swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Lazcluze

International non-proprietary name:	lazertinib
Pharmaceutical form:	film-coated tablets
Dosage strength(s):	80 mg and 240 mg
Route(s) of administration:	oral
Marketing authorisation holder:	Janssen-Cilag AG
Marketing authorisation no.:	69751
Decision and decision date:	approved on 07.02.2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for lazertinib, lazertinib mesylate monohydrate in the above-mentioned medicinal product.

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is coordinated by the FDA and provides a framework for concurrent submission and review of oncology products among international partners.

2.2 Indication and dosage

2.2.1 Requested indication

Lazcluze is indicated in combination with amivantamab for 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.

2.2.2 Approved indication

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 (see "Warnings and Precautions" and "Clinical Efficacy").

2.2.3 Requested dosage

Summary of the requested standard dosage:
The proposed dosing regimen for lazertinib is 240 mg administered orally once daily.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	8 February 2024
Formal control completed	13 February 2024
Preliminary decision	30 August 2024
Response to preliminary decision	20 October 2024
Labelling corrections and/or other aspects	26 November 2024
Response to labelling corrections and/or other aspects	29 December 2024
Final decision	7 February 2025
Decision	approval

3 Medical context

Treatment of lung cancer patients depends on the histology, molecular characteristics, tumour stage, and an assessment of the patient's overall medical condition. An improved understanding of the molecular pathways that drive malignancy in NSCLC has led to the development of agents that target specific molecular pathways in malignant cells. Therapy can then be individualised based on the specific abnormality, if any, present in a given patient. Among patients with NSCLC, the most prevalent of these abnormalities are driver mutations that result in the activation of EGFR, which are identified in approx. 10-15% of adenocarcinomas in Western populations. EGFR driver mutations in other histological subtypes are rare.

The most frequently identified EGFR mutations are exon 19del and L858R, prevalent in 80-85% of patients with activating EGFR mutations. These can be effectively targeted by multiple EGFR tyrosine kinase inhibitors (TKIs) that are already approved for the treatment of advanced or metastatic EGFR-mutated (mEGFR+) NSCLC.

4 Quality aspects

4.1 Drug substance

INN: lazertinib mesylate
Chemical name: N-[5-[[4-[4-[(Dimethylamino)methyl]-3-phenyl-1H-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: 668.77 g/mol
Molecular structure:

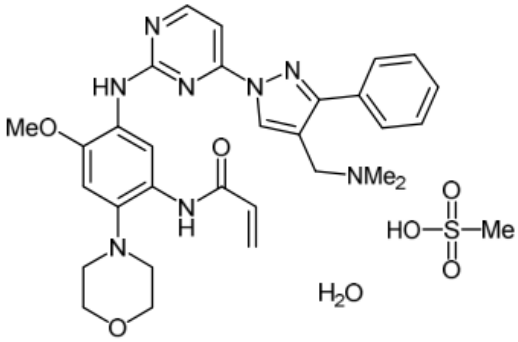

Figure 1 - Molecular structure

Physicochemical properties:
Lazertinib mesylate monohydrate is an almost white to slightly yellow-brown powder, which shows pH-dependent solubility in aqueous media and belongs to BCS class 2. It is present in its stable polymorph form 1.

Synthesis:
The drug substance is manufactured by a multiple step chemical synthesis. Two alternative synthesis pathways are described. Adequate information is provided regarding the manufacturing process, materials, critical steps, and intermediates.

Specification:
The drug substance specification includes tests for appearance, identification, assay, chromatographic purity, water content, residual solvents, residue on ignition, and particle size. The applied limits are justified and in line with the relevant guidelines and the European Pharmacopoeia, if applicable. The proposed acceptance criteria and analytical methods were considered appropriate for quality control of the drug substance.

Stability:
The bulk drug substance is packaged in double low-density polyethylene (LDPE) bags, which are placed in a drum or equivalent. A stability study, according to the current guideline recommendations, was carried out. Based on the results of this study, a satisfactory retest period has been established.

4.2 Drug product

Description and composition:
Lazcluze drug product is provided as an immediate-release (IR) film-coated tablet. The film-coated tablets are provided in 2 dosage strengths and contain 80 mg or 240 mg of the drug substance lazertinib.
The 80 mg dosage strength is an oval shaped film-coated tablet, which is yellow in colour. The tablet is debossed on one side with LZ and on the other side with 80.
The 240 mg dosage strength is an oval shaped film-coated tablet, which is reddish purple in colour. The tablet is debossed on one side with LZ and on the other side with 240.
In addition to the drug substance lazertinib mesylate monohydrate, the following excipients are present in the core tablet: silica hydrophobic colloidal, cellulose, microcrystalline, mannitol, croscarmellose sodium, and magnesium stearate.
The tablet film coating consists of glycerol monocaprylocaprate type I, iron oxide black (in 240 mg strength tablets), iron oxide red (in 240 mg strength tablets), iron oxide yellow (in 80 mg strength tablets), macrogol (PEG) polyvinyl alcohol graft copolymer, polyvinyl alcohol- partially hydrolysed, talc, and titanium dioxide.

Pharmaceutical development:
The formulation development has been adequately described. The manufacturing process development focuses on the tablet production using continuous manufacturing.

Manufacture:
The manufacturing process can be subdivided into the following stages: preblending the drug substance with an excipient in batch mode, followed by continuous feeding, in-line blending, and direct compression, followed by film coating in batch mode.
Adequate process parameters and in-process controls are defined in order to ensure a consistent quality of the tablets.

Specification:
The applied test methods for the drug product are adequately validated according to the recommendations of the current scientific guidelines. The drug product specifications include tests for appearance, identification, assay, chromatographic purity, dissolution, uniformity of dosage units, water content, and microbial purity. For release of the drug product, real-time release testing by near-infrared spectroscopy (NIR) is performed for the tests identification, assay, and uniformity of dosage units. The proposed acceptance criteria and analytical methods were considered appropriate for quality control of the drug product.

Container closure system:
Lazcluze film-coated tablets are packaged in polyvinyl chloride-polychlorotrifluoroethylene (PVC-PCTFE) film with push-through aluminium foil blisters.

Stability:
Appropriate stability data are presented for 80 mg and 240 mg Lazcluze . Based on these data, a shelf-life was established. The storage recommendation is “Do not store above 30°C” and “Store out of reach of children”.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

5.1 Pharmacology

In *in vitro* assays, lazertinib inhibited EGFR single mutants del19 (IC_{50} 5.3 nM), exon 21 L858R (IC_{50} 20.6 nM), resistant mutation T790M (IC_{50} 1.7 nM), and double mutants L858R/T790M (IC_{50} 3.7 nM) and del19/T790M (IC_{50} 3.5 nM). The compound is an irreversible inhibitor, hence the binding resulted in prolonged inhibition of downstream signalling from EGFR and its mutants. Lazertinib induced Caspase-3/7 activity and protein BimEL in PC9/del19 cells, which demonstrates its apoptotic activity.
Lazertinib showed growth inhibition (GI) of both PC9 and H1975 cell lines with mutant EGFRs del19 and L858R/T790M, with GI_{50} values of 4.7 nM and 6.3 nM in comparison to a GI_{50} of 711 nM in wild-type EGFR H2073 cells. *In vivo* studies showed that lazertinib monotherapy resulted in dose-dependent anti-tumour activity in relevant mutant subcutaneous xenograft models and models of intracranial metastatic disease in mice, while activity was reduced in one epidermoid carcinoma model with wild-type EGFR.
The combination of lazertinib and amivantamab was evaluated in a double mutant and a TKI-resistance model after administration for 21 days.
The *in vivo* anti-tumour activity of lazertinib alone and in combination with amivantamab was investigated in mice implanted SC with EGFR L858R/T790M mutant H1975 NSCLC cells engineered to overexpress hepatocyte growth factor (H1975-HGF cells), the ligand of c-MET. Treatment with 5 mg/kg/day oral lazertinib in combination with 10 mg/kg intraperitoneal (IP) amivantamab increased *in vivo* anti-tumour activity and survival compared to either agent alone. Single-agent lazertinib exhibited reduced anti-tumour activity against H1975-HGF xenografts compared to H1975 xenografts, presumably due to increased MET signalling in the H1975-HGF xenograft model. Combined treatment with lazertinib and amivantamab increased *in vivo* anti-tumour activity compared to either agent alone in mice bearing H1975 xenografts without HGF overexpression.
In vitro studies on secondary pharmacology showed inhibition of the 5-HT transporter (99.2%) and 5-HT2B (78.4%) at $IC_{50'}$ values of 40 nM and 180 nM. However, in further cellular and tissue functional assays with both transporters, effects were only observed at concentrations 12-fold and 54-fold the C_{max}, at the recommended clinical dose.
The applicant conducted safety pharmacology studies to investigate potential effects on the cardiovascular, respiratory, and central nervous systems. Lazertinib inhibited hERG potassium channel current at an IC_{50} of 5.3 µM, corresponding to 570-fold the C_{max} at the recommended clinical dose. Therefore, it is unlikely that lazertinib affects cardiac repolarisation. No relevant effects were observed in the respiratory and central nervous systems.

5.2 Pharmacokinetics

Studies provided to characterise the PK profile of lazertinib included single intravenous and oral administration in mice, rats, and dogs as well as repeated oral administration in rats and dogs.
All species rapidly absorbed lazertinib after oral administration (T_{max} 0.5-4 h), similar to human absorption. The oral bioavailability was moderate to high across species (75% to 80% in mice, 34% to 48% in rats, and 58% to 78% in dogs). Mean Vss was moderate to high, suggesting extensive tissue distribution. Plasma concentrations decreased in a biphasic manner in all species, with a mean t1/2 of 4.7 – 7.8 h.
No significant sex differences in PK parameters were observed in rats and dogs. Exposure increased proportionately to dose, with minor accumulation in repeated-dose studies (≤2.1-fold).
In a tissue distribution study with oral administration of 10 mg/kg ^{14}C-lazertinib to pigmented rats, high concentrations of radioactivity were found in the uveal tract, adrenal gland, and stomach, with low levels in muscle, spinal cord, bone, and brain. Higher radioactivity in pigmented tissues indicated melanin binding.

Plasma protein binding was high (99.1% in humans and mice, 99.0%-99.5% in rats and dogs). Lazertinib showed some partitioning to red blood cells in dogs and humans (mean blood-to-plasma ratio 1.42 and 1.15) but not in rats (0.95).
Metabolism studies using ^{14}C-lazertinib in rat, dog, and human liver microsomes and hepatocytes identified glutathione (GSH) conjugation as the major pathway, forming metabolite M11 with subsequent GSH catabolism (major metabolites M12 and M14). The major human metabolite M12 was observed *in vitro* and *in vivo* in dogs only. M12 was not qualified in nonclinical studies. This can be accepted according to ICH S9.
The major route of excretion in nonclinical species and humans was faecal, with minor renal excretion. Neither passage into milk nor placental transfer were investigated.

5.3 Toxicology

The nonclinical safety profile of lazertinib was characterised in rats and dogs. The oral route of administration as well as the duration of the studies in rodents and non-rodents support the clinical use.
The toxicity of lazertinib was evaluated in studies with daily dosing for up to 13 weeks in rats and dogs and recovery periods of 8 weeks. Developmental toxicology studies were also conducted in rabbits.
The main target organs for toxicity were skin, heart, lungs, liver, kidney, eye, and gastrointestinal, haematopoietic, and reproductive systems.
Rats and dogs had significant body weight loss and decreased food consumption, which contributed to the poor condition of the animals. The pharmacological activity or consequences thereof caused the majority of the adverse effects in rats and dogs. These included epithelial atrophy, degenerative erosions, inflammation, and necrosis in organs and tissues containing epithelial cell lines.
The safety margins in the repeat-dose toxicity studies were low (1.8-fold in rats and 0.9-fold in dogs at HNSTD of 4 mg/kg/day). This can be accepted considering the proposed indication.
Lazertinib was not genotoxic in a series of *in vitro* and *in vivo* assays under the conditions tested.
In line with ICH S9, no carcinogenicity studies were conducted with lazertinib.
In a fertility and embryonic development study conducted in male and female rats with oral administration of lazertinib at doses up to 30 mg/kg/day, no effects were observed on mating, fecundity, fertility indices, or sperm assessments. However, an increase in post-implantation loss was observed at 30 mg/kg/day.
In an embryo-fetal development study in rats and rabbits with oral administration of doses up to 60 mg/kg/day and 45 mg/kg/day lazertinib, lower fetal weights correlated with maternal toxicity were observed in rats. In rabbits, only maternal toxicity was observed at 45 mg/kg/day.
Lazertinib was not phototoxic *in vitro* in the neutral red uptake phototoxicity assay in BALB/c 3T3 mouse fibroblasts or *in vivo* in female Long-Evans pigmented rats orally administered doses up to 75 mg/kg/day for 6 days followed by UV exposure.
There are no concerns related to excipients or impurities.
The summary of the key findings from the nonclinical studies is adequately described in the RMP.
Based on the ERA, lazertinib poses no environmental risk at the prescribed dose.

5.4 Nonclinical conclusions

In conclusion, the pharmaco-toxicological profile of lazertinib was well characterised. The application is approvable from the nonclinical view. The relevant information has been included in the Information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

The ADME characteristics of lazertinib have been adequately characterised in the intended patient population. For details concerning ADME characteristics of lazertinib please refer to the attached Information for healthcare professionals.
No dose adjustments are required for patients with mild to severe renal impairment and patients with mild and moderate hepatic impairment. Lack of data in patients with end-stage renal disease or severe hepatic impairment precludes use in these subpopulations. Lazertinib is subject to drug-drug interactions and also causes interaction with other drugs. However, the resulting risks could be addressed by appropriate wording in the Information for healthcare professionals.
For details concerning use in special populations and drug-drug interactions, please refer to the attached Information for healthcare professionals.

6.2 Dose finding and dose recommendation

The recommended Phase 2 dose (RP2D) of amivantamab 1050 mg (<80 kg body weight)/1400 mg (≥80 kg bodyweight) and lazertinib 240 mg was selected based on the totality of exposure, safety, and efficacy data. No dose-limiting toxicities (DLTs) were observed with the proposed doses and regimens for both amivantamab and lazertinib, and PK data analysis was consistent with no drug-drug interaction between amivantamab and lazertinib.
No clinical data are available for the combination of lazertinib with amivantamab at different dose levels. Therefore, no conclusion is possible regarding whether a lower dose of lazertinib is associated with comparable efficacy but lower toxicity.

6.3 Efficacy

The applicant submitted 1 pivotal Phase 3 study, the MARIPOSA study. MARIPOSA is a randomised study to evaluate the efficacy and safety of the combination of amivantamab and lazertinib (A+L) versus osimertinib (Osi) as a first-line treatment in participants with EGFRm NSCLC.

Patients were randomly assigned to study treatment in a 2:2:1 ratio (A+L arm, Osi arm, and Lazertinib only arm [not approved as a single agent]). Randomisation was stratified by mutation type (exon 19del versus exon 21 L858R), race (Asian versus non-Asian), and history of brain metastasis (present versus absent).

For details regarding dosing, please refer to the attached Information for healthcare professionals.

Eligible patients were aged ≥18 years, ECOG 0-1 with locally advanced or metastatic NSCLC with EGFR exon 19del or exon 21 L858R substitution. Patients were treatment naïve and not amenable to curative therapy including surgical resection or chemoradiation.

The primary endpoint was BICR-assessed progression-free survival (PFS) of the A+L combination compared with Osi. Overall survival (OS) was a relevant secondary endpoint.

At the time of the interim PFS analysis (data cut-off [DCO] 15 January 2023), there were 321 PFS events by BICR observed from the A+L and Osi arms combined. The efficacy stopping criteria had been met for PFS (HR=0.75 [95% CI: 0.60, 0.93], p=0.0097), in favour of the combination of A+L. At the time of the DCO for the interim PFS analysis, the median duration of follow-up was short at 15.1 months, meaning data observed at the interim analysis might not have reflected the true treatment

effect. Therefore, the study continued and blinding was maintained until the next protocol-specified PFS analysis (final PFS analysis based on 450 PFS events from the A+L and Osi arms combined).

At a median follow-up of 22 months, BICR-assessed PFS was statistically significantly improved for the A+L arm compared to the Osi arm, with an HR=0.70 (95% CI: 0.58, 0.85) and corresponding median PFS of 23.7 months for the A+L arm vs. 16.6 months for the Osi arm. At this DCO, PFS benefit was not translated into statistically significant OS.

The applicant provided updated OS data (latest cut-off 4 December 2024). The updated median follow-up was approximately 37.8 months and a total of 490 deaths were reported. The final OS analysis shows a statistically significant improvement in OS for the combination of A+L over Osi (HR=0.75, 95% CI: 0.61, 0.92; p=0.00489).

Additional subgroup analyses were performed for PFS and OS. For patients ≥65 years, the HR for PFS at DCO August 2023 was 1.06 (CI95% 0.80, 1.41) compared to an HR of 0.50 (CI95% 0.39, 0.65) in patients <65 years. For patients ≥65 years, the HR for OS at DCO December 2024 was 1.11 (CI95% 0.84, 1.48) compared to an HR of 0.53 (CI95% 0.40, 0.70) in patients <65 years.

6.4 Safety

In the MARIPOSA study, treatment with A+L was associated with increased toxicity compared to Osi, including higher frequency of grade ≥3 TEAEs (75.1% vs. 42.8%), SAEs (48.7% vs. 33.4%), and grade 5 AEs (9.3% vs. 6.8%).
The most common TEAEs (≥20%) in the A+L arm were paronychia, infusion-related reactions, rash, hypoalbuminaemia, ALT increased, oedema peripheral, dermatitis acneiform, constipation, diarrhoea, stomatitis, AST increased, COVID 19, decreased appetite, pruritus, nausea, and hypocalcaemia.

Treatment with amivantamab in combination with lazertinib is associated with relevant safety risks. In particular, the risk of venous thromboembolism (VTE) in patients treated in the A+L arm was increased compared to the Osi arm. A warning including prophylactic anticoagulation for the first 4 months in patients who are treated with A+L was included.

Treatment with A+L was associated with a higher frequency of ≥ grade 3 TEAEs, SAEs, and grade 5 TEAEs in patients ≥65 years compared to patients <65 years.

For details regarding safety, please refer to the attached Information for healthcare professionals.

6.5 Final clinical benefit-risk assessment

In the MARIPOSA study, statistically significant PFS and OS results were shown for lazertinib in combination with amivantamab compared to Osi. The associated toxicity is manageable, and safety, including specific risks such as VTEs and increased toxicity in older patients, is adequately described in the Information for healthcare professionals. Therefore, the benefit-risk assessment was regarded as positive for A+L for first-line treatment in patients with locally advanced and metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutation.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Lazcluze was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Lazcluze

Composition

Active substances

Lazertinib (as mesylate monohydrate).

Excipients

Lazcluze, film-coated tablets

Tablet core:
Microcrystalline cellulose (E 460i), mannitol (E 421), croscarmellose sodium (E 468), magnesium stearate (E 572), hydrophobic colloidal silica.
Film-coating 80 mg, film-coated tablets:
Macrogol poly(vinyl alcohol) grafted copolymer (E 1209), talc (E 553b), titanium dioxide (E 171), glycerol monocaprylocaprate (E 471), iron oxide yellow (E 172), poly(vinyl alcohol) (E 1203).
Film-coating 240 mg, film-coated tablets:
Macrogol poly (vinyl alcohol) grafted copolymer (E 1209), talc (E 553b), titanium dioxide (E 171), glycerol monocaprylocaprate (E 471), poly(vinyl alcohol) (E 1203), iron oxide red (E 172), iron oxide black (E 172).
One film-coated tablet contains a maximum of 0.8 mg sodium per 80 mg tablet or 2.5 mg sodium per 240 mg tablet.

Pharmaceutical form and active substance quantity per unit

Film-coated tablets.

Lazcluze 80 mg, film-coated tablets

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

Lazcluze 240 mg, film-coated tablets

Each film-coated tablet contains 240 mg Lazertinib.
Reddish purple, oval film-coated tablet debossed with “LZ” on one side and “80” on the other side.

Indications/Uses

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 (see “Warnings and Precautions” and "Clinical Efficacy").

Dosage/Administration

Usual 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 prescribing information and section “Properties/Effects” for recommended amivantamab dosing information.

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, the missed dose should **not** be administered and the next dose should be administered per the usual dosing schedule.

Concomitant medication

When initiating treatment with Lazcluze in combination with amivantamab, administer anticoagulant prophylaxis to prevent venous thromboembolic events (VTE) for the first four months of treatment (see “Warnings and Precautions”). If there are no signs or symptoms of VTE during the first four months of treatment, consider discontinuation of anticoagulant prophylaxis at the discretion of the healthcare provider.

Dose modifications

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

Table 1: Recommended Dose Reductions for Adverse Reactions

	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.

Refer to the amivantamab Information for professionals for information about dose modifications for amivantamab.

Table 2: Recommended Lazcluze Dose Modifications for Adverse Reactions

Adverse Reaction	Severity	Dose Modification*
Interstitial Lung Disease (ILD) (see *Warnings and Precautions*)	Any Grade	Withhold if ILD/pneumonitis is suspected. Permanently discontinue if ILD/pneumonitis is confirmed.
Venous Thromboembolic Events (VTE) (see *Warnings and Precautions*)	Events with clinical instability (e.g., respiratory failure or cardiac dysfunction)	Withhold both 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.
	Recurrent VTE despite therapeutic level anticoagulation	The combination of Lazcluze and amivantamab should be permanently discontinued.
Skin and Nail Reactions (see *Warnings and Precautions*)	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 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 ≤ Grade 2 or baseline. Upon recovery to ≤ Grade 2, resume Lazcluze at the same dose or consider dose reduction.
Other Adverse Reactions	Grade 3-4	• Withhold treatment until adverse reaction improves to ≤ Grade 1 or baseline. • Resume treatment at reduced dose. • Permanently discontinue if recovery does not occur within 4 weeks.

* Refer to the amivantamab prescribing information for information about dose modifications for amivantamab.

Special dosage instructions

Patients with hepatic disorders

No dose adjustment is required for patients with mild or moderate hepatic impairment. Lazertinib has not been studied in patients with severe hepatic impairment (see “Pharmacokinetics”, “Hepatic impairment”).

Patients with renal disorders

No dose adjustment is required for patients with mild, moderate or severe renal impairment. Lazertinib has not been studied in patients with end stage renal disease (see *“*Pharmacokinetic*s”, “*Renal impairment*”*).

Elderly patients (≥ 65 years)

Among 421 patients with non-small cell lung cancer treated with Lazcluze in combination with amivantamab in NSC3003, 44.7% were 65 years and older and 11.6% were 75 years and older. No adjustment of the starting dose is recommended based on age. In elderly patients >65 years of age an increase in toxicity was observed with Lazcluze in combination with amivantamab (see sections “Warnings and Precautions” and “Undesirable effects: Elderly patients”).

Children and adolescents (≤ 17 years)

Lazcluze is not approved for use in the paediatric population.

Mode of 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 TRADENAME, take the next dose the next day.

Contraindications

Hypersensitivity to the active substance or to any of the excipients according to the composition.

Warnings and precautions

Venous Thromboembolic Events (VTE)

In patients treated with Lazcluze in combination with amivantamab VTE (e.g. deep vein thrombosis and pulmonary embolism), including serious and fatal events, may occur (see “Undesirable Effects”). VTE occurred in 36% of patients treated with Lazcluze in combination with amivantamab, including Grade 3 in 10%, Grade 4 in 0.5% and two fatal cases of VTE (0.5%). In 62% of patients, the first VTE occurred within the first four months of treatment; 38% of VTE occurred after the fourth month. On-study VTEs occurred during anticoagulation therapy in 1.2% of patients. Prophylactic anticoagulants are recommended to be used for the first four months of treatment. Anticoagulants use should align

with clinical guidelines; use of Vitamin K antagonists is not recommended. In the event of recurrence despite appropriate anticoagulation, discontinue Lazcluze and amivantamab until clinically stable. Patients should be monitored for signs and symptoms of VTE and treated as medically appropriate (see section 'Dosage/Administration').

Interstitial Lung Disease (ILD/Pneumonitis)

Interstitial lung disease (ILD)/pneumonitis, including fatal events, have been reported in patients receiving Lazcluze (see "Undesirable effects"). 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 "Dosage/Administration" and "Undesirable Effects").

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 (see "Undesirable effects").
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 events, 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, reduce dose, or permanently discontinue Lazcluze and amivantamab based on severity (see "Dosage/Administration").

Eye Disorders

Keratitis occurred in patients receiving Lazcluze with amivantamab (see "Undesirable effects"). Refer patients presenting with new eye symptoms or worsening eye symptoms promptly to an ophthalmologist and advise discontinuation of contact lenses until symptoms are evaluated.

Age

Elderly patients (≥ 65 years) may be at increased risk of developing a serious adverse event. Close monitoring is recommended in these patients. In patients aged ≥65 who received Lazcluze in combination with amivantamab an increase in serious adverse events and grade 5 undesirable effects was observed (see "Undesirable effects" section). In addition, there was a higher frequency of adverse events that led to discontinuation compared to patients < 65 years of age.

Sodium

Lazcluze contains less than 1 mmol sodium (23 mg) per 80 mg or 240 mg film-coated tablet, that is to say it is essentially ‘sodium-free’.

Interactions

Effect of other agents on lazertinib

Strong CYP3A4 Inducers

The co-administration of lazertinib with strong and moderate CYP3A4 inducers should be avoided, as efficacy could be reduced. An alternative concomitant medication that does not have the potential to induce CYP3A4 should be considered.
The co-administration of 240 mg lazertinib with rifampin (strong CYP3A4 inducer) decreased lazertinib plasma exposure by more than 80%. Lazertinib geometric mean ratios (90% CI) for Cmax and AUC0-120h 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, co-administration of efavirenz (moderate CYP3A4 inducer) with Lazcluze is expected to decrease steady-state Lazertinib Cmax by at least 32% and AUC by at least 44%.
The effects of co-administration of weak CYP3A4 inducers on Lazertinib Cmax or AUC are unknown.

Strong CYP3A4 Inhibitors

No dose adjustments are required when Lazcluze is used with 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 Cmax and AUC0-120h were 1.19 (1.08, 1.30) and 1.46 (1.39, 1.53) respectively, when co-administered with itraconazole, relative to lazertinib alone.

Gastric acid reducing medicinal products

No clinically relevant change in lazertinib plasma exposure was observed when co-administered with gastric acid reducing medicinal product. No dose adjustments are required when Lazcluze is used with gastric acid reducing medicinal products.

Amivantamab

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

Effect of lazertinib on other agents

CYP3A4 Substrates

Lazertinib is a weak inhibitor of CYP3A4 enzyme. Monitor for adverse reactions associated with a CYP3A4 substrate where minimal concentration changes may lead to serious adverse reactions, as recommended in the approved product labeling for the CYP3A4 substrate.
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 Cmax and AUC0-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.

BCRP Substrates

Lazertinib is an inhibitor of BCRP transporter. Monitor for adverse reactions associated with a BCRP substrate where minimal concentration changes may lead to serious adverse reactions, as recommended in the approved product labeling for the 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 Cmax and AUC0-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.

OCT1 Substrates

Lazertinib is not an inhibitor of OCT1 transporter. 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 Cmax and AUC0-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.

UGT1A1 Substrates

In vitro findings suggest that lazertinib may inhibit UGT1A1; however no clinically relevant interaction is expected.

Other interactions

In vitro results indicate that lazertinib is not an inducer of CYP1A2, CYP2B6 and CYP3A4.

Pregnancy, lactation

Contraception

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.

Pregnancy

There are no data from the use of lazertinib in pregnant women. Studies in animals have shown a reproductive toxicity (see “Preclinical Data”). 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.

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.

Fertility

There are no data on the effect of Lazcluze on human fertility. Studies in animals have shown that lazertinib may impair female and male fertility (see “Preclinical data”).

Effects on 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.

Undesirable effects

The safety data described below reflect exposure to lazertinib + 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 Study NSC3003. Median treatment duration was 18.5 months (range: 0.2 to 31.4 months) for the lazertinib + amivantamab arm and the median treatment duration was 18 months (range: 0.2 to 32.7) for the osimertinib arm.
Serious adverse reactions in >1% of patients were venous thromboembolism (11%), interstitial lung disease (2.8%), rash (2.1%), alanine aminotransferase increased (1.9%) and fatigue (1.2%). Adverse reactions leading to Lazcluze discontinuation in ≥1% of patients were ILD (2.8%), venous thromboembolism (1.7%) and rash (1.2%).

Adverse reactions observed during clinical studies are listed by MedDRA system organ class and frequency according to following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (frequency cannot be estimated from the available data).

Table 3 Adverse Reactions in Patients Receiving Lazertinib in Combination with Amivantamab

System Organ Class **Frequency Category**	**Adverse Reaction**
Metabolism and nutrition disorders	
Very common	Decreased appetite (24%)
Nervous system disorders	
Very common	Paraesthesia[a] (34%)
Eye disorders	

Common	Keratitis
Vascular disorders	
Very common	Venous thromboembolism[b] (36%)
Respiratory, thoracic and mediastinal disorders	
Common	Interstitial lung disease[c]
Gastrointestinal disorders	
Very common	Stomatitis[d] (43%), Diarrhoea (29%), Constipation (29%), Nausea (21%), Vomiting (12%)
Hepatobiliary disorders	
Very common	Alanine aminotransferase increased (36%), Aspartate aminotransferase increased (29%)
Skin and subcutaneous tissue disorders	
Very common	Rash[e] (88%), Nail toxicity[f] (71%), Dry skin[g] (26%), Pruritus (24%)
Common	Palmar-plantar erythrodysaesthesia syndrome, Urticaria
Musculoskeletal and connective tissue disorders	
Very common	Muscle spasms (17%)
General disorders and administration site conditions	
Very common	Fatigue[h] (32%), Pyrexia (12%)

a Dysaesthesia, Hypoaesthesia, Neuropathy peripheral, Paraesthesia, Peripheral motor neuropathy, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Polyneuropathy

b 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

c Interstitial lung disease, Pneumonitis

d Angular cheilitis, Aphthous ulcer, Mouth ulceration, Mucosal inflammation, Stomatitis

e Acne, Dermatitis, Dermatitis acneiform, Erythema, Folliculitis, Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash pruritic, Rash pustular, Skin lesion

f Ingrowing nail, Nail disorder, Nail infection, Nail toxicity, Onychoclasis, Onycholysis, Onychomadesis, Paronychia

g Dry skin, Eczema, Eczema asteatotic, Skin fissures, Xeroderma, Xerosis

h Asthenia, Fatigue

Venous Thromboembolic Events (VTE)

VTE events, including deep venous thrombosis (DVT) and pulmonary embolism (PE), were reported in 36% of the 421 patients receiving LAZCLUZE in combination with amivantamab in MARIPOSA.

Most cases were Grade 1 or 2, with Grade 3-4 events occurring in 11% of patients receiving LAZCLUZE in combination with amivantamab, and Grade 5 events occurring in 0.5% of patients (2 patients). For information on prophylactic anticoagulants and management of VTE events, see sections “Dosage/Administration” and “Warnings and Precautions”.

Interstitial Lung Disease (ILD/Pneumonitis)

ILD occurred in 3.1% of patients treated with Lazcluze in combination with amivantamab, including Grade 3 in 1.0% and Grade 4 in 0.2% of patients. There was one fatal case (0.2%) of ILD and 2.9% of patients permanently discontinued Lazcluze and amivantamab due to ILD.

Skin and nail reactions

Rash (including dermatitis acneiform) occurred in 88.4% patients treated with lazertinib alone or in combination with amivantamab. Most cases were Grade 1 or 2, with Grade 3-4 rash events occurring in 26.4% of patients. Rash leading to LAZCLUZE discontinuation occurred in 1.2% 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 11.4% of patients.

Eye disorders

Eye disorders, including keratitis (2.6%), occurred in patients treated with lazertinib in combination with amivantamab. Most events were Grade 1-2, some Grade 3-4 keratitis events were observed.

Special patient groups

Elderly

Out of 421 patients who participated in the MARIPOSA study and received Lazcluze in combination with amivantamab, 45% were 65 years of age or older, and 12% of these were 75 years of age or older.
There are limited clinical data with Lazcluze in patients 75 years or over. Older patients (≥ 65 years of age) reported more Grade 3 or higher adverse events (81% vs. 70%), more serious adverse events 62% vs. 38%) and more grade 5 events (14% vs. 3%) compared to patients < 65 years of age. While the rates of drug interruptions and dose reductions were similar, the rate of adverse events leading to any treatment discontinuation was higher in patients ≥ 65 years of age compared to patients < 65 years of age (47% vs. 25%).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms

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

Treatment

There is no known specific antidote for Lazcluze overdose. In the event of an overdose, stop Lazcluze, undertake general supportive measures until clinical toxicity has diminished or resolved**.**

Properties/Effects

ATC code

L01EB09

Mechanism of action

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

Pharmacodynamics

The exposure-response relationship and time-course of pharmacodynamic response of lazertinib have not been fully characterized.

Effect on QT/QTc interval and cardiac electrophysiology

Cardiac electrophysiology

The QTc interval prolongation potential of lazertinib was evaluated by a exposure-response (E-R) analysis conducted with data from 243 NSCLC patients who received doses of 20 mg to 320 mg lazertinib once daily. The E-R analysis revealed a relationship between lazertinib plasma concentration and change in QTc interval. The 2-sided upper bound of 90% CI at steady state Cmax 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 efficacy

NSC3003 (MARIPOSA) is a randomized, active-controlled, multicenter 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. Patients with asymptomatic or previously treated and stable intracranial metastases were eligible to enroll.

Patients were randomized (2:2:1) to receive Lazcluze in combination with amivantamab (n=429), osimertinib monotherapy (n=429), or Lazcluze monotherapy (an unapproved regimen for NSCLC) until disease progression or unacceptable toxicity. The evaluation of efficacy for the treatment of untreated metastatic NSCLC relied upon comparison between:

- LAZCLUZE administered at 240 mg orally once daily in combination with amivantamab 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 administered at a dose of 80 mg orally once daily.

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). Tumor assessments were performed every 8 weeks for 30 months, and then every 12 weeks until disease progression.

A total of 858 patients were randomized between the two study arms, 429 to the LAZCLUZE in combination with amivantamab arm and 429 to the osimertinib arm. The median age was 63 (range: 25–88) years with 45% of patients ≥ 65 years; 61% were female; and 58% 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; 3% had Stage III NSCLC at screening and 97% had Stage IV NSCLC at screening. 97% of patients had adenocarcinoma. With regard to EGFR mutation status, 60% were exon 19 deletions and 40% were exon 21 L858R substitution mutations.

Lazcluze in combination with amivantamab demonstrated a statistically significant improvement in progression-free survival (PFS, by BICR assessment, DCO August 2023) compared with osimertinib monotherapy (HR=0.70 [95% CI: 0.58, 0.85], p=0.0002; median PFS 23.7 months vs 16.6 months).

The final OS analysis (DCO December 2024, with a median follow-up 37.8 months) showed a statistically significant improvement in OS for patients in the Lazcluze in combination with amivantamab study arm compared to patients in the osimertinib arm (HR=0.75, 95% CI: 0.61, 0.92; p=0.0048).

The confirmed ORR according to BICR (DCO August 2023) was 80% (95% CI: 76%, 84%) in the Lazcluze+amivantamab arm and 76% (95% CI: 71%, 80%) in the osimertinib arm. The median duration of response (DOR, DCO August 2023) for confirmed response was 25.8 months (95% CI: 20.1, NE) in the Lazcluze+amivantamab arm versus 16.8 months (95% CI: 14.8, 18.5) in the osimertinib arm.

Subgroup Analysis

No formal statistical testing was planned for subgroup analyses and the clinical interpretation of the subgroup analyses is therefore limited.

Table 4: Progression-free Survival for Predefined Subgroups (DCO August 2023, median follow-up 22.0 months)

Subgroups	HR (95% CI)
Age	
<65	0.50 (0.39, 0.65)
≥65	1.06 (0.80, 1.41)
<75	0.70 (0.57, 0.85)
≥75	0.77 (0.46, 1.30)

Table 5: Overall Survival for Predefined Subgroups (DCO December 2024, median follow-up 37.8 months)

Subgroups	HR (95% CI)
Age	
<65	0.53 (0.40, 0.70)
≥65	1.11 (0.84, 1.48)
<75	0.75 (0.60, 0.93)
≥75	0.79 (0.47, 1.33)

The outcomes of the further subgroup analyses with regard to age, sex, race, weight, mutation types, ECOG performance status, history of smoking, and history of brain metastasis were generally consistent with the primary analysis and can be considered supportive.

Of the total of 858 randomized patients, 367 (43%) had intracranial lesions at baseline (BICR, modified RECIST criteria). In an exploratory analysis in this population, the combination of Lazcluze and amivantamab demonstrated similar intracranial ORR (by BICR) to osimertinib (76.7% versus 76.5%), with an intracranial complete response rate of 62.2% versus 57.8%.

Pharmacokinetics

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.

Absorption

The median time to reach single dose and steady state C_{max} was comparable and ranged from 2 to 4 hours. The absolute bioavailability of lazertinib has not been determined. 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. The lazertinib geometric mean ratios (90% CI) for C_{max} and AUC_{last} were 0.94 (0.83, 1.05) and 1.14 (1.06, 1.22) respectively, when co-administered with high-fat meal, relative to administration in fasted state.

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 metabolized primarily by glutathione conjugation, either enzymatic via Glutathione S transferase (GST) or non-enzymatic, as well as CYP3A4 mediated oxidation. The most abundant metabolites are glutathione catabolites and considered clinically inactive. The plasma exposure of lazertinib was affected by GSTM1-status. In non-null GSTM1 patients, Lazertinib exposure (AUC0-24h,ss) was 44% lower than in null GSTM1 patients. No dose adjustment is required based on GSTM1 status.

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 (<0.5% as unchanged).

Kinetics in specific patient groups

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. The total lazertinib geometric mean ratios (90% CI) for C_{max} and AUC_{last} were 0.80 (0.61, 1.04) and 0.95 (0.76, 1.18) respectively, when administered in participants with moderate hepatic impairment, relative to normal hepatic function participants. In a population PK analysis, no significant influence of liver function on the pharmacokinetics of Lazertinib was found in patients with mild hepatic impairment (n=142, total bilirubin ≤ ULN and AST > ULN or ULN < total bilirubin ≤ 1.5×ULN) compared to patients with normal liver function (n=1245). No data are available in patients with severe hepatic impairment (total bilirubin >3×ULN and any AST).

Renal impairment

Based on population PK analysis, no significant influence of renal function on the pharmacokinetics of Lazertinib was found for patients with mild (n=706), moderate (n=124) or severe (n=3) renal impairment with estimated glomerular filtration rate (eGFR) of 15 to 89 mL/min compared to patients with normal renal function (n=556) with eGFR of greater than or equal to 90 mL/min. Data in patients with severe renal impairment (eGFR of 15 to 29 mL/min) are limited (n=3). No data are available in patients with end stage renal disease (eGFR < 15 mL/min).

Elderly patients (≥ 65 years)

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

Children and adolescents (≤ 17 years)

The pharmacokinetics of Lazcluze in pediatric patients have not been investigated.

Other populations

No clinically meaningful differences in lazertinib PK were observed based on age (21 – 88 years), sex (38% men, 62% women), body weight (28.5 – 122 kg), race, ethnicity (30% Caucasians, 67% asians), 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.

Preclinical data

In a 13-week repeated-dose oral general toxicology study in rats at a dose of 50 mg/kg/day, lazertinib induced renal toxicity characterized by papillary necrosis, increased urea nitrogen, and tubular degeneration/regeneration (exposure approximately 4 (male)-5.2 (female) times the human exposure at the recommended dose). In the 13-week oral study in dogs, renal cell carcinoma was observed in one animal at a dose of 8 mg/kg/day (approximately twice the human exposure at the recommended dose). Other findings included tubular degeneration/regeneration.
In a dog 4-week study, microscopic findings in the hearts (degeneration/necrosis of the myocardium, degeneration/necrosis of vessel, inflammation of vessel, mixed cell inflammation, fibrosis, thrombus, and hemorrhage) of 2 males administered 20 mg/kg/day, including 1 male euthanized early, correlated with the macroscopic finding of red discoloration in the heart of the other affected male, and a markedly increased cardiac Troponin I concentration. These effects were observed at exposures approximately 2 times the human exposure at the recommended dose.

Carcinogenicity and Mutagenicity

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

Reproductive toxicity

In a fertility and early embryonic development study in male and female rats, lazertinib induced embryo lethality and reduced numbers of live fetuses at 30 mg/kg/day at an exposure 1.7 times the clinical exposure. In embryo-fetal development studies, decreases in fetal body weights in association with maternal toxicity were observed in rats at 60 mg/kg/day, a maternal exposure approximately 4 times higher than the clinical exposure. There were no effects on embryo-fetal development in rabbits at 45 mg/kg/day, a maternal exposure approximating the human clinical exposure at 240 mg.
In repeat dose general toxicity studies in rats of up to 13 weeks duration, tubular degeneration in the testes, degeneration/necrosis and reduced sperm count in the epididymis, reduced corpora lutea in

the ovaries, and atrophy in the uterus and vagina were observed at exposures in males approximately 6 times the human exposure at the recommended dose and in females approximately 2.5 times the human exposure. Findings in the female reproductive organs were reversible, whereas findings in the male reproductive organs were not fully reversible. In the 4-week dog study, tubular degeneration of the testes was observed at a dose of ≥5 mg/kg/day. Findings were observed at an exposure 0.9 times the human exposure).

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Do not store above 30 °C.
Keep out of the sight and reach of children.

Instructions for handling

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

Authorisation number

69751 (Swissmedic).

Packs

LAZCLUZE 80 mg, film-coated tablets

Packs containing 56, film-coated tablets [A]

LAZCLUZE 240 mg, film-coated tablets

Packs containing 28 film-coated tablets [A]

Marketing authorisation holder

Janssen-Cilag AG, Zug

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