepaks containing 14 tablets each).

Bottle

White opaque high-density polyethylene (HDPE) bottle with polypropylene child-resistant closure.

- 80 mg tablets packaged in a 60-count bottle or 90-count bottle.
- 240 mg tablets packaged in a 30-count bottle.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

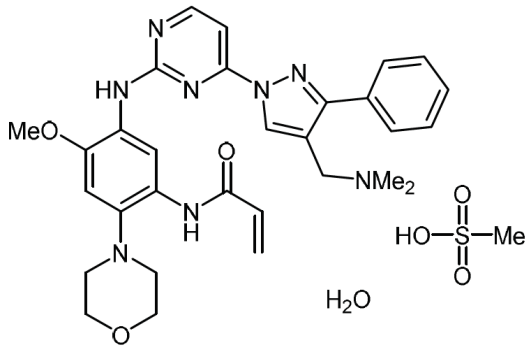
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Lazertinib mesilate monohydrate is an almost white to slightly yellow-brown powder. It is soluble below pH 3.9, practically insoluble at or above pH 3.9 in aqueous media, and slightly soluble to

freely soluble in organic solvents. There are two dissociation constants, a pKa_1 of 2.5 (basic oxazine moiety) and a pKa_2 of 8.2 (basic amine moiety).

Chemical structure



Molecular formula: $C_{30}H_{34}N_8O_3 \bullet CH_4O_3S \bullet H_2O$
Molecular weight: 668.77 (lazertinib mesilate monohydrate salt) 554.66 (free base)

CAS number

1903008-80-9 lazertinib
2411549-88-5 lazertinib mesilate monohydrate

7. MEDICINE SCHEDULE (POISON STANDARD)

S4 Prescription Medicine

8. SPONSOR

Janssen-Cilag Pty Ltd
1-5 Khartoum Road
Macquarie Park NSW 2113
AUSTRALIA

Telephone: 1800 226 334

9. DATE OF FIRST APPROVAL

15 Apr 2025

10. DATE OF REVISION

21 October 2025

Summary table of changes

Section changed	Summary of new information
4.2, 4.8	Addition of hepatotoxicity as adverse reactions