Date: 9 June 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Alunbrig

International non-proprietary name: brigatinib
Pharmaceutical form: film coated tablet
Dosage strength(s): 180 mg, 90 mg, 30 mg
Route(s) of administration: oral
Marketing Authorisation Holder: Takeda Pharma AG
Marketing Authorisation No.: 66738
Decision and Decision date: approved on 4 May 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

AE	Adverse event
ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
BCRP	Breast cancer resistance protein
BID	twice daily
BIRC	blinded independent review committee
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
iORR	intracranial confirmed objective response rate
iPFS	intracranial progression-free survival
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
NSCLC	Non-small cell lung cancer
PD	Pharmacodynamics
P-gp	P-glycoprotein
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PFS	progression-free survival
PSP	Pediatric Study Plan (US-FDA)
QD	once daily
ORR	objective response rate
OS	overall survival
QTc	heart rate–corrected QT interval (calculated)
QTcF	QT interval corrected (Fridericia)
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TEAE	treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance brigatinib of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 1 or 2 of the TPA. The Orphan Status was granted on 3 July 2017.

2.2 Indication and Dosage

2.2.1 Requested Indication

Alunbrig is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive, advanced, non-small cell lung cancer (NSCLC), who have previously not been treated with an ALK-inhibitor.

Alunbrig is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive, advanced, non-small cell lung cancer (NSCLC), who have previously been treated with crizotinib.

2.2.2 Approved Indication

Alunbrig is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) previously untreated with an ALK inhibitor.

Alunbrig is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on previous treatment with crizotinib.

2.2.3 Requested Dosage

90 mg orally once daily for the first 7 days, if tolerated increase to 180 mg orally once daily.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	3 March 2020
Formal control completed	13 March 2020
List of Questions (LoQ)	9 July 2020
Answers to LoQ	7 October 2020
Predecision	5 January 2021
Answers to Predecision	4 February 2021
Final Decision	4 May 2021
Decision	approval

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3 Medical Context

Lung cancer is the leading cause of cancer death in men and the second leading cause of cancer death in women in the Western world. In Switzerland, approximately 4,400 new patients are diagnosed each year with lung cancer (www.nicer.org). Non-small cell lung cancer (NSCLC) accounts for 80%-90% of lung cancers, and 3 to 5% of patients with NSCLC, predominantly adenocarcinoma, have tumours containing ALK gene rearrangements. A total prevalence of approximately 100 to 300 patients with ALK-positive NSCLC can be estimated in Switzerland.

Metastatic NSCLC is invariably fatal, even if overall survival appears more favourable in ALK rearranged patients, at 6.8 years [Pacheco et al., JTO, 2019], compared to patients without a molecular target, who had a median overall survival of less than 1 year before the advent of immune checkpoint inhibitors [Abernethy et al., PLoS One, 2017]. The development of tyrosine kinase inhibitors (TKIs) targeting ALK-translocations improved the outcome for these patients. However, adverse event profiles, as well as the development of resistance to the first-generation inhibitors, still leave a medical need to develop new and better treatments in this setting.

4 Quality Aspects

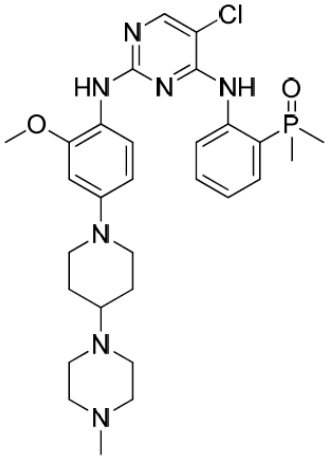
4.1 Drug Substance

Alunbrig film-coated tablets contain the drug substance brigatinib, which is isolated in crystalline form as a free base.

The chemical IUPAC name for brigatinib is 5-chloro-N^4-[2-(dimethylphosphoryl)phenyl]-N^2-{2-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl}pyrimidine-2, 4-diamine

The molecular formula for brigatinib is $C_{29}H_{39}ClN_7O_2P$ and the corresponding molecular weight is 584.10 g/mol.

The chemical structure of brigatinib is as follows:



Brigatinib is an off-white to beige/tan solid. It is achiral. Brigatinib is isolated as crystalline Form A, which is an anhydrous, non-solvated and non-hygroscopic form.

The synthesis of the drug substance has been adequately described and the process is controlled with appropriate in-process controls and tests for isolated intermediates.

The drug substance specification includes tests for description (visual), identity (FTIR, HPLC), assay (HPLC), impurities (HPLC), residual solvents (HS-GC), solid form confirmation (XRPD), particle size distribution (laser diffraction), melting temperature (differential scanning calorimetry), residue on

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ignition (gravimetric) and water content (KF). The specifications are in line with the recommendations of the relevant ICH guidelines and are considered appropriate in order to ensure a consistent drug substance quality.

The bulk drug substance is packaged in LLDPE continuous liner bags, which are placed in LDPE bags and then in an HDPE drum. Appropriate stability data have been presented indicating that the drug substance is sufficiently stable.

4.2 Drug Product

Alunbrig is presented as immediate-release white to off-white film-coated tablets containing 30 mg, 90 mg or 180 mg brigatinib. Alunbrig 30 mg film-coated tablets are round debossed with “U3” on one side and plain on the other side. Alunbrig 90 mg film-coated tablets are oval debossed with “U7” on one side and plain on the other side. Alunbrig 180 mg film-coated tablets are oval debossed with “U13” on one side and plain on the other side.
The composition of the drug product is adequately described, qualitatively and quantitatively. The tablet cores contain lactose monohydrate.

Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process.

The manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data. Batch manufacturing formulas and in-process controls are included.
Adequate validation data pertaining to the commercial manufacturing process are available.

For the control of the finished product, adequate tests and acceptance criteria for release and at shelf-life are established. The specifications include the parameters description (visual), identity (FT-IR, RP-HPLC), assay (RP-HPLC), degradation products (RP-HPLC), uniformity of dosage units (Ph. Eur., RP-HPLC), water determination (KF), dissolution (RP-HPLC) and microbial enumeration (Ph.Eur.). The corresponding test procedures are validated according to international guidelines. Batch data show consistent quality of the drug product.

Alunbrig film-coated tablets are packaged in Aclar / foil blisters.

Appropriate stability data have been generated in the packaging material intended for commercial use and following the relevant international guidelines. Based on these data, a shelf life of 36 months was established for Alunbrig film-coated tablets 30 mg, 90 mg and 180 mg. The storage recommendation is “Do not store above 30°C”.

4.3 Quality Conclusions

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

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5 Nonclinical Aspects

The applicant provided a comprehensive nonclinical study package based on the requirements outlined in ICH S9. Pivotal studies for safety assessment of brigatinib were conducted in compliance with GLP.

Pharmacology

Brigatinib showed *in vitro* activity against anaplastic lymphoma kinase (ALK), ROS1, insulin-like growth factor-1 receptor (IGF-1R), FLT3 and certain mutant variants of epidermal growth factor receptor (EGFR) at concentrations that have been achieved at the maximum recommended human dose (MRHD) of 180 mg. Brigatinib inhibited the phosphorylation of ALK and downstream signalling proteins in human NSCLC cell lines. These cell lines expressed the fusion protein EML4-ALK, resulting in inhibition of cellular and anchorage-independent growth. Brigatinib also potently inhibited the viability of Ba/F3 cells expressing secondary ALK mutations associated with resistance to crizotinib and/or other approved ALK inhibitors. *In vivo*, brigatinib showed anti-tumour activity in mice bearing human EML4-ALK-positive NSCLC xenografts and in Ba/F3 xenografts expressing four crizotinib-resistant ALK mutations (L1196M, G1269S, S1206R, and G1202R). In a murine NSCLC orthotopic brain tumour model, oral administration of brigatinib prolonged survival, suggesting that the drug may have activity against metastases in the central nervous system (CNS).
In an *in vitro* secondary pharmacology screen, brigatinib (10 µM) exhibited significant activity against the nonselective sigma receptor and the sodium ion channel. The clinical relevance of these off-target interactions is unknown.
Brigatinib did not inhibit the hERG potassium channel at clinically relevant concentrations (IC_{50} > 10 µM), and no QT or QTc prolongation was seen *in vivo* in monkeys following single or repeated oral administration at clinically relevant exposure. Decreases in mean pulse pressure and heart rate occurred within 1-6 hours following single oral administration to monkeys. There were also delayed effects on cardiopulmonary function (elevated heart rate, blood pressure, body temperature, and respiratory frequency). Bradycardia, hypertension and pulmonary toxicity were seen in the clinical trials with brigatinib.
No adverse effect on CNS function was seen in rats following single oral administration of doses associated with exposures about 2.5x clinical C_{max}.

Pharmacokinetics

In the preclinical species for toxicity testing (rat and monkey), pharmacokinetics of brigatinib after single oral administration was characterised by rapid absorption (t_{max} within 4 hours), similarly as in humans. Plasma half-life ($t_{1/2}$) was 4 hours in rats and 7 hours in monkeys, i.e. shorter than the $t_{1/2}$ in humans (25 hours). Oral bioavailability was about 40-50% in rats and monkeys. In rats, there were no apparent gender differences in exposure, and no accumulation occurred with repeated dosing. In monkeys, repeated administration of 15 mg/kg/day led to higher exposure in males than in females, and there was accumulation up to 5-fold in individual males at this dose level. In female monkeys, no accumulation occurred up to the 15 mg/kg/day dose.
Brigatinib was moderately bound to plasma proteins and did not show preferential distribution into red blood cells across species. In rats, drug-derived radioactivity was rapidly and widely distributed to tissues, including CNS, following single oral administration. Very high concentrations were observed in pigmented eye uvea, and elimination from this tissue was very slow.
Metabolite profiles observed in rat and monkey *in vitro* and *in vivo* after oral administration were qualitatively similar to the metabolites detected in humans. The main human plasma metabolite AP26123 was detected at similar levels in the preclinical species.
Drug elimination was predominantly via faecal excretion in rats and monkeys, as in humans.
CYP2C8 and CYP3A4 were the major enzymes for brigatinib metabolism *in vitro*. Potential drug-drug interactions with inducers or inhibitors of these enzymes were evaluated in clinical studies. Adequate *in vitro* studies to investigate the interaction potential of brigatinib with metabolic enzymes and drug transporters were conducted, and relevant aspects are mentioned in the information for healthcare professionals.

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Toxicology
Repeated-dose toxicity of brigatinib was assessed in rats and monkeys in studies of up to 6 months' duration. There was dose-limiting toxicity, including mortality, in both species. Brigatinib-related lethality occurred at exposure (AUC) levels in rats at 1.7x and in monkeys at 0.4x the clinical exposure at the 180 mg dose. The cause of death was generally due to toxicity in multiple organs, such as kidney, heart and gastrointestinal system, and immunosuppression. The key target organs of brigatinib toxicity identified in the general toxicity studies were kidney, liver, haematopoietic system, immune system, heart, lung, gastrointestinal system, pancreas, eye, testes/epididymides, and bone. Adverse histological changes and/or correlating changes in clinical pathology parameters, e.g. decreases in lymphocytes and increases in ALT, AST and serum creatinine, occurred in both preclinical species at exposures below the clinical exposure at MRHD. Organ toxicities were generally reversible, except for effects noted in the rat eyes (cataract, retinal degeneration) and testes (tubular degeneration). In monkeys, foamy alveolar macrophages were observed in clinically relevant exposures; however, there was no evidence of alteration of pulmonary function in these animals. The lack of safety margins and lack of reversibility of several adverse findings are acceptable for the requested indication for treatment of patients with advanced cancer. Most organ toxicities observed in the nonclinical studies correlate with findings in the clinical studies. The potential effects on male fertility are addressed in the information for healthcare professionals.
Brigatinib was not genotoxic in *in vitro* bacterial and mammalian assays. There was evidence for chromosomal damage (aneugenicity) in an *in vivo* oral gavage micronucleus test in rats at ≥ 50 mg/kg, which is associated with an exposure ~2x human AUC. Due to the potential of brigatinib for genotoxic effects, female patients and male patients with female partners of child-bearing potential should use contraceptive measures.
Carcinogenicity studies with brigatinib were not conducted and are not required (ICH S9).
Dedicated studies to assess potential effects of brigatinib on fertility were not conducted, in accordance with ICH S9. Based on the results of the repeated-dose toxicity studies, effects on male fertility/reproductive function are possible (see above).
Brigatinib induced adverse effects on embryo-foetal survival and development in rats at clinically relevant exposure levels (decreased foetal weight and increased incidence in skeletal variations at 0.7x clinical AUC; increased post-implantation loss and external, visceral and skeletal malformations at 1.26x clinical AUC). Due to the lack of safety margins for developmental toxicity, brigatinib should not be used during pregnancy, and women of child-bearing potential should use adequate contraception. Transfer of brigatinib and/or metabolites to milk was not studied but is considered likely. Breast-feeding should be discontinued during treatment with brigatinib.
Juvenile animal studies were not conducted and are not required for the requested indication (treatment of adult patients). The EU-PIP for treatment of ALK-positive anaplastic large cell lymphoma in paediatric patients from 1 year of age does not contain any nonclinical studies.
Brigatinib showed no potential for phototoxicity in an *in vivo* study in pigmented rats.
The description and evaluation of the findings in the nonclinical studies in the RMP are considered adequate.
Impurities are adequately controlled. There are no new excipients.
Based on the ERA, brigatinib is not expected to pose a risk to the environment.

Nonclinical Conclusions
Overall, the submitted nonclinical documentation is considered sufficient to support the approval of Alunbrig with the new active substance brigatinib in the proposed indication. The pharmacological activity spectrum and the toxicological profile of brigatinib were adequately characterised in nonclinical studies. Most findings in the nonclinical safety studies correlate with findings in clinical trials. All nonclinical data that are relevant for safety are described in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

ADME
The pharmacokinetic profile of brigatinib has been investigated in the intended patient population.

Absorption: Maximal brigatinib plasma concentrations were observed at a median time of ~2 to 4 h postdose, both after a single dose administration and at steady state. The absolute bioavailability of brigatinib has not been determined, but a fraction absorbed of at least ~60% was estimated, based on mass balance data.

C_{max} and $AUC_{0\text{-}24h}$ increased dose proportionally in the dose range of 60 to 240 mg QD after single and multiple doses. Limited data at 300 mg QD indicated a less than dose proportional increase between 240 mg QD and 300 mg QD.
At steady state, brigatinib accumulated ~2-fold at doses of 90 mg, 120 mg and 180 mg and attainment of steady state is expected after 5 days.

At steady state, at doses of 90 mg and 180 mg QD, the geometric mean Cmax of brigatinib was 552 ng/mL and 1452 ng/mL, and the geometric mean $AUC_{0\text{-}\tau}$ was 8165 h*ng/mL and 20.276 h*ng/mL, respectively.

Food effect: Intake of 2 x 90 mg brigatinib tablets with a high-fat meal caused a ~13% decrease in C_{max} and a 3h delay in the median t_{max}, while AUC was not affected. Alunbrig can be taken irrespective of meals.

Distribution: The in vitro blood-to-plasma partition ratio was 0.69, and the *ex vivo* protein binding was 91.2%. The volume of distribution following i.v. administration was not determined. Following administration of 180 mg once daily, the apparent volume of distribution at steady state was 307 L. Distribution to body compartments other than plasma (e.g. cerebrospinal fluid) has not been investigated in humans.

Metabolism and Elimination: Brigatinib was eliminated by metabolism (CYP2C8 and CYP3A4/5-dependent) and possibly by biliary/intestinal secretion (P-gp- and BCRP-dependent).
N-demethylation (forming M36, N-desmethyl brigatinib) and cysteine conjugation (forming M28) were proposed as the two major metabolic clearance pathways of brigatinib. Brigatinib was the major radioactive species in plasma. Two minor metabolites M36 and M41 (methyl brigatinib) together contributed < 5% of the total radioactivity in plasma.
Twenty-five percent of the administered dose was recovered in urine. Brigatinib accounted for 21% and M36 for 1.5% of the administered dose recovered in urine.
Sixty-five percent of the administered dose was recovered in faeces: 26% of the administered dose was recovered in the form of brigatinib, 25% as M36 (N-desmethyl brigatinib), 9% as M28 (brigatinib cysteine adduct), 0.7% as M27 and 0.4% as M25.

Brigatinib was eliminated from plasma in a multiphasic manner, with a pre-terminal elimination phase up to 96 to 120 h (mean half-life of ~25h), followed by a slower terminal elimination phase with a mean half live of 49 h.

Special Populations / Intrinsic Factors

Hepatic impairment
Impaired hepatic function had a clinically relevant effect on the PK of brigatinib: mean brigatinib protein binding was 91.5%, 88.9% and 89.2% in healthy subjects and subjects with mild and

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moderate hepatic impairment, respectively. However, in subjects with severe hepatic impairment, mean protein binding was reduced to 76.9%. When comparing the PK parameters of unbound brigatinib, $C_{max,u}$ and $AUC_{0-t,u}$ in subjects with mild and moderate hepatic impairment were similar to healthy subjects. In subjects with severe hepatic impairment, $C_{max,u}$ was increased to 165% and $AUC_{0-t,u}$ was increased to 134% compared to healthy subjects.
No dose adjustment for patients with mild and moderate hepatic impairment is required. For patients with severe hepatic impairment a reduced starting dose of 60 mg QD for 7 days followed by 120 mg QD is recommended.

Renal Impairment
In subjects with severe renal impairment, the total brigatinib C_{max} was increased to 130% and AUC_{0-t} to 202%. The brigatinib fraction excreted in urine (Fe_{0-168}) was decreased to ~50%, and the renal clearance of brigatinib was reduced to approximately 20% in subjects with severe renal impairment compared to healthy subjects. Brigatinib plasma protein binding was 91% in healthy control subjects and 92% in patients with severe renal impairment. As a consequence of the increased exposure, a reduced starting dose is warranted in patients with severe renal impairment.
The effect of mild and moderate renal impairment was assessed using a PopPK approach, which indicated that the PK of brigatinib was similar in patients with normal renal function and patients with mild or moderate renal impairment. Therefore, no adjustment of the starting dose for subjects with mild and moderate renal impairment is recommended. Nevertheless, serious adverse events and adverse events of grade 3-5 were observed more frequently with decreasing renal function, and the data in patients with moderate renal impairment are limited (n=30).

The PK of brigatinib was similar between Caucasians and Japanese, with a tendency for a slightly lower exposure in Japanese.
No adjustment of the starting dose based on age, weight, gender, ethnic background or albumin is recommended.

Pharmacokinetic Interactions / Extrinsic Factors

Effects of other drugs on brigatinib

CYP3A inducers and inhibitors
Brigatinib is a substrate of CYP3A. Consequently, brigatinib exposure was affected to a clinically relevant extent by both strong induction and strong inhibition of CYP3A:
Co-administration of brigatinib with itraconazole (a strong CYP3A4 inhibitor) increased the mean brigatinib AUC_{0-inf} to 201.2% and mean C_{max} to 121.2% as compared with intake of brigatinib alone.
The effect of moderate CYP3A inhibitors was assessed using a PBPK analysis, which predicted an increase in brigatinib exposure up to 140% upon concomitant use with a moderate CYP3A4 inhibitor.
Concomitant use of strong or moderate CYP3A4 inhibitors should be avoided. In case this is not possible, a reduction of the brigatinib dose is recommended.

Co-administration of brigatinib with rifampicin (strong inducer) decreased the mean brigatinib AUC to 20% and the mean C_{max} to 40%, as compared with intake of brigatinib alone.
Concomitant use of both strong and moderate inducers should be avoided. If this is not possible, increasing the brigatinib dose during concomitant use of moderate inducers is recommended.

Co-administration of brigatinib with gemfibrozil (strong CYP2C8 inhibitor) decreased the mean brigatinib AUC to 88.5% and the mean C_{max} to 59.1% as compared with intake of brigatinib alone.
These results indicated that CYP2C8 does not contribute to a great extent to the metabolism of brigatinib in humans. No dose adjustment is recommended.

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For detailed dosing recommendations with regard to concomitant medications see the attached information for healthcare professionals in Chapter 7.1 of this report.

Effects of brigatinib on other drugs

In vitro data indicated a potential for clinically relevant interaction effects of brigatinib on other drugs. This potential has not been investigated in clinical interaction studies.

Transporter substrates
Brigatinib is an inhibitor of P-gp, BCRP, OCT1, MATE1 and MATE2K in vitro. In consequence, exposure of substrates of these transporters might be elevated. Close monitoring is recommended in case of coadministration of sensitive substrates (e.g. dabigatran).

CYP3A substrates
In vitro, brigatinib induced CYP3A. Concomitant use of CYP3A substrates with a narrow therapeutic index should be avoided and, as regards contraception, a non-hormonal method should be used. A clinical interaction study with a CYP3A substrate is ongoing as a post marketing requirement.

Based on in vitro data, brigatinib is not an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, BSEP, CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5.

Pharmacodynamics

Mechanism of Action and primary Pharmacology
Brigatinib is an ALK - inhibitor.
Secondary Pharmacology (Safety)
Brigatinib`s potential to cause a QT prolongation was assessed as part of a dose escalation study. A categorical analysis of absolute QTcF times indicated that two (1.6%) of 123 patients had new QTcF > 480 ms. There were no reports of new QTcF > 500 ms. These results do not indicate a high risk for QT prolongation. In contrast to these results, QT prolongation has been recorded as a common adverse event (AE).
In view of the safety data under brigatinib and the established risk for a QT prolongation for other drugs of the same class, Swissmedic sees a risk for QT prolongation under brigatinib, and a warning is included in the information for healthcare professionals.

6.2 Dose Finding and Dose Recommendation

The phase 1/phase 2 cohort expansion trial AP26113-11-101 served as the basis for the recommended dose for the phase 2 trial AP26113-13-201 (ALTA). Due to early and delayed pulmonary toxicity, the 90 mg and 180 mg doses with 90 mg run-in for 7 days were selected for further phase 2 development. The phase 2 trial ALTA in second line showed a numerically superior response rate, progression-free survival (PFS) and overall survival (OS) for the 180 mg dose with 90 mg run-in for 7 days, and this is the dosing that was finally chosen for the phase 3 trial ALTA 1L (study AP26113-11-301), which is the basis for the marketing authorisation application for first-line treatment.

6.3 Efficacy

First-line treatment
The ALTA 1L study is an international, multicentre, 1:1 randomised, open-label, comparative phase 3 study of brigatinib (AP26113) versus crizotinib in patients with ALK-positive advanced non-small cell lung cancer (NSCLC). Between 05 May 2016 and 15 August 2017, the study randomised 275 patients with locally advanced or metastatic ALK-positive NSCLC who had not previously been exposed to an

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ALK-inhibitor. Patients were to receive either brigatinib 90 mg QD for 7 days followed by 180 mg QD, or crizotinib 250 mg twice daily (BID) until progression, intolerable toxicity or withdrawal of consent. Patients who progressed in the crizotinib arm were allowed to cross over to brigatinib after 10 days of washout at the investigator's discretion.

Primary endpoint was progression-free survival (PFS) as assessed by a blinded independent review committee (BIRC). Secondary endpoints were confirmed objective response rate (ORR), intracranial confirmed ORR (iORR), intracranial PFS (iPFS), overall survival (OS), safety and tolerability.

Eligible were adult patients with histologically or cytologically confirmed stage IIIB or stage IV NSCLC with documented ALK rearrangement by a positive result from the Vysis ALK Break-Apart FISH (fluorescence in situ hybridisation) Probe Kit (Abbott Molecular) or the Ventana ALK (D5F3) CDx (companion diagnostic) Assay. If ALK rearrangement was determined by a different test, adequate tissue had to be available for central laboratory testing by a US FDA-approved test. Patients had to have measurable disease, have recovered from toxicities of prior anticancer therapy, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, adequate organ function and a normal QT interval on screening ECG. The main exclusion criteria were prior tyrosine kinase inhibitor (TKI) treatment (any target), more than one regimen of systemic anticancer therapy for locally advanced or metastatic disease, symptomatic brain metastases, other prior malignancies, major comorbidities or uncontrolled hypertension.

The ALTA 1L trial randomised 275 patients, 137 to the brigatinib arm and 138 to the crizotinib arm. Two patients, one in each arm, never received study treatment. At the time of the second interim analysis (IA2), presented in this application, 75 (54.7%) patients in the brigatinib and 23 (16.7%) in the crizotinib arms were still on study treatment. Of the 75 patients still on brigatinib, 20 (14%) were receiving treatment beyond progression. Reasons for treatment discontinuation were similar between the two arms except for progressive disease (PD), which was more frequent in the crizotinib arm with 90 patients (65.2%) compared to brigatinib with 31 (22.6%). The main reason for study discontinuation was death, reported for 33 patients (24.1%) in the brigatinib arm and 25 patients (18.1%) in the crizotinib arm. Withdrawal by subject was the second reason for study discontinuation and was more frequent in the brigatinib arm, with 14 patients (10.2%) compared to the crizotinib arm with 5 patients (3.6%). Out of 114 patients who progressed on crizotinib, 61 crossed over to receive brigatinib. Of these 61 patients, 35 (57.4%) continue on study treatment, 10 (16.4%) patients are alive and in follow-up and 12 (19.7%) patients died. The primary reason for treatment discontinuation was documented PD in 20 (32.8%) of patients. In total, at IA2, 70 deaths have been observed, 33 in the brigatinib arm and 37 in the crizotinib arm.

The primary endpoint of improving PFS was reached with a hazard ratio (HR) of 0.492 (95% confidence interval [CI]: 0.33, 0.74) and a log-rank p-value of 0.0007 (therefore reaching the predefined 0.0044 significance level). Median PFS at IA1 was not reached in the brigatinib arm and was 9.76 months in the crizotinib arm. At IA2, after a median follow-up of 24.9 months in the brigatinib arm and 15.2 months in the crizotinib arm, median PFS was 24.0 months in the brigatinib arm and 11.0 months in the crizotinib arm. While in the crizotinib arm, 63.0% of the expected events have occurred, this proportion is only 46.0% in the brigatinib arm.

Key secondary efficacy endpoints were confirmed ORR, iORR, iPFS, and OS. ORR was 73.7% in the brigatinib arm versus 61.6% in the crizotinib arm, with an odds ratio of 1.73 and a p-value of 0.0342. The predefined alpha level for significance of secondary endpoints at the second interim analysis was 0.0183. This means that the first key secondary endpoint does not fulfil the statistical criteria for significance and, therefore, all other secondary endpoints are exploratory. iORR was higher in the brigatinib arm, with 66.0% versus 16.3% in the crizotinib arm for patients with any brain metastases (measurable and non-measurable). This difference is clinically meaningful and was observed in patients with measurable and non-measurable lesions alike. Time to response was rapid, with 1.9 months and 1.8 months for brigatinib and crizotinib, respectively. Intracranial PFS was also a

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secondary endpoint and showed an important benefit for brigatinib particularly in patients with brain metastases at baseline, who achieved a median iPFS of 24.0 months compared to 5.6 months in the crizotinib arm. Finally, OS is not mature, with 33 (24.1%) and 37 (26.8%) deaths in the brigatinib and crizotinib arms, respectively. In the Kaplan Meier analysis, no difference between the two arms has been observed to date. The final analysis is planned for June 2021.

Subgroup analyses show benefit for all analysed subgroups. Patients aged 65 years or older may have a lower benefit and the 95% CI crosses 1. Asians seem to benefit more than non-Asians. However, there does not seem to be a difference in benefit for never smokers or former smokers. Overall, all subgroups are consistent with the primary result of improved PFS of brigatinib over crizotinib.

Second-line treatment
The applicant has submitted study AP26113-13-201 (ALTA) as supportive evidence for the first-line indication and as the pivotal study for the requested second-line indication. ALTA is a non-comparative randomised phase 2 study of brigatinib (AP26113) in patients with ALK-positive NSCLC previously treated with crizotinib. Patients were randomised to two dose-levels of brigatinib in a non-comparative trial without a control arm.

The ALTA study randomised patients with metastatic ALK-positive NSCLC who had previously been treated with an ALK inhibitor to receive brigatinib either at 90 mg QD (arm A) or 180 mg QD after a 7-day run-in with 90 mg QD. The primary endpoint of the study was investigator-assessed ORR, and statistical significance was defined as an ORR > 20% including the lower 95% CI. This endpoint was reached in both arms. Investigator-assessed ORR was 45.5% in arm A and 57.8% in arm B. However, a blinded independent central review showed an ORR of 51.8% in arm A and 56.4% arm B. The study was not designed to be comparative, and no superiority can be concluded for arm B. Intracranial response rate was an important secondary endpoint and showed an iORR of 50.0% in arm A versus 66.7% in arm B. However, intracranial disease control rate was 84.6% in arm A and 83.3% in arm B. Toxicity was higher in the 180 mg cohort.

Duration of response was identical in both arms. Investigator-assessed median PFS was superior in arm B with 15.6 months compared to 9.2 months in arm A. Median overall showed a numerical benefit in favour of arm B with 40.6 months (95% CI: 32.5, not reached) compared to 25.9 months (95% CI: 18.2, 45.8) in arm A.

In conclusion, both arms reached the primary endpoint of ORR > 20%. Although the study was not designed to compare the two arms, the numerical superiority of arm B led to the design of the phase 3 trial with the higher dose despite higher toxicity.

6.4 Safety

Safety data were submitted from the two trials described above, ALTA and ALTA 1L. ALTA (study 201) was a phase 2 trial with two arms with different dosages of brigatinib. Only the 110 patients of arm B who received brigatinib 90 mg QD for 7 days followed by 180 mg QD were included in the overall safety database. The other study was the ALTA 1L (study 301) trial, which included 136 patients who received at least one dose of brigatinib with the 7-day run-in phase at 90 mg QD followed by 180 mg QD.

Study 201 almost exclusively included patients who were previously exposed to crizotinib (96%), while study 301 included patients who were tyrosine kinase inhibitor (TKI) naïve. Exposure to brigatinib in study 301 was longer (24.3 months) than in study 201 (17.1 months). Median duration of exposure to crizotinib was 8.4 months in study 301. Therefore, the combined exposure of crizotinib followed by brigatinib in second line approximately equals brigatinib exposure upfront.

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Nearly all patients in the pooled brigatinib population (99.6%) developed treatment-emergent adverse events (TEAEs). In the brigatinib population, 93.1% of patients developed TEAEs considered treatment-related. Grade 3-5 TEAEs occurred in 72.0% of patients treated with brigatinib and 51.2% were considered treatment-related. Serious adverse events (SAEs) developed in 11.4% of patients treated with brigatinib. TEAEs leading to treatment discontinuation occurred in 11.8% of patients on brigatinib. TEAEs leading to treatment interruption were observed in 64.2% of patients and 34.1% of patients required dose reductions due to TEAEs.

Common Adverse Events
Patients treated with brigatinib presented the following TEAEs: increased creatine phosphokinase (CPK) (41.5%), cough (37.4%), hypertension (29.7%), pancreatic enzyme elevation (38.6%), skin disorders (54.1%), nausea (39.0%), vomiting (26.8%), eye disorders (20.3%) such as blurred vision (7.7%), eye pain, visual impairment, and visual acuity reduced (1.5% each).

Four patients treated with brigatinib developed interstitial lung disease. Pneumonitis was observed in 16 patients.

Grade ≥ 3 TEAEs
Grade 3-5 TEAEs were observed in 72.0% of brigatinib-treated patients. This seems to be mostly driven by the system organ class (SOC) of investigations, primarily through the observed increase in creatine phosphokinase (CPK) in brigatinib-treated patients (19.9%). High-grade hypertension was observed in 10.6% of patients and pneumonitis in 2.4% of patients. Other grade 3-5 toxicities observed frequently were pulmonary embolism (2.4%), lipase increased (10.2%), amylase increased (4.1%), pneumonia (4.5%), alanine aminotransferase increased (3.7%), and aspartate aminotransferase increased (3.3%).

Deaths
On-treatment deaths occurred in 8.1% of brigatinib-treated patients. There is no signal for toxic deaths related to treatment. Indeed, except for one sudden death on study day 3, where the investigator felt that a relationship with the study drug could not be excluded, none of the deaths were considered to be related to the study drug.

Serious Adverse Events (SAEs)
SAEs occurred in 43.5% of patients treated with brigatinib. The most frequently observed SAEs in the brigatinib arm were pneumonitis and interstitial lung disease (combined 5.7%), pneumonia (6.5%), as well as pyrexia and asthenia. Other SAEs were dyspnoea and pulmonary embolism.

TEAEs leading to treatment interruption
Treatment interruptions occurred in 64.2% of patients treated with brigatinib. The most frequent TEAEs leading to treatment interruption were elevated CPK, elevated pancreatic enzymes, hypertension, pneumonitis, and QT prolongation.

TEAEs leading to dose reduction
Dose reductions were required in 34.1% of patients treated with brigatinib. The most frequent TEAEs leading to dose reduction of brigatinib were increased CPK, lipase, amylase, hypertension and pneumonitis. One patient had a dose reduction due to bradycardia and two due to QT-prolongation.

TEAEs leading to study drug discontinuation
Study drug was discontinued in relatively few patients. In the brigatinib cohort, 11.8% of patients discontinued study treatment due to an AE, most frequently pneumonitis/ILD, pneumonia, and bradycardia.

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6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Metastatic NSCLC is invariably fatal, even if overall survival appears more favourable in ALK rearranged patients, at 6.8 years [Pacheco et al., JTO, 2019], compared to patients without a molecular target, who had a median overall survival of less than 1 year before the advent of immune checkpoint inhibitors [Abernethy et al., PLoS One, 2017]. Although the introduction of TKIs targeting ALK has improved the outcome in these patients, adverse effect profiles as well as the development of resistance to first-generation inhibitors still leave a medical need to develop new and better treatments in this setting.

Beneficial Effects

Brigatinib is an orally available ALK-inhibitor. The basic PK characteristics of brigatinib (PK after single and multiple doses, mass balance, PK bridging between formulations) have been sufficiently investigated. Furthermore, a lack of a relevant food effect has been shown.

First-line treatment
Brigatinib was compared to the first-generation ALK inhibitor crizotinib in an open, randomised phase 3 clinical trial (ALTA 1L) of ALK-positive advanced NSCLC patients who had not been previously exposed to an ALK-inhibitor. The trial showed superiority in terms of the primary endpoint, which was blinded independent review committee (BIRC) assessed progression-free survival (PFS). At the first interim analysis, median PFS for brigatinib had not been reached, but the hazard ratio (HR) for PFS was 0.492 (95% CI: 0.33, 0.74) with a log-rank p-value of 0.0007 (therefore reaching the predefined 0.0044 significance level). At the second interim analysis, median PFS for brigatinib was 24.0 months compared to 11.0 months for crizotinib. Therefore, brigatinib more than doubled PFS in these ALK-inhibitor-naïve locally advanced (7.2% of the study population) or metastatic NSCLC patients.

While there is a clinically relevant improvement in PFS with brigatinib over crizotinib in first-line treatment, no mature data on OS are available to date, and no trend is visible. It remains unknown how patients will respond to further lines of treatment when progressing on brigatinib, while the combined PFS of crizotinib, followed by brigatinib is similar to brigatinib upfront. The final results of the ALTA 1L study will only be available by June 2021. The applicant has committed to submitting the data when they become available.

Second-line treatment
In the phase 2 ALTA study, which evaluated two dose regimens of brigatinib in patients previously treated with and progressing on crizotinib, both arms reached the primary endpoint of an objective response rate (ORR) of > 20%. The higher dosing regimen of 180 mg once daily (QD) after a 7-day run-in with 90 mg QD showed a numerically better PFS and OS, although this study was not designed to be comparative. The ORR as well as PFS and OS appear clinically interesting, with 15.6 months median PFS in previously treated patients. With a median follow-up of 19.6 months for the 90 mg arm and 28.3 months in the 180 mg arm, the median OS was 25.9 months and 40.6 months, respectively. The difference was not statistically significant in an exploratory post-hoc analysis.

Unfavourable Effects

Brigatinib is eliminated both via the hepatic and renal routes. Brigatinib exposure is increased to a clinically relevant extent in subjects with severely impaired hepatic or renal function, which necessitates adjustment of the dosing regimen in these patients.

Brigatinib is subject to clinically relevant drug-drug interactions, which limits concomitant use with other drugs (moderate and strong inducers) or necessitates adjustment of the starting dose (moderate and strong CYP3A4 inhibitors). The recommended dose adjustments have not been established in

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clinical studies, but are based on theoretical considerations. In light of brigatinib's linear PK, and since patients will be carefully monitored for AEs in clinical practice, this is acceptable.

Patients with ESRD under dialysis have not been studied. Thus, no dosing recommendation can be given.

In vitro data indicated a potential for clinically relevant interaction effects of brigatinib on other drugs by inhibition of various transporters and by CYP3A induction. However, this potential has not been investigated in clinical interaction studies. Although the risk that results from the lack of data is adequately communicated in the information for healthcare professionals, especially the risk for a clinically relevant CYP3A induction, this significantly limits the options for concomitant use of other drugs. The uncertainty about this risk should be reduced in order to avoid potentially unnecessary restrictions. Therefore, a clinical DDI study has to be submitted as a post-authorisation requirement.

No dedicated thorough QT study has been performed. ECG analyses during the phase 2 and 3 trials indicate that approximately 10% of patients develop QTc prolongations of > 60 ms. Concurrent medication known to possibly induce torsade-de-pointes were prohibited, and QT-prolonging medication was to be avoided. The safety database with a total of 246 patients remains small, and infrequent adverse effects may not have been detected. This relevant information on QT prolongation is reflected in the "Warnings and Precautions" section of the information for healthcare professionals.

Only 30 patients with moderate renal impairment were included in the clinical trial programme and toxicity appears to be higher in these patients compared to patients with normal renal function. Dose recommendations for these patients are unclear. This uncertainty is currently reflected in the information for healthcare professionals, and updated safety data in patients with renal impairment have to be submitted as a post-authorisation requirement.

Brigatinib has a high incidence of grade 3-5 TEAEs (72%) and SAEs (42%). However, this is mostly due to CPK and pancreatic enzyme elevations, which are asymptomatic in the majority of patients. Other relevant toxicities are nausea, vomiting, visual disturbance, liver enzyme elevations, hyperglycaemia, skin rash, pneumonitis/interstitial lung disease, dyspnoea and asthenia. There is no signal for excess mortality due to brigatinib. Overall, the safety profile of brigatinib seems manageable.

First-line treatment
The improvement of median PFS from 11 to 24 months in a first-line treatment of an incurable disease with an acceptable safety profile is clinically relevant. However, OS data are immature, and updated analyses for OS will be important for an adequate benefit-risk evaluation. It is of note that, so far, none of the authorised ALK inhibitors has demonstrated an overall survival benefit. The benefit risk evaluation is positive.

Second-line treatment
Regarding second-line treatment after progression on crizotinib, the ORR, PFS and OS are of clinical relevance despite the drawback of the absence of a comparator arm. Data from the phase 3 ALTA 1L trial support efficacy of brigatinib over crizotinib and increase the safety population. The benefit risk evaluation is positive.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order 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. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. 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 occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Alunbrig 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 reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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.

Alunbrig

Composition

Active substances

Brigatinib

Excipients

Tablet core: Lactose monohydrate (56.06 mg in 30 mg tablet, 168.17 mg in 90 mg tablet, 336.33 mg in 180 mg tablet), Microcrystalline cellulose, Sodium starch glycolate (type A) (equivalent to 0.13 - 0.19 mg sodium per 30 mg tablet, 0.38 - 0.57 mg sodium per 90 mg tablet, 0.76 - 1.13 mg sodium per 180 mg tablet), Silica, hydrophobic colloidal, Magnesium stearate

Tablet coating: Talc, Macrogol 3350, Polyvinyl alcohol, Titanium dioxide

Pharmaceutical form and active substance quantity per unit

Film-coated tablet (tablet) with 30 mg, 90 mg and 180 mg brigatinib.
Alunbrig 30 mg film-coated tablets
Round, white to off-white film-coated tablet of approximately 7 mm in diameter with debossed “U3” on one side and plain on the other side.
Alunbrig 90 mg film-coated tablets
Oval, white to off-white film-coated tablet of approximately 15 mm in length with debossed “U7” on one side and plain on the other side.
Alunbrig 180 mg film-coated tablets
Oval, white to off-white film-coated tablet of approximately 19 mm in length with debossed “U13” on one side and plain on the other side.

Indications/Uses

Alunbrig is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) previously untreated with an ALK inhibitor.

Alunbrig is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on previous treatment with crizotinib.

Dosage/Administration

The use of Alunbrig should be supervised by a physician experienced in the use of anticancer medicinal products.

ALK-positive NSCLC status should be known prior to initiation of Alunbrig therapy. A validated ALK assay is necessary for the identification of ALK-positive NSCLC patients (see “Pharmacodynamics” section). Assessment for ALK-positive NSCLC status should be performed by laboratories with demonstrated proficiency in the required specific technology.

Dosage

The recommended starting dose of Alunbrig is 90 mg once daily for the first 7 days, then 180 mg once daily.
If treatment with Alunbrig is interrupted for 14 days or longer, re-escalation is recommended: treatment should be restarted at 90 mg once daily for 7 days before increasing to the previously tolerated dose, or one level lower, based on dose modification recommendations. Please refer to Table 2 for dose modifications related to adverse reactions (see also “Undesirable effects” section).
If a dose is missed or vomiting occurs after taking a dose, an additional dose should not be administered and the next dose should be taken at the scheduled time.
Treatment should continue as long as clinical benefit is observed or until uncontrollable toxicity.

Dose adjustment

Dosing interruption and/or dose reduction may be required depending on undesirable drug effects. Alunbrig dose reduction levels are summarised in Table 1.

Table 1: Recommended Alunbrig dose reduction levels

Dose	**Dose reduction levels**		
	First	**Second**	**Third**
90 mg once daily (first 7 days)	reduce to 60 mg once daily	permanently discontinue	not applicable
180 mg once daily	reduce to 120 mg once daily	reduce to 90 mg once daily	reduce to 60 mg once daily

Alunbrig should be permanently discontinued if patient is unable to tolerate the 60 mg once daily dose.
Recommendations for dose modifications of Alunbrig for the management of adverse reactions are summarised in Table 2.

Table 2: Recommended Alunbrig dose modifications for adverse reactions

Adverse reaction	Severity*	Dose modification
Interstitial lung disease (ILD)/pneumonitis	Grade 1	• If event occurs during the first 7 days of treatment, Alunbrig should be withheld until recovery to baseline, then resumed at same dose level and not escalated to 180 mg once daily. • If ILD/pneumonitis occurs after the first 7 days of treatment, Alunbrig should be withheld until recovery to baseline, then resumed at same dose level. • If ILD/pneumonitis recurs, Alunbrig should be permanently discontinued.
	Grade 2	• If ILD/pneumonitis occurs during the first 7 days of treatment, Alunbrig should be withheld until recovery to baseline, then resumed at next lower dose level (see Table 1) and not escalated to 180 mg once daily. • If ILD/pneumonitis occurs after the first 7 days of treatment, Alunbrig should be withheld until recovery to baseline. Alunbrig should be resumed at next lower dose level as described in Table 1 • If ILD/pneumonitis recurs, Alunbrig should be permanently discontinued.
	Grade 3 or 4	• Alunbrig should be permanently discontinued.
Hypertension	Grade 3 hypertension (SBP ≥ 160 mmHg or DBP ≥ 100 mmHg, medical intervention indicated, more than one anti-hypertensive medicinal product, or more intensive therapy than previously used indicated)	• Alunbrig should be withheld until hypertension has recovered to Grade ≤ 1 (SBP < 140 mmHg and DBP < 90 mmHg), then resumed at same dose. • If Grade 3 hypertension recurs, Alunbrig should be withheld until hypertension has recovered to Grade ≤ 1 then resumed at the next lower dose level per Table 1 or permanently discontinued.
	Grade 4 hypertension (life threatening consequences, urgent intervention indicated)	• Alunbrig should be withheld until hypertension has recovered to Grade ≤ 1 (SBP < 140 mmHg and DBP < 90 mmHg), then resumed at the next lower dose level per Table 1 or permanently discontinued. • If Grade 4 hypertension recurs, Alunbrig should be permanently discontinued.

Adverse reaction	Severity*	Dose modification
Bradycardia (Heart Rate less than 60 bpm)	Symptomatic bradycardia	• Alunbrig should be withheld until recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above. • If a concomitant medicinal product known to cause bradycardia is identified and discontinued, or its dose is adjusted, Alunbrig should be resumed at same dose upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above. • If no concomitant medicinal product known to cause bradycardia is identified, or if contributing concomitant medications are not discontinued or dose modified, Alunbrig should be resumed at the next lower dose level per Table 1 upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above.
	Bradycardia with life-threatening consequences, urgent intervention indicated	• If contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, Alunbrig should be resumed at the next lower dose level per Table 1 upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. • Alunbrig should be permanently discontinued if no contributing concomitant medicinal product is identified. • Alunbrig should be permanently discontinued in case of recurrence.
Elevation of CPK	Grade 3 or 4 elevation of CPK (> 5.0 × ULN) with Grade ≥ 2 muscle pain or weakness	• Alunbrig should be withheld until recovery to Grade ≤ 1 (≤ 2.5 × ULN) or to baseline, then resumed at the same dose. • If Grade 3 or 4 elevation of CPK recurs with Grade ≥ 2 muscle pain or weakness, Alunbrig should be withheld until recovery to Grade ≤ 1 (≤ 2.5 × ULN) or to baseline, then resumed at the next lower dose level per Table 1.
Elevation of lipase or amylase	Grade 3 elevation of lipase or amylase (> 2.0 × ULN)	• Alunbrig should be withheld until recovery to Grade ≤ 1 (≤ 1.5 × ULN) or to baseline, then resumed at same dose. • If Grade 3 elevation of lipase or amylase recurs, Alunbrig should be withheld until recovery to Grade ≤ 1 (≤ 1.5 × ULN) or to baseline, then resumed at the next lower dose level per Table 1.

Adverse reaction	Severity*	Dose modification
	Grade 4 elevation of lipase or amylase (> 5.0 x ULN)	• Alunbrig should be withheld until recovery to Grade ≤ 1 (≤ 1.5 × ULN), then resumed at the next lower dose level per Table 1.
Hepatotoxicity	Grade ≥ 3 elevation (> 5.0 × ULN) of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with bilirubin ≤ 2 × ULN	• Alunbrig should be withheld until recovery to baseline or less than or equal to 3 × ULN, then resumed at next lower dose per Table 1.
	Grade ≥ 2 elevation (> 3 × ULN) of ALT or AST with concurrent total bilirubin elevation > 2 × ULN in the absence of cholestasis or haemolysis	• Alunbrig should be permanently discontinued.
Hyperglycaemia	Grade 3 or greater (> 250 mg/dL or 13.9 mmol/L)	• If adequate hyperglycaemic control cannot be achieved with optimal medical management, Alunbrig should be withheld until adequate hyperglycaemic control is achieved. Once blood glucose levels are again within the normal range, Alunbrig may either be resumed at the next lower dose per Table 1 or permanently discontinued.
Visual disturbance	Grade 2 or 3	• Alunbrig should be withheld until recovery to Grade 1 or baseline, then resumed at the next lower dose level per Table 1.
	Grade 4	• Alunbrig should be permanently discontinued.
Other adverse reactions	Grade 3	• Alunbrig should be withheld until recovery to baseline, then resumed at the same dose level. • If the Grade 3 event recurs, Alunbrig should be withheld until recovery to baseline, then resumed at the next lower dose level as per Table 1 or permanently discontinued.
	Grade 4	• Alunbrig should be withheld until recovery to baseline, then resumed at the next lower dose level as per Table 1. • If the Grade 4 event recurs, Alunbrig should be withheld until recovery to baseline, then resumed at the next lower dose level as per Table 1 or permanently discontinued.
min = minute; CPK = Creatine Phosphokinase; ULN = upper limit of normal		

*Graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4).

Dose adjustment following interactions

For dose adjustments when taking accompanying medication see “Interactions” section.

Special populations

Elderly patients

The limited data (N = 96) on the safety and efficacy of Alunbrig in patients aged 65 years and older suggest that a dose adjustment is not required in elderly patients (see “Undesirable effects” section). There are no available data on patients over 85 years of age. In clinical studies, Grade 3-5 undesirable effects occurred in 81% of patients aged 65 years and older compared to 69% of patients under 65 years of age treated with Alunbrig at the recommended dose.

Patients with impaired hepatic function

No dose adjustment of Alunbrig is required for patients with mild hepatic impairment (Child-Pugh class A) or moderate hepatic impairment (Child-Pugh class B). The dose of Alunbrig should be reduced by approximately 40% (i.e., from 180 mg to 120 mg, 120 mg to 90 mg, or from 90 mg to 60 mg) for patients with severe hepatic impairment (Child-Pugh class C) (see “Pharmacokinetics” section).

Patients with impaired renal function

No dose adjustment of Alunbrig is required for patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥ 30 mL/min/1.73 m^2).
In clinical studies, serious adverse events and Grade 3-5 adverse events increased with worsening renal function and limited data are available in patients with moderate renal impairment (N = 30).

Based on the results of a pharmacokinetic study, the dose of Alunbrig should be reduced by approximately 50% (i.e., from 180 mg to 90 mg, or from 90 mg to 60 mg) for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) (see “Pharmacokinetics” section). No clinical data are available in patients with severe renal impairment.

Children and adolescents

The safety and efficacy of Alunbrig in patients less than 18 years of age have not been established. No data are available.

Mode of administration

Alunbrig is for oral use. The tablets should be swallowed whole and with water. Alunbrig may be taken with or without food.
Grapefruit or grapefruit juice may increase plasma concentrations of brigatinib and should be avoided (see “Interactions” section).

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in “Composition” section.

Warnings and precautions

Pulmonary adverse reactions

Severe, life-threatening, and fatal pulmonary adverse reactions, including those with features consistent with ILD/pneumonitis, can occur in patients treated with Alunbrig (see “Undesirable effects” section).
Most pulmonary adverse reactions were observed within the first 7 days of treatment. Grade 1-2 pulmonary adverse reactions resolved with interruption of treatment or dose modification. Increased age and shorter intervals (less than 7 days) between the last dose of crizotinib and the first dose of Alunbrig were independently associated with an increased rate of these pulmonary adverse reactions. These factors should be considered when initiating treatment with Alunbrig. Patients with a history of ILD or drug-induced pneumonitis were excluded from the pivotal trials.
Some patients experienced pneumonitis later in treatment with Alunbrig.
Patients should be monitored for new or worsening respiratory symptoms (e.g., dyspnoea, cough, etc.), particularly in the first week of treatment. Evidence of pneumonitis in any patient with worsening respiratory symptoms should be promptly investigated. If pneumonitis is suspected, the dose of Alunbrig should be withheld, and the patient evaluated for other causes of symptoms (e.g., pulmonary embolism, tumour progression, and infectious pneumonia). The dose should be modified accordingly (see “Dosage/Administration” section).

Hypertension

Hypertension has occurred in patients treated with Alunbrig (see “Undesirable effects” section).
Blood pressure should be monitored regularly during treatment with Alunbrig. Hypertension should be treated according to standard guidelines to control blood pressure. For severe hypertension (≥ Grade 3), Alunbrig should be withheld until hypertension has recovered to Grade 1 or to baseline. The dose should be modified accordingly (see “Dosage/Administration” section).

QT Prolongation

QT prolongation has occurred in patients treated with Alunbrig. Patients with pre-existing prolonged QTcF (corrected QT by the Fridericia method) were excluded from the pivotal trials. Caution should be exercised when administering Alunbrig to patients with QT prolongation or when administering Alunbrig in combination with other agents known to cause QT prolongation (see “Properties/Effects”, “Pharmacokinetics” sections).

Bradycardia

Bradycardia has occurred in patients treated with Alunbrig (see “Undesirable effects” section). Caution should be exercised when administering Alunbrig in combination with other agents known to cause bradycardia. Heart rate and blood pressure should be monitored regularly.
If symptomatic bradycardia occurs, treatment with Alunbrig should be withheld and comedication should concurrently be evaluated for agents known to have the potential to cause bradycardia. Upon resolution of symptoms, the dose should be modified accordingly (see “Dosage/Administration” section). In case of life-threatening bradycardia, or if no concomitant medication known to cause bradycardia is identified, or in case of recurrence, treatment with Alunbrig must be discontinued (see “Dosage/Administration” section).

Visual disturbance

Visual disturbance adverse reactions have occurred in patients treated with Alunbrig (see “Undesirable effects” section). Patients should be advised to report any visual symptoms. For new or worsening pre-existing visual symptoms, an ophthalmologic evaluation and dose reduction should be considered (see “Dosage/Administration” section).

Creatine phosphokinase (CPK) elevation

Elevations of CPK have occurred in patients treated with Alunbrig (see “Undesirable effects” section). Patients should be advised to report any unexplained muscle pain, tenderness, or weakness. CPK levels should be monitored regularly during Alunbrig treatment. Based on the severity of the CPK elevation, and if associated with muscle pain or weakness, treatment with Alunbrig should be withheld, and the dose modified accordingly (see “Dosage/Administration” section).

Elevations of pancreatic enzymes

Elevations of amylase and lipase have occurred in patients treated with Alunbrig (see “Undesirable effects” section). Lipase and amylase should be monitored regularly during treatment with Alunbrig. Based on the severity of the laboratory abnormalities, treatment with Alunbrig should be withheld, and the dose modified accordingly (see “Dosage/Administration” section).

Hepatotoxicity

Elevations of hepatic enzymes (aspartate aminotransferase, alanine aminotransferase) and bilirubin have occurred in patients treated with Alunbrig (see “Undesirable effects” section). Liver function, including AST, ALT and total bilirubin, should be assessed prior to the initiation of Alunbrig and then every 2 weeks during the first 3 months of treatment. Thereafter, monitoring should be performed periodically. Based on the severity of the laboratory abnormalities, treatment should be withheld, and the dose modified accordingly (see “Dosage/Administration” section).

Hyperglycaemia

Elevations of serum glucose have occurred in patients treated with Alunbrig. Fasting serum glucose should be assessed prior to initiation of Alunbrig and monitored periodically thereafter. Antihyperglycaemic treatment should be initiated or optimised as needed. If adequate hyperglycaemic control cannot be achieved with optimal medical management, Alunbrig should be withheld until adequate hyperglycaemic control is achieved; thereafter, reducing the dose as described in Table 1 may be considered or Alunbrig may be permanently discontinued.

Embryo-foetal toxicity

Animal studies indicate that Alunbrig can cause foetal damage when used in pregnant women (see “Preclinical data”). Pregnant women who receive Alunbrig should be informed of the potential risk of damage to the foetus.
Women of childbearing age must use effective non-hormonal contraception during treatment with Alunbrig and for at least 4 months following the final dose. Men with female partners of childbearing age must be advised to use effective contraception during treatment and for at least 3 months after the last dose of Alunbrig (see “Pregnancy, lactation” section).

Lactose

Alunbrig contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, i.e. it is essentially "sodium-free".

Interactions

Effect of other substances on the pharmacokinetics of brigatinib

Concomitant use should be avoided

CYP3A inhibitors

In vitro studies demonstrated that brigatinib is a substrate of CYP3A4/5. In healthy subjects, coadministration of multiple 200 mg twice daily doses of itraconazole, a strong CYP3A inhibitor, with a single 90 mg brigatinib dose increased brigatinib C_{max} by 21%, $AUC_{0\text{-}INF}$ by 101% (to 2-fold), and $AUC_{0\text{-}120}$ by 82% (to 1.82-fold), relative to a 90 mg brigatinib dose administered alone. The concomitant use of strong CYP3A inhibitors with Alunbrig, including but not limited to certain antivirals (e.g., indinavir, nelfinavir, ritonavir, saquinavir), macrolide antibiotics (e.g., clarithromycin, telithromycin, troleandomycin), antifungals (e.g., ketoconazole, voriconazole), and nefazodone should be avoided. If concomitant use of strong CYP3A inhibitors cannot be avoided, the dose of Alunbrig should be reduced by approximately 50% (e.g., from 180 mg to 90 mg, or from 90 mg to 60 mg). After discontinuation of a strong CYP3A inhibitor, Alunbrig should be resumed at the dose that was tolerated prior to the initiation of the strong CYP3A inhibitor.
Moderate CYP3A inhibitors (e.g., diltiazem and verapamil) may increase the AUC of brigatinib by approximately 40% based on simulations from a physiologically-based pharmacokinetic model. The concomitant use of moderate CYP3A inhibitors with Alunbrig should be avoided. If concomitant use of moderate CYP3A inhibitors cannot be avoided, the dose of Alunbrig should be reduced by approximately 40% (i.e. from 180 mg to 120 mg, 120 mg to 90 mg, or from 90 mg to 60 mg). After discontinuation of a moderate CYP3A inhibitor, Alunbrig should be resumed at the dose that was tolerated prior to the initiation of the moderate CYP3A inhibitor.
Grapefruit or grapefruit juice may also increase plasma concentrations of brigatinib and should be avoided (see “Dosage/Administration” section).

CYP3A inducers

In healthy volunteers, coadministration of multiple 600 mg doses of rifampicin, a potent CYP3A inducer, with a single dose of 180 mg brigatinib led to a reduction in brigatinib C_{max} by 60%, in $AUC_{0\text{-}INF}$ by 80% (to 0.2-fold) and in $AUC_{0\text{-}120}$ by 80% (to 0.2-fold), relative to a 180 mg brigatinib dose administered alone. The concomitant administration of potent CYP3A inducers with Alunbrig, including but not limited to rifampicin, carbamazepine, phenytoin, rifabutin, phenobarbital and St John’s wort, should be avoided.
Simulations with a physiologically based pharmacokinetic model showed that moderate CYP3A inducers can reduce the AUC of brigatinib by approximately 50%. The concomitant administration of moderate CYP3A inducers with Alunbrig, including but not limited to efavirenz, modafinil, bosentan, etravirine and nafcillin, should be avoided. If concomitant administration of moderate CYP3A inducers

cannot be avoided, the dose of Alunbrig should be increased after 7 days of treatment with the currently tolerated dose of Alunbrig in 30 mg steps to a maximum of twice the dose of Alunbrig that was tolerated before administration of the moderate CYP3A inducer. After discontinuation of a moderate CYP3A inducer, Alunbrig should again be administered at the dose that was tolerated before starting the moderate CYP3A inducer.

Other interactions

CYP2C8 inhibitors

In vitro studies showed that brigatinib is a substrate of CYP2C8. In healthy subjects, coadministration of multiple 600 mg twice daily doses of gemfibrozil, a strong CYP2C8 inhibitor, with a single 90 mg brigatinib dose reduced brigatinib C_{max} by 41% (to 0.59-fold), $AUC_{0\text{-}INF}$ by 12% (to 0.88-fold), and $AUC_{0\text{-}120}$ by 15% (to 0.85-fold), relative to a 90 mg brigatinib dose administered alone. The effect of gemfibrozil on the pharmacokinetics of brigatinib is not clinically meaningful and the underlying mechanism for the decreased exposure of brigatinib is unknown. No dose adjustment is recommended for Alunbrig during coadministration with strong CYP2C8 inhibitors.

P-gp and BCRP inhibitors

Brigatinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) *in vitro*. Given that brigatinib exhibits high solubility and high permeability, inhibition of P-gp and BCRP is not expected to result in a clinically meaningful change in the systemic exposure of brigatinib. No dose adjustment is recommended for Alunbrig during coadministration with P-gp and BCRP inhibitors.

Inhibitors of other transporters

Brigatinib is not a substrate of organic anion transporting polypeptides (OATP1B1, OATP1B3), organic anion transporters (OAT1, OAT3), organic cation transporters (OCT1, OCT2), multidrug and toxin extrusion proteins (MATE1, MATE2K), or bile salt export pump (BSEP).

Effect of brigatinib on the pharmacokinetics of other substances

Concomitant use should be avoided

CYP3A substrates

In vitro studies in hepatocytes have shown that brigatinib is an inducer of CYP3A4. Clinical drug-drug interaction studies with sensitive CYP3A substrates have not been conducted. Brigatinib may reduce plasma concentrations of coadministered medicinal products that are predominantly metabolised by CYP3A. Therefore, coadministration of Alunbrig with CYP3A substrates with a narrow therapeutic index (e.g., alfentanil, fentanyl, quinidine, cyclosporine, sirolimus, tacrolimus, hormonal contraceptives) should be avoided as their effectiveness may be reduced.

Alunbrig may also induce other enzymes and transporters (e.g., CYP2C, P-gp) via the same mechanisms responsible for induction of CYP3A (e.g., pregnane X receptor activation).

Special caution with coadministration

Transporter substrates (P-gp, BCRP, OCT1, MATE1, and MATE2K)

Brigatinib is an inhibitor of P-gp, BCRP, OCT1, MATE1, and MATE2K *in vitro*. Therefore, brigatinib may have the potential to increase concentrations of co-administered substrates of these transporters. Patients should be closely monitored when Alunbrig is co-administered with substrates of these transporters with a narrow therapeutic index (e.g., digoxin, dabigatran, methotrexate).

Other interactions

Other transporter substrates

Based on *in vitro* data, brigatinib at clinically relevant concentrations did not inhibit OATP1B1, OATP1B3, OAT1, OAT3, OCT2, or BSEP.

Other CYP-Substrates

Based on *in vitro* data, brigatinib at clinically relevant concentrations did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5.

Pregnancy, lactation

Contraception in males and females

Women of childbearing age being treated with Alunbrig should be advised not to become pregnant. Men being treated with Alunbrig should be advised not to father a child during treatment.
Women of childbearing age must use effective non-hormonal contraception during treatment with Alunbrig and for at least 4 months following the final dose. Because of the genotoxic potential, male patients with female partners of childbearing age must use effective contraception during treatment and for at least 3 months after the last dose of Alunbrig (see “Preclinical data”).

Pregnancy

Based on animal studies with brigatinib (see “Preclinical data” section) and its mechanism of action, Alunbrig can cause damage to the foetus when administered to a pregnant woman. There are no clinical data on the use of Alunbrig in pregnant women. Alunbrig should not be used during pregnancy unless the clinical condition of the expectant mother requires treatment. If Alunbrig is used during pregnancy, or if the patient becomes pregnant while taking this medicinal product, the patient should be apprised of the potential hazard to the foetus.

Lactation

It is unknown whether brigatinib or its metabolites are excreted in human milk. A risk to the infant cannot be ruled out. Breast-feeding should be stopped during treatment with Alunbrig and for at least 1 week after the final dose.

Fertility

No human data on the effect of Alunbrig on fertility are available. The results of repeat-dose toxicity studies suggest that Alunbrig may cause reduced fertility in males (see “Preclinical data”).

Effects on ability to drive and use machines

No corresponding studies have been performed. However, based on the observed side effects of visual disturbances, dizziness or fatigue, caution is advised when driving or using machinery.

Undesirable effects

Summary of the safety profile

The safety profile is based on the analysis of 274 patients who were included in studies ALTA 1L, ALTA, and Study 101.

The most common adverse reactions (≥ 25%) reported in patients treated with Alunbrig at the recommended dosing regimen were increased AST (68%), increased CPK (64%), hyperglycaemia (61%), increased lipase (54%), hyperinsulinaemia (53%), diarrhoea (49%), increased ALT (49%), increased amylase (47%), anaemia (47%), nausea (40%), fatigue (40%), hypophosphataemia (39%), decreased lymphocyte count (39%), cough (38%), increased alkaline phosphatase (37%), rash (37%), increased APTT (36%), myalgia (34%), headache (33%), hypertension (30%), decreased white blood cell count (28%), dyspnoea (27%), and vomiting (26%).
Serious adverse reactions occurred in 43% of the patients treated with Alunbrig at the recommended dosing regimen. The most common serious adverse reactions (≥ 2%) reported in patients treated with Alunbrig at the recommended dosing regimen other than events related to neoplasm progression were pneumonia, pneumonitis, dyspnoea, and pyrexia.
Treatment-emergent adverse events that led to dose reduction occurred in 32.8% of patients treated with Alunbrig at the recommend dose. No detrimental impact on efficacy was observed in those patients who experienced a dose-reduction due to toxicity.

List of adverse reactions

Adverse reactions reported at the recommended dosing regimen are presented in Table 3 and are listed by system organ class, preferred term and frequency. Frequency categories are very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of frequency.

Table 3: Adverse reactions reported in patients treated with Alunbrig (per Common Terminology Criteria for Adverse Events (CTCAE) version 4.03) at the 180 mg regimen (N = 274)

System organ class	Frequency category	Adverse reactions† all grades	Adverse reactions Grade 3-4
Infections and infestations	Very common	Pneumonia[a,b] (15%) Upper respiratory tract infection (12%)	
	Common		Pneumonia[a]
Blood and lymphatic system disorders	Very common	Anaemia (47%) Lymphocyte count decreased (39%) APTT increased (36%) White blood cell count decreased (28%) Neutrophil count decreased (11%)	Lymphocyte count decreased
	Common	Decreased platelet count	APTT increased Anaemia
	Uncommon		Neutrophil count decreased
Metabolism and nutrition disorders	Very common	Hyperglycaemia (61%) Hyperinsulinaemia[c] (53%) Hypophosphataemia (39%) Hypomagnesaemia (22%) Hypercalcaemia (21%) Hyponatraemia (20%) Hypokalaemia (19%) Decreased appetite (17%)	
	Common		Hypophosphataemia Hyperglycaemia Hyponatraemia Hypokalaemia Decreased appetite
Psychiatric disorders	Common	Insomnia	
Nervous system disorders	Very common	Headache[d] (33%) Peripheral neuropathy[e] (20%) Dizziness (15%)	
	Common	Memory impairment Dysgeusia	Headache[d] Peripheral neuropathy[e]
	Uncommon		Dizziness
Eye disorders	Very common	Visual disturbance[f] (14%)	
	Common		Visual disturbance[f]

System organ class	Frequency category	Adverse reactions† all grades	Adverse reactions Grade 3-4
Cardiac disorders	Common	Bradycardia[g] Electrocardiogram QT prolonged Tachycardia[h] Palpitations	Electrocardiogram QT prolonged
	Uncommon		Bradycardia[g]
Vascular disorders	Very common	Hypertension[i] (30%)	Hypertension[i]
Respiratory, thoracic and mediastinal disorders	Very common	Cough (38%) Dyspnoea[j] (27%)	
	Common	Pneumonitis[k]	Pneumonitis[k] Dyspnoea[j]
Gastrointestinal disorders	Very common	Lipase increased (54%) Diarrhoea (49%) Amylase increased (47%) Nausea (40%) Vomiting (26%) Abdominal pain[l] (22%) Constipation (21%) Stomatitis[m] (12%)	Lipase increased
	Common	Dry mouth Dyspepsia Flatulence	Amylase increased Nausea Abdominal pain[l] Diarrhoea
	Uncommon		Vomiting Stomatitis[m] Dyspepsia
Hepatobiliary disorders	Very common	AST increased (68%) ALT increased (49%) Alkaline phosphatase increased (37%)	
	Common	Serum lactate dehydrogenase increased Hyperbilirubinaemia	ALT increased AST increased Alkaline phosphatase increased
	Uncommon		Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Very common	Rash[n] (37%) Pruritus[o] (17%)	
	Common	Dry skin Photosensitivity reaction	Rash[n] Photosensitivity reaction
	Uncommon		Dry skin Pruritus[o]
Musculoskeletal and connective tissue disorders	Very common	Blood CPK increased (64%) Myalgia[p] (34%) Arthralgia (18%)	Blood CPK increased

System organ class	Frequency category	Adverse reactions[†] all grades	Adverse reactions Grade 3-4
	Common	Musculoskeletal chest pain Pain in extremity Musculoskeletal stiffness	
	Uncommon		Pain in extremity Musculoskeletal chest pain Myalgia[p]
Renal and urinary disorders	Very common	Blood creatinine increased (21%)	
General disorders and administration site conditions	Very common	Fatigue[q] (40%) Oedema[r] (18%) Pyrexia (14%)	
	Common	Non-cardiac chest pain Chest discomfort Pain	Fatigue[q]
	Uncommon		Pyrexia Oedema[r] Non-cardiac chest pain
Investigations	Common	Blood cholesterol increased[s] Weight decreased	
	Uncommon		Weight decreased

[†] The frequencies for ADR terms associated with chemistry and haematology laboratory changes were determined based on the frequency of abnormal laboratory shifts from baseline.
[a] Includes atypical pneumonia, pneumonia, pneumonia aspiration, pneumonia cryptococcal, lower respiratory tract infection, lower respiratory tract infection viral, lung infection
[b] Includes Grade 5 events
[c] Grade not applicable
[d] Includes headache, sinus headache, head discomfort, migraine, tension headache
[e] Includes paraesthesia, peripheral sensory neuropathy, dysaesthesia, hyperaesthesia, hypoaesthesia, neuralgia, neuropathy peripheral, neurotoxicity, peripheral motor neuropathy, polyneuropathy, burning sensation, post herpetic neuralgia
[f] Includes altered visual depth perception, cataract, colour blindness acquired, diplopia, glaucoma, intraocular pressure increased, macular oedema, photophobia, photopsia, retinal oedema, vision blurred, visual acuity reduced, visual field defect, visual impairment, vitreous detachment, vitreous floaters, amaurosis fugax
[g] Includes bradycardia, sinus bradycardia
[h] Includes sinus tachycardia, tachycardia, atrial tachycardia, heart rate increased
[i] Includes blood pressure increased, diastolic hypertension, hypertension, systolic hypertension
[j] Includes dyspnoea, dyspnoea exertional
[k] Includes interstitial lung disease, pneumonitis
[l] Includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort
[m] Includes aphthous stomatitis, stomatitis, aphthous ulcer, mouth ulceration, oral mucosal blistering
[n] Includes dermatitis acneiform, erythema, exfoliative rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, dermatitis, dermatitis allergic, dermatitis contact, generalised erythema, rash follicular, urticaria, drug eruption, toxic skin eruption
[o] Includes pruritus, pruritus allergic, pruritus generalised, pruritus genital, vulvovaginal pruritus
[p] Includes musculoskeletal pain, myalgia, muscle spasms, muscle tightness, muscle twitching, musculoskeletal discomfort
[q] Includes asthenia, fatigue
[r] Includes eyelid oedema, face oedema, oedema peripheral, periorbital oedema, swelling face, generalised oedema, peripheral swelling, angioedema, lip swelling, periorbital swelling, skin swelling, swelling of eyelid
[s] Includes blood cholesterol increased, hypercholesterolemia

Description of selected undesirable effects

Pulmonary adverse reactions

In ALTA 1L, 2.9% of patients experienced any Grade ILD/pneumonitis early in treatment (within 8 days), with Grade 3-4 ILD/pneumonitis in 2.2% of patients. There were no fatal ILD/pneumonitis. Additionally, 3.7% of patients experienced pneumonitis later in treatment.
In ALTA, 6.4% of patients experienced pulmonary adverse reactions of any grade, including ILD/pneumonitis, pneumonia and dyspnoea, early in treatment (within 9 days, median onset: 2 days); 2.7% of patients had Grade 3-4 pulmonary adverse reactions and 1 patient (0.5%) had fatal pneumonia. Following Grade 1-2 pulmonary adverse reactions, treatment with Alunbrig was either interrupted and then restarted or the dose was reduced. Early pulmonary adverse reactions also occurred in a dose escalation study in patients (n = 137) (Study 101) including three fatal cases (hypoxia, acute respiratory distress syndrome and pneumonia). Additionally, 2.3% of patients in ALTA experienced pneumonitis later in treatment, with 2 patients having Grade 3 pneumonitis (see “Dosage/Administration” and “Warnings and precautions” sections).

Elderly patients

In ALTA, 13.5% of patients ≥ 65 years of age experienced an early pulmonary adverse reaction compared with 4.2% of patients < 65 years of age.

Hypertension

Hypertension was reported in 30% of patients treated with Alunbrig at the 180 mg regimen with 11% having Grade 3 hypertension. Dose reduction for hypertension occurred in 1.5% at the 180 mg regimen. Mean systolic and diastolic blood pressure, in all patients, increased over time (see “Dosage/Administration” and “Warnings and precautions” sections).

Bradycardia
Bradycardia was reported in 8.4% of patients treated with Alunbrig 180 mg.
Heart rates of less than 50 beats per minute (bpm) were reported in 8.4% of patients at the 180 mg regimen (see “Dosage/Administration” and “Warnings and precautions” sections).

Visual disturbance

Visual disturbance adverse reactions were reported in 14% of patients treated with Alunbrig 180 mg. Of these, three Grade 3 adverse reactions (1.1%) including macular oedema and cataract were reported.

Dose reduction for visual disturbance occurred in two patients (0.7%) at the 180 mg regimen (see “Dosage/Administration” and “Warnings and precautions” sections).

Peripheral neuropathy

Peripheral neuropathy adverse reactions were reported in 20% of patients treated with Alunbrig 180 mg. Thirty-three percent of patients had resolution of these adverse reactions. The median duration of these adverse reactions was 6.6 months, with a maximum duration of 28.9 months.

Creatine phosphokinase (CPK) elevation

In ALTA 1L and ALTA, elevations of CPK were reported in 64% of patients treated with Alunbrig 180 mg. The incidence of Grade 3-4 elevations of CPK was 18%. The median time to onset for CPK elevations was 28 days.
Dose reduction for CPK elevation occurred in 10% of patients at the 180 mg regimen (see “Dosage/Administration” and “Warnings and precautions” sections).

Elevations of pancreatic enzymes

Elevations of amylase and lipase were reported in 47% and 54% of patients treated with Alunbrig 180 mg, respectively. For elevations to Grade 3 and 4, the incidences for amylase and lipase were 7.7% and 15%, respectively. The median time to onset for amylase elevations and lipase elevations was 17 days and 29 days, respectively.
Dose reduction for elevation of lipase and amylase occurred in 4.7% and 2.9% of patients treated with 180 mg, respectively (see “Dosage/Administration” and “Warnings and precautions” sections).

Elevation of hepatic enzymes

In ALTA, elevations of ALT and AST were reported in 49% and 68% of patients treated with Alunbrig 180 mg, respectively. For elevations to Grade 3 and 4, the incidences for ALT and AST were 4.7% and 3.6%, respectively.
Dose reduction for elevation of ALT and AST occurred in 0.7% and 1.1% of patients treated with 180 mg, respectively (see “Dosage/Administration” and “Warnings and precautions” sections).

Hyperglycaemia

Sixty-one percent of patients experienced hyperglycaemia. Grade 3 hyperglycemia occurred in 6.6% of patients.
No patients had dose reductions due to hyperglycaemia.

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

There is no specific antidote for overdose with Alunbrig. In the event of an overdose, monitor the patient for adverse reactions (see “Undesirable effects” section) and provide appropriate supportive care.

Properties/Effects

ATC code

L01ED04

Mechanism of action

Brigatinib is a tyrosine kinase inhibitor that targets ALK, c-ros oncogene 1 (ROS1), and insulin-like growth factor 1 receptor (IGF-1R). Brigatinib inhibited autophosphorylation of ALK and ALK-mediated phosphorylation of the downstream signalling protein STAT3 in *in vitro* and *in vivo* assays.

Brigatinib inhibited the *in vitro* proliferation of cell lines expressing EML4-ALK and NPM-ALK fusion proteins and demonstrated dose-dependent inhibition of EML4-ALK-positive NSCLC xenograft growth in mice. Brigatinib inhibited the *in vitro* and *in vivo* viability of cells expressing mutant forms of EML4-ALK associated with resistance to ALK inhibitors, including G1202R and L1196M.

Pharmacodynamics

ECG findings

In Study 101, the QT interval prolongation potential of Alunbrig was assessed in 123 patients with advanced malignancies following once daily brigatinib doses of 30 mg to 240 mg. The maximum mean QTcF (corrected QT by the Fridericia method) change from baseline was less than 10 msec. An exposure-QT analysis suggested no concentration-dependent QTc interval prolongation. In the combined analysis of the pivotal clinical studies, QTcF prolongation by > 60 msec occurred in 9.8% (24/246) of patients, and for patients with baseline QTcF < 500 msec, 2.8% (7/246) of the patients had an increase in QTcF to > 500 msec.

Clinical efficacy

ALTA 1L

The safety and efficacy of Alunbrig was evaluated in a randomised (1:1), open-label, multicentre trial (ALTA 1L) in 275 adult patients with advanced ALK-positive NSCLC who had not previously received an ALK-targeted therapy. Eligibility criteria permitted enrolment of patients with a documented ALK rearrangement based on a local standard of care testing and an ECOG Performance Status of 0-2. Patients were allowed to have up to 1 prior regimen of chemotherapy in the locally advanced or

metastatic setting. Neurologically stable patients with treated or untreated central nervous system (CNS) metastases, including leptomeningeal metastases, were eligible. Patients with a history of pulmonary interstitial disease, drug-related pneumonitis, or radiation pneumonitis were excluded.

Patients were randomised in a 1:1 ratio to receive either Alunbrig 180 mg once daily with a 7-day lead-in at 90 mg Alunbrig once daily (n = 137) or crizotinib 250 mg orally twice daily (n = 138). Randomisation was stratified by brain metastases (present, absent) and prior chemotherapy use for locally advanced or metastatic disease (yes, no).

The primary endpoint was progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumours (RECIST v1.1) as evaluated by a Blinded Independent Review Committee (BIRC). Additional endpoints as evaluated by the BIRC included confirmed objective response rate (ORR), duration of response (DOR), time to response, disease control rate (DCR), intracranial ORR, intracranial PFS, and intracranial DOR. Investigator-assessed endpoints included PFS and overall survival.

Baseline demographics and disease characteristics in ALTA 1L were median age 59 years old (range 27 to 89; 32% 65 and over), 59% Caucasian and 39% Asian, 55% female, 39% ECOG PS 0, and 56% ECOG PS 1, 58% never smokers, 93% Stage IV disease, 96% adenocarcinoma histology, 30% CNS metastases at baseline, 14% prior radiotherapy to the brain, and 27% prior chemotherapy. Sites of extra-thoracic metastases included brain (30% of patients), bone (31% of patients), and liver (20% of patients).

At the primary analysis performed at a median follow-up duration of 11 months (range: 0-20) in the Alunbrig arm, the ALTA 1L study met its primary endpoint demonstrating a statistically significant improvement in PFS by BIRC. A protocol specified efficacy analysis performed at a median follow-up duration of 24.9 months (range: 0-34.1) in the Alunbrig arm formed the basis for the results from this study (Table 4).

Table 4: Efficacy results in ALTA IL (ITT population)

Efficacy parameters	**Alunbrig n = 137**	**Crizotinib n = 138**
Median duration of follow-up (months)	24.9 (range: 0–34.1)	15.2 (range: 0.1–36)
PFS (BIRC)		
Number of Patients with Event, n (%)	63 (46%)	87 (63%)
Progressive Disease, n (%)	56 (40.9%)[a]	82 (59.4%)[b]
Death, n (%)	7 (5.1%)	5 (3.6%)
Median (in months) (95% CI)	24 (18.5, NE)	11 (9.2, 12.9)
Hazard ratio (95% CI)	0.49 (0.35, 0.68)	

Log-rank p-value[c]	< 0.0001

BIRC = Blinded Independent Review Committee; NE = Not Estimable; CI = Confidence Interval
[a] includes 2 patients with palliative radiotherapy to the brain
[b] includes 8 patients with palliative radiotherapy to the brain
[c] Stratified by presence of iCNS metastases at baseline and prior chemotherapy for locally advanced or metastatic disease for log-rank test and Cochran-Mantel-Haenszel test, respectively

The confirmed ORR by BIRC was 73.7% (101/137) for Alunbrig and 61.6% (85/138) for crizotinib (p-value = 0.0342). Complete response was observed in 14.6% and 8.7% of Alunbrig-treated and criztonib-treated patients, respectively. The median DOR was not reached (95% CI: 19.4-not estimable) for Alunbrig and was 13.8 months (95% CI: 9.3-20.8) for crizotinib.
The PFS for patients with CNS metastases at baseline (HR = 0.25, 95% CI: 0.14-0.46, median PFS for Alunbrig = 24 months, 95% CI: 18.37-NE, median PFS for crizotinib = 5.6 months, 95% CI: 3.84-9.4) and without CNS metastases at baseline (HR = 0.65, 95% CI: 0.44-0.97, median PFS for Alunbrig = 24 months, 95% CI: 15.67-NE, median PFS for crizotinib = 13 months, 95% CI: 9.46-21.13), indicated therapeutic benefit from Alunbrig over crizotinib in both subgroups.

At the data cut-off point, overall survival data was not yet mature. A total of 70 patients died, 33 (24.1%) in the Alunbrig arm and 37 (26.8%) in the crizotinib arm.

Duration of intracranial response was measured from date of first intracranial response until intracranial disease progression (new lesions, intracranial target lesion diameter growth ≥ 20% from nadir, or unequivocal progression of intracranial non-target lesions) or death.
In patients with measurable brain metastases at baseline, the confirmed intracranial ORR by BIRC was 77.8% (14/18) for Alunbrig and 26.1% (6/23) for crizotinib (p-value = 0.0014). Complete response was observed in 27.8% of Alunbrig-treated patients; none of the crizotinib-treated patients achieved a complete response. The intracranial median DOR was not reached (95% CI: 5.7, not estimable) for Alunbrig and was 9.2 months (95% CI: 3.9, 9.2) for crizotinib.

ALTA

The safety and efficacy of Alunbrig was evaluated in a randomised (1:1), open-label, multicentre trial (ALTA) in 222 adult patients with locally advanced or metastatic ALK-positive NSCLC who had progressed on crizotinib. Eligibility criteria permitted enrolment of patients with a documented ALK rearrangement based on a validated test, ECOG Performance Status of 0-2, and prior chemotherapy. Additionally, patients with central nervous system (CNS) metastases were included, provided they were neurologically stable and did not require an increasing dose of corticosteroids. Patients with a history of pulmonary interstitial disease or drug-related pneumonitis were excluded.

Patients were randomised in a 1:1 ratio to receive Alunbrig either 90 mg once daily (90 mg arm, n = 112) or 180 mg once daily with 7-day lead-in at 90 mg once daily (180 mg arm, n = 110). The

median duration of follow-up for the 180 mg arm was 28.3 months. Randomisation was stratified by brain metastases (present, absent) and best prior response to crizotinib therapy (complete or partial response, any other response/unknown).

The primary endpoint was confirmed objective response rate (ORR) according to RECIST v1.1 as evaluated by investigator. Additional endpoints included confirmed ORR as evaluated by an Independent Review Committee (IRC); time to response; progression free survival (PFS); duration of response (DOR); overall survival; and intracranial ORR and intracranial DOR as evaluated by an IRC.

Baseline demographics and disease characteristics in ALTA were median age 54 years old (range 18 to 82; 23% 65 and over), 67% Caucasian and 31% Asian, 57% female, 34% ECOG PS 0 and 58% ECOG PS 1, 7% ECOG PS 2, 1% ECOG missing, 60% never smoker, 35% former smoker, 5% current smoker, 98% Stage IV, 97% adenocarcinoma, and 74% prior chemotherapy. The most common sites of extra-thoracic metastasis included 69% brain (of whom 62% had received prior radiation to the brain), 39% bone, and 26% liver.

Efficacy results from ALTA analysis for the 180 mg arm are summarised in Table 5.

Table 5: Efficacy results in ALTA 180 mg arm† (N = 110)

Efficacy parameter	Investigator assessment	IRC assessment
Objective response rate		
(%)	57%	56%
CI‡	(46, 68)	(47, 66)
Time to response		
Median (months)	1.9	1.9
Duration of response		
Median (months)	13.8	15.7
95% CI	(10.8, 17.6)	(13.6, 22.1)

CI = Confidence Interval

† Arm receiving 180 mg once daily with 7-day lead-in at 90 mg once daily

‡ Confidence Interval for investigator assessed ORR is 97.5% and for IRC assessed ORR is 95%.

The IRC-assessed median PFS for Alunbrig-treated patients treated at the 180 mg regimen was 16.7 months (95% CI: 11.6, 21.4). The median overall survival for these patients was 40.6 months (95% CI: 32.5, NE) and 5-year overall survival rate was 43.1%.

In patients with measurable brain metastases by RECIST 1.1 at baseline, the intracranial ORR and intracranial disease control rate was 67% (95% CI: 41, 87) and 83% (95% CI: 59, 96) respectively, in

the 180 mg arm (N = 18). The median duration of intracranial response in these patients was 16.6 months (95% CI: 3.7, NE).

In patients with any brain metastases at baseline, intracranial disease control rate was 86.5% (95% CI: 77, 93) in the 180 mg arm (n = 74).

Safety and efficacy in paediatric patients

The European Medicines Agency has waived the obligation to submit the results of studies with Alunbrig in all subsets of the paediatric population in lung carcinoma (small cell and non-small cell carcinoma) (see “Dosage/Administration” section for information on paediatric use).

Pharmacokinetics

Absorption

Following administration of a single oral dose of brigatinib (30-240 mg), the median time to peak concentration (T_{max}) was 1-4 hours. After a single dose and at steady state, systemic exposure was dose proportional over the dose range of 60-240 mg once daily. Modest accumulation was observed upon repeated dosing (geometric mean accumulation ratio: 1.9 to 2.4). The geometric mean steady state C_{max} of brigatinib at doses of 90 mg and 180 mg once daily was 552 and 1’452 ng/mL, respectively, and the corresponding $AUC_{0-\tau}$ was 8’165 and 20’276 h·ng/mL, respectively. Brigatinib is a substrate of the transporter proteins P-gp and BCRP.

In healthy subjects, compared to fasting state, a high fat meal reduced brigatinib C_{max} by 13% with no effect on AUC.

Distribution

Brigatinib was moderately bound (91%) to human plasma proteins and binding was not concentration-dependent. The blood-to-plasma concentration ratio is 0.69. In patients given brigatinib 180 mg once daily, the geometric mean apparent volume of distribution (V_z/F) of brigatinib at steady state was 307 L, indicating moderate distribution into tissues.

Metabolism

In vitro studies demonstrated that brigatinib is primarily metabolised by CYP2C8 and CYP3A4, and to a much lesser extent by CYP3A5.

Following oral administration of a single 180 mg dose of [^{14}C]brigatinib to healthy subjects, N-demethylation and cysteine conjugation were the two most important metabolic pathways for clearance. In urine and faeces combined, 48% of the radioactive dose was excreted as unchanged brigatinib, 27% as N-desmethyl brigatinib (AP26123) and 9.1% as brigatinib cysteine conjugate. Unchanged brigatinib was the major circulating radioactive component (92%) along with AP26123

(3.5%), the primary metabolite. In patients, the plasma AUC of AP26123 was < 10% of brigatinib exposure at steady state. In *in vitro* kinase and cellular assays, the metabolite AP26123 showed an approximately 3 times less potent inhibition of ALK than brigatinib.

Elimination

In patients given brigatinib 180 mg once daily, the geometric mean apparent oral clearance (CL/F) of brigatinib at steady state was 8.9 L/h and the median plasma elimination half-life was 24 h.

The primary route of excretion of brigatinib is in faeces. In six healthy male subjects given a single 180 mg oral dose of [^{14}C]brigatinib, 65% of the administered dose was recovered in faeces and 25% of the administered dose was recovered in urine. Unchanged brigatinib represented 41% and 86% of the total radioactivity in faeces and urine, respectively, the remainder being metabolites.

Kinetics in specific patient groups

Hepatic impairment

The pharmacokinetics of brigatinib was characterised in patients with normal hepatic function (n = 9), and patients with mild hepatic impairment (Child-Pugh class A, n = 6), moderate hepatic impairment (Child-Pugh class B, n = 6), or severe hepatic impairment (Child-Pugh class C, n = 6). The pharmacokinetics of brigatinib was similar between patients with normal hepatic function and patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. The $AUC_{0\text{-}INF}$ of the unbound (free) brigatinib portion was 37% higher in patients with severe hepatic impairment (Child-Pugh class C) as compared to healthy subjects with normal hepatic function (see “Dosage/Administration” section).

Renal impairment

In a pharmacokinetic study, the $AUC_{0\text{-}INF}$ of the unbound (free) brigatinib portion was 92% higher in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2, n = 8) as compared to patients with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2, n = 8) (see “Dosage/Administration” section). The results of a population pharmacokinetic analysis indicated similar pharmacokinetics of brigatinib in patients with normal renal function (n = 190) and in patients with mild (n = 209) or moderate (n = 44) renal impairment (eGFR ≥ 30 mL/min/1.73 m^2).

Race and gender

In population pharmacokinetic analyses, no ethnic origin or gender-related effects on the pharmacokinetics of brigatinib were found.

Age, body weight, and albumin concentration

In population pharmacokinetic analyses, no clinically relevant effects of body weight, age, and albumin concentration on the pharmacokinetics of brigatinib were found.

Preclinical data

Safety pharmacology

Safety pharmacology studies with brigatinib identified potential for pulmonary adverse effects (altered respiration rate at 1-2 times the human therapeutic C_{max}), cardiovascular effects (altered heart rate and blood pressure at 0.5 times the human therapeutic C_{max}), and renal effects (reduced renal function at 1-2.5 times the human therapeutic C_{max}), but did not indicate any evidence of QT prolongation or neurofunctional effects.

Repeat dose toxicity

Adverse reactions seen in animals at exposure levels similar to clinical exposure levels with possible relevance to clinical use involved the following organ systems: gastrointestinal tract, bone marrow, eyes, testes, liver, kidney, bone, and heart. These effects were generally reversible during the non-dosing recovery period; however, effects in the eyes and testes were notable exceptions due to lack of recovery.
In repeat dose toxicity studies, lung changes (foamy alveolar macrophages) were noted in monkeys at ≥ 0.2 times the human therapeutic AUC; however, these were minimal and similar to those reported in the control group of naive monkeys, and there was no clinical evidence of respiratory distress in these monkeys.

Genotoxicity and carcinogenicity

Brigatinib did not show genotoxic potential *in vitro* in the bacterial Ames test or the mammalian cell chromosomal aberration assay, but ~~*in*~~ *vivo* slightly increased the number of micronuclei in the bone marrow of rats. The mechanism of micronucleus induction was abnormal chromosome segregation (aneugenicity). This effect was observed at a dose that corresponds to approximately twice the human therapeutic exposure resulting from the 180 mg once daily dose.
No carcinogenicity studies have been performed with brigatinib.

Reproductive toxicity

No animal studies have been performed to investigate effects on fertility. Testicular toxicity was observed in toxicity studies. In rats, findings included lower weight of testes, seminal vesicles and prostate gland, and testicular tubular degeneration. These effects were not reversible during the non-dosing interval. A reduced size of testes along with microscopic evidence of hypospermatogenesis was observed in monkeys. These effects were reversible during the non-dosing interval. Overall, these effects on the male reproductive organs in rats and monkeys occurred at exposures ≥ 0.2-times the AUC (observed in patients at the 180 mg once daily dose). No effects on female reproductive organs were observed in general toxicology studies in rats and monkeys.

In an embryo-foetal development study in which pregnant rats were administered daily doses of brigatinib during organogenesis, dose-related skeletal anomalies were observed at an exposure equivalent to approximately 0.7-times the human AUC at the 180 mg once daily dose. Findings included embryo-lethality, reduced foetal growth, and skeletal abnormalities.

Other information

Incompatibilities

Not applicable.

Effects on diagnostic methods

Not applicable.

Shelf life

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

Special precautions for storage

Keep out of the reach of children.

Do not store above 30°C.

Instructions for handling

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

Authorisation number

66738 (Swissmedic)

Packs

Alunbrig 30 mg: carton containing 28, 56 or 112 film-coated tablets (cartons containing 56 and 112 film-coated tablets currently not marketed) [A].
Alunbrig 90 mg: carton containing 7 or 28 film-coated tablets [A].
Alunbrig 180 mg: carton containing 28 film-coated tablets [A].
Alunbrig is available as a multipack for treatment initiation. Each multipack consists of an outer carton with two inner cartons containing:
Alunbrig 90 mg: carton containing 7 film-coated tablets [A].
Alunbrig 180 mg: carton containing 21 film-coated tablets [A].

Marketing authorisation holder

Takeda Pharma AG, 8152 Opfikon

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