Date: 3 August 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Exkivity

International non-proprietary name: mobocertinib

Pharmaceutical form: hard capsules

Dosage strength(s): 40 mg

Route(s) of administration: oral

Marketing Authorisation Holder: Takeda Pharma AG

Marketing Authorisation No.: 68147

Decision and Decision date: temporary authorisation in accordance with Art. 9a TPA approved on 1 June 2022

Note:

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

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.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CNS	Central nervous system
cORR	Confirmed objective response rate
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
exon20ins	Exon 20 insertion mutations
FDA	U.S. Food and Drug Administration
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
ICI	Immune checkpoint inhibitors
Ig	Immunoglobulin
INN	International nonproprietary name
Ins	Insertion mutations
IRC	Independent Review Committee
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MOB	Mobocertinib
mOS	Median overall survival
mPFS	Median progression-free survival
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics

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PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PPP	Pooled prior platinum population
PS	Performance status
PSP	Pediatric Study Plan (US-FDA)
QD	Once daily
RMP	Risk Management Plan
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TKIs	Tyrosine kinase inhibitors
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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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 mobocertinib of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA.
The Orphan Status was granted on 6 October 2020.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Art. 9a TPA.

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is a programme coordinated by the US FDA for promising cancer treatments. It provides a framework for concurrent submission and review of oncology products among international partners. It currently involves the regulatory authorities of: Australia (TGA), Brazil (ANVISA), Israel (MOH), Canada (HC), Singapore (HSA), Switzerland (Swissmedic) and the United Kingdom (MHRA).

2.2 Indication and Dosage

2.2.1 Requested Indication

Exkivity as monotherapy is indicated for the treatment of adult patients with epidermal growth factor receptor (EGFR) exon 20 insertion mutation-positive locally advanced or metastatic non-small cell lung cancer (NSCLC), who have received prior platinum-based chemotherapy.

2.2.2 Approved Indication

Exkivity as monotherapy is indicated for the treatment of adult patients with epidermal growth factor receptor (EGFR) exon 20 insertion mutation-positive unresectable or metastatic non-small cell lung cancer (NSCLC), whose disease has progressed on or after platinum-containing chemotherapy.

2.2.3 Requested Dosage

Summary of the applied standard dosage:

The recommended dosage is 160 mg Exkivity once daily. Exkivity treatment should be continued until disease progression or until treatment is no longer tolerated by the patient.

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	31 August 2021
Formal control completed	1 September 2021
List of Questions (LoQ)	5 November 2021
Answers to LoQ	25 February 2022
Predecision	14 April 2022
Answers to Predecision	13 May 2022
Final Decision	1 June 2022
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical Context

Treatment of lung cancer patients depends on the histology, molecular characteristics, tumour stage and an assessment of the patient's overall medical condition. An improved understanding of the molecular pathways that drive malignancy in non-small cell lung cancer (NSCLC) has led to the development of agents that target specific molecular pathways in malignant cells. Therapy can then be individualised based on the specific abnormality if present in a given NSCLC patient. The most frequent targetable abnormalities are activating epidermal growth factor receptor (EGFR) gene mutations, which are identified in approx. 10-15% of adenocarcinomas in western populations[1]. EGFR driver mutations in other histological lung cancer subtypes are rather rare.

The most frequently identified EGFR mutations are exon19del and L858R, which are identified in 80-85% of subjects with activating EGFR mutations[2], and are effectively targeted by multiple approved EGFR tyrosine kinase inhibitors (TKIs).

Although the EGFR exon 20 insertion mutations (ins) in NSCLC patients are believed to share a similar biology with other EGFR-mutated NSCLC[3], the protein structure associated with this group of EGFR mutations hinders access to the receptor active site for some EGFR TKIs. Thus, EGFR exon20ins are associated with *de novo* resistance to most approved EGFR inhibitors and correlate with a poor patient prognosis. Compounds with the ability to effectively target EGFR exon20ins present an unmet medical need. Currently, no targeted therapy for the treatment of NSCLC with EGFR exon20ins has received a regular approval in Switzerland.

Mobocertinib is a small molecule oral tyrosine kinase inhibitor (TKI) with activity against activating EGFR mutations, including exon 20 insertions.

[1] J Remon et al, 2020 EGFR exon 20 insertions in advanced non-small cell lung cancer: A new history begins. Cancer Treat Rev. 2020 Nov;90:102105.
[2] ME Arcila et al. EGFR exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics, Mol Cancer Ther. 2013 Feb;12(2):220-9.
[3] F Wang et al. EGFR exon 20 insertion mutations in non-small cell lung cancer, Translational Cancer Research, Vol 9, No 4, April 2020.

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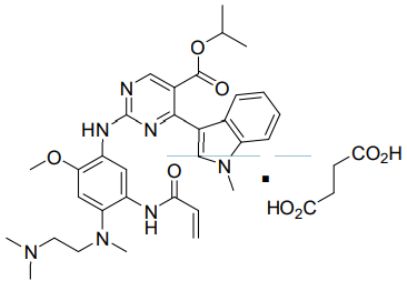
4 Quality Aspects

4.1 Drug Substance

INN: mobocertinib
Chemical name: propan-2-yl 2-[5-(acryloylamino)-4- {[2(dimethylamino)ethyl](methyl)amino}-2-methoxyanilino]-4-(1-methyl1H-indol-3-yl)pyrimidine-5-carboxylate succinat
Molecular formula: $C_{32}H_{39}N_7O_4$ +$C_4H_6O_4$ (succinate salt)
Molecular mass: 703.80 g/mol (as succinate salt)
Molecular structure:



Physico-chemical properties:

- Solubility: Highly soluble over the pH range of 1 to 6.8

Synthesis:
Mobocertinib succinate is synthesised via a multistep process.

Specification:
The proposed specifications and analytical methods were considered appropriate for quality control of the drug substance.

Stability:
Appropriate stability data have been presented and justify the established re-test period.

4.2 Drug Product

Description and composition:
Mobocertinib is supplied as an immediate-release capsule containing 40 mg of the active ingredient, a freebase equivalent as a succinate salt.

Pharmaceutical development:
Suitable pharmaceutical development data have been provided

Manufacture:
The commercial manufacturing process of mobocertinib capsules was adequately described in the quality documents.

Specification:
Adequate specifications at release and at shelf life have been described. Analytical methods have been described in detail and have been validated according to ICH requirements.

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Container closure system:
Mobocertinib capsules are packaged in a polychlorotrifluoroethylene (PCTFE) / polyvinyl chloride (PVC) blister containing one capsule per blister. The blisters have a peelable aluminium lidding foil.

Stability:
Appropriate stability data have been presented for three registration stability batches, along with appropriate supportive stability studies.
The available stability data support the storage of mobocertinib capsule for 24 months under the following storage conditions: Do not store above 30°C. Do not freeze.

4.3 Quality Conclusions

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

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5 Nonclinical Aspects

Regarding the marketing authorisation application for Exkivity (mobocertinib), the Nonclinical Assessment Division conducted an abridged evaluation based on the assessment report submitted by the FDA (NDA 213310, dated 15 September 2021) as part of Project Orbis.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Exkivity in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised and all nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals and in the RMP.

There are no safety concerns regarding impurities and excipients.

According to the ERA, the risk of mobocertinib to the environment is assumed to be low.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the FDA. The available assessment report and corresponding product information from this authority were used as a basis for the clinical pharmacology evaluation.

For further details concerning clinical pharmacology, see section 8 (Appendix) of this report.

6.2 Dose Finding and Dose Recommendation

Dose finding of mobocertinib (MOB) was conducted during the dose escalation part of Study AP32788-15-101 using the classical 3+3 design. The determined recommended phase 2 dose (RP2D) was 160 mg daily (QD). However, pharmacokinetic (PK) analyses suggested no meaningful steady-state exposure increase for the 160 mg versus the 120 mg dose due to suspected auto-induction. To address this issue, the applicant assessed patients from dose escalation and some patients from the dose expansion part of the study. This early analysis showed numerically higher efficacy for 160 mg QD versus 120 mg QD. The toxicity was higher in patients treated with 160 mg versus 120 mg, mainly driven by diarrhoea, which frequently resolved after supportive measures and dose modification. Based on these findings, the confirmed RP2D was 160 mg QD.

6.3 Efficacy

To support the requested indication the applicant submitted a *pooled prior platinum population* (PPP) analysis of patients with unresectable or metastatic non-small cell lung cancer (NSCLC) and EGFR exon 20 insertion mutations (exon20ins) who were treated with RP2D in the single-arm Phase I/II Study AP32788-15-101. This study consisted of three parts: the dose escalation part of the study was designed to determine the RP2D in patients with advanced NSCLC, the expansion part tested the RP2D of MOB within distinct molecularly defined cohorts and the extension part tested MOB in previously treated (any anticancer therapy) advanced NSCLC patients with exon20ins. The submitted PPP analysis set consisted of a total of 114 patients, of whom six were from the dose escalation part, 22 were from the expansion part and 86 were from the extension part of the study. In this population, all subjects had received prior platinum-based chemotherapy. Considering the lack of data to support the use of immune checkpoint inhibitors (ICI) and other EGFR tyrosine kinase inhibitors (TKIs) for patients with exon20ins, the selection of a population after platinum-containing therapy as pivotal for the requested indication population is appropriate.

In the PPP, patients received MOB 160mg QD. The duration of one treatment cycle was 28 days. Patients were treated until they experienced progressive disease that required an alternate therapy in the opinion of the investigator or intolerable toxicity.

All patients were required to have adequate renal, hepatic and bone marrow function. Patients with active brain metastases were not included (patients with previously treated stable brain metastases were allowed). Patients with QTc interval prolongation, relevant cardiovascular disease and interstitial lung were excluded from the study.

The disease stage was initially assessed using computer tomography or magnetic resonance imaging (with contrast media, unless contraindicated) at baseline. Imaging of the brain was mandatory at baseline and was repeated for patients with baseline central nervous system (CNS) metastases. Radiological disease re-assessment occurred every 8 weeks until cycle 14 and every 12 weeks thereafter. The radiological response to treatment was evaluated according to RECIST 1.1 criteria. An Independent Review Committee (IRC) reviewed the radiological images.

The median age of patients in the PPP was 60 years; 66% were women, 60% were Asian, 37% were Caucasian. The median time from initial diagnosis was 14.7 months. The majority of patients had stage IV disease at study entry (99%) and 98% had adenocarcinoma histology. Regarding baseline

organ involvement, 35% had brain metastases, 41% had bone metastases and 21% had liver metastases. Regarding ECOG PS, 75% had a PS score of 1 and 25% had a PS score of 0. Most patients were from Asia Pacific (48%) and North America (47%); 5% were from Europe.

With 25.8 months of median follow-up, the confirmed objective response rate (cORR) assessed by IRC for the PPP was 28%, median progression-free survival (mPFS) was 7.3 months and median overall survival (mOS) was 20.2 months. These results are considered as encouraging for the requested indication. The applicant's own analyses of retrospective data and publications for pre-treated NSCLC with EGFR exon20ins demonstrated low ORR for ICIs[4] and EGFR TKIs[5] (approx. 3.5% and approx. 10%, respectively). Regarding the efficacy of docetaxel in pre-treated NSCLC (irrespective of EGFR status), the historical ORR was in the range of 5.5-14%[6].

The main deficiency of the submitted dossier is the lack of randomised data. Considering the requested temporary authorisation, this deficiency could be mitigated by positive confirmatory study results to support the conversion to a regular authorisation.

Relevant ongoing studies
Study TAK-788-3001 (EXCLAIM-2) is an ongoing randomised Phase III study that tests MOB versus platinum doublet as the first-line therapy for NSCLC with EGFR exon20ins. Even though this study is testing MOB in a different treatment line compared to the requested indication, positive Study 3001 results could provide evidence to support the conversion to a regular approval for the currently requested indication.

6.4 Safety

The applicant included data from 358 patients who received at least one dose of MOB. The median time on MOB treatment in this population was 5.3 months.

Most patients experienced at least one treatment-emergent adverse event (TEAE) of any grade. The most frequent TEAEs of any grade were diarrhoea, nausea, decreased appetite, rash, vomiting, dry skin, stomatitis, paronychia, anaemia, fatigue, blood creatinine increased, amylase increased, weight decreased and dermatitis acneiform. The most frequent adverse events that were considered as treatment-related were diarrhoea, nausea, vomiting, rash, decreased appetite, dry skin, stomatitis and paronychia.

The most common SAEs were dyspnoea, pneumonia, diarrhoea, vomiting, acute kidney injury and dehydration.

The most frequent reported grade 3-4 TEAEs in the overall safety population were diarrhoea, anaemia, hypertension, dyspnoea, pneumonia, amylase increased, ECG QT prolonged, lipase increased and lymphocyte count decreased.

The following grade 5 TEAEs were reported in more than one patient: neoplasm progression, non-small cell lung cancer, respiratory failure, pneumonia, malignant lung neoplasm, metastases to central nervous system, metastases to meninges, cardiac failure, dyspnoea, disease progression, and multiple organ dysfunction syndrome.

[4] P Christopoulos et al., Systematic review and meta-analysis of immunotherapy effectiveness for pretreated patients with non-small cell lung cancer harboring EGFR exon 20 insertions, Annals of Oncology 2021, 32 (suppl_5): S949-S1039.
[5] GM O'Kane et al., Uncommon EGFR mutations in advanced non-small cell lung cancer, Lung Cancer Volume 109, July 2017, Pages 137-144.
[6] FVFossella, Docetaxel in Second-Line Treatment of non-small-Cell Lung Cancer, Clinical Lung Cancer Volume 3, Supplement 2, May 2002, Pages S23-S28.

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MOB therapy is associated with a concentration-dependent QTc prolongation effect and a clinically relevant QTc prolongation was observed at the recommended dose.

Overall, the reported toxicities are manageable, consistent with other approved EGFR TKIs and sufficiently addressed in the information for healthcare professionals.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

For decades, the standard treatment of metastatic or unresectable NSCLC was palliative cytostatic therapy. Recent improved understanding of molecular malignancy pathways allows individualised therapy of tumours with specific mutations. The most frequent targetable mutations are epithelial growth factor receptor (EGFR) gene alterations, which are found in approx. 10-15% of adenocarcinoma tumours. Common EGFR mutations are exon19 deletions or L858R substitutions, which are targetable by approved TKIs. However, not all EGFR alterations are targetable by EGFR TKIs approved in Switzerland. One example is exon20ins mutations occurring in about 2% of all NSCLC patients. Until recently, international guidelines for the first-line treatment of advanced NSCLC with exon20ins were the same as for patients without targetable mutations, and the treatment recommendations for these patients consisted of platinum doublet chemotherapy with or without immunotherapy. Regarding treatment options after platinum-based chemotherapy, publications report low efficacy of EGFR TKIs, immunotherapy and chemotherapy for patients with exon20ins. There is an unmet medical need to improve the outcomes of NSCLC patients with EGFR exon20ins with disease progression on or after the standard platinum-based chemotherapy. Mobocertinib (MOB) is an oral TKI with activity against EGFR mutations including exon20ins.

To support the requested indication, the applicant submitted data from a *pooled prior platinum population* (n=114) from the Phase I/II Study AP32788-15-101 that included patients with unresectable or metastatic non-small cell lung cancer (NSCLC) and EGFR exon 20 insertion mutations (exon20ins).In this pivotal study population, the reported confirmed ORR was 28%, median PFS was 7.3 months and the median OS was clinically relevant with 20.2 months.

The main deficiency of the submitted dossier is the lack of randomised clinical data to support the efficacy of mobocertinib compared to the standard of care. However, there is an ongoing randomised Phase III Study TAK-788-3001 (EXCLAIM-2), which tests mobocertinib monotherapy versus platinum doublet as first-line therapy in NSCLC patients with exon20ins. Although MOB is being tested in a different treatment line compared to the currently requested indication, this study could provide confirmatory evidence for the current indication.

Relevant reported toxicities for MOB included QTc interval prolongation, interstitial lung disease (including pneumonitis), heart failure, diarrhoea, stomatitis, rash and paronychia. Relevant fatal toxicities included pneumonitis and cardiac disorders. Overall, adverse drug reactions were manageable and are adequately described in the information for healthcare professionals. However, due to the design of Study AP32788-15-101, a direct comparison of safety to other agents was not possible.

Conclusion
The reported efficacy benefit for MOB in patients with metastatic and/or unresectable NSCLC EGFR exon20ins after platinum-based chemotherapy is clinically meaningful and the safety profile is manageable in the hands of oncologists. The benefit-risk ratio is positive for a temporary authorisation. The clinical results from an ongoing Phase III Study TAK-788-3001 (EXCLAIM-2) could provide confirmatory evidence to support the conversion of temporary authorisation into regular authorisation.

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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

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Exkivity, hard capsules, 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 currently 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.
EXKIVITY is temporarily authorised – see "*Properties/Effects*" section.

EXKIVITY®

Composition

Active substances

Mobocertinib (as Mobocertinib succinate).

Excipients

Capsule shell: Gelatin, titanium dioxide (E171).
Printing ink: Shellac, propylene glycol, black iron oxide (E172), potassium hydroxide.

Pharmaceutical form and active substance quantity per unit

Each hard capsule contains 40 mg of mobocertinib (as 48.06 mg mobocertinib succinate).
White, size 2 (length of 17.7 to 18.3 mm) gelatin hard capsule, imprinted with “MB 788” on the cap and “40 mg” on the body in black ink.

Indications/Uses

EXKIVITY as monotherapy is indicated for the treatment of adult patients with epidermal growth factor receptor (EGFR) exon 20 insertion mutation-positive unresectable or metastatic non-small cell lung cancer (NSCLC), whose disease has progressed on or after platinum-containing chemotherapy.

Dosage/Administration

Treatment with EXKIVITY should be initiated and supervised by a doctor experienced in the use of anticancer therapies.

Patients with unresectable or metastatic NSCLC should be selected for treatment with EXKIVITY based on the presence of an *EGFR* exon 20 insertion mutation. *EGFR* mutation status should be established using a validated test prior to initiation of EXKIVITY therapy.

Usual dosage

The recommended dosage is 160 mg (4 hard capsules) EXKIVITY once daily. EXKIVITY treatment should be continued until disease progression or intolerable toxicity.

If a patient misses the daily dose by more than 6 hours, the patient should skip the dose and take the next dose the following day at its scheduled time.

If a patient vomits after taking a dose, the patient should not repeat the dose, but should resume the usual dosing as prescribed on the following day.

Dose adjustment

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability.

EXKIVITY recommended dosage reduction levels for adverse reactions are summarised in Table 1.

Table 1. Recommended EXKIVITY Dosage Reductions

Dose Reduction Schedule	Dose Level
First dose reduction	120 mg once daily
Second dose reduction	80 mg once daily

Recommended dosage modifications of EXKIVITY and management of adverse reactions are provided in Table 2.

Table 2. Recommended EXKIVITY Dose Modifications and Management for Adverse Reactions

Adverse Reaction	Severity*	Dose Modification
QTc interval prolongation (see “Warnings and precautions”)	Grade 2 (QTc interval 481-500 msec)	<u>First Occurrence</u> • Withhold EXKIVITY until ≤ Grade 1 or baseline. • Upon recovery, resume EXKIVITY at the same dose. <u>Recurrence</u> • Withhold EXKIVITY until ≤ Grade 1 or baseline. • Upon recovery, resume EXKIVITY at the next lower dose or permanently discontinue EXKIVITY.

Table 2. Recommended EXKIVITY Dose Modifications and Management for Adverse Reactions

Adverse Reaction	Severity*	Dose Modification
	Grade 3 (QTc interval ≥501 msec or QTc interval increase of >60 msec from baseline)	First Occurrence • Withhold EXKIVITY until ≤ Grade 1 or baseline. • Upon recovery, resume EXKIVITY at the next lower dose or permanently discontinue EXKIVITY. Recurrence • Permanently discontinue EXKIVITY.
	Grade 4 (Torsades de Pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia)	Permanently discontinue EXKIVITY.
Interstitial Lung Disease (ILD)/Pneumonitis (see “Warnings and precautions”)	Any grade	• Withhold EXKVITY if ILD/pneumonitis is suspected. • Permanently discontinue EXKIVITY if ILD/pneumonitis is confirmed.
Decreased left ventricular ejection fraction or heart failure (see “Warnings and precautions”)	Grade 2 decreased ejection fraction	• Withhold EXKIVITY until ≤ Grade 1 or baseline. • If recovered to ≤ Grade 1 or baseline within 2 weeks, resume EXKIVITY at the same dose or the next lower dose. • If not recovered to ≤ Grade 1 or baseline within 2 weeks, permanently discontinue EXKIVITY.
	Grade 3 or 4 decreased ejection fraction	Permanently discontinue EXKIVITY.
	≥ Grade 2 heart failure	Permanently discontinue EXKIVITY.
Diarrhoea (see “Warnings and precautions”)	Grade 1, First Occurrence or Tolerable Grade 2	No dose modification is required. Initiate treatment with anti-diarrhoeal medicinal products (e.g. loperamide) at first onset of diarrhoea.
	Intolerable or recurrent Grade 2 or Grade 3	• Withhold EXKIVITY until recovery to ≤ Grade 1. • Resume EXKIVITY at the same dose or the next lower dose.
	Grade 4	First occurrence

Table 2. Recommended EXKIVITY Dose Modifications and Management for Adverse Reactions

Adverse Reaction	Severity*	Dose Modification
		• Withhold EXKIVITY until recovery to ≤ Grade 1. • If recovered within 2 weeks, resume EXKIVITY at the next lower dose. • If not recovered to ≤ Grade 1 within 2 weeks, permanently discontinue EXKIVITY <u>Recurrence</u> • Permanently discontinue EXKIVITY
Amylase/lipase elevation (see “Undesirable effects”)	Grade 2 (>2.0 - 5.0 x ULN and asymptomatic)	Continue EXKIVITY at the same dose or the next lower dose.
	Asymptomatic Grade 3 (>5.0 × ULN)	• Withhold EXKIVITY until recovery to ≤ Grade 1. • If recovered within 2 weeks, resume EXKIVITY at the same dose or the next lower dose. • If not recovered to ≤ Grade 1 within 2 weeks, permanently discontinue EXKIVITY.
	Symptomatic Grade 3 or Grade 4	• Withhold EXKIVITY until recovery to ≤ Grade 1. • If recovered within 2 weeks, resume EXKIVITY at the next lower dose. • If not recovered to ≤ Grade 1 within 2 weeks, permanently discontinue EXKIVITY
Other Non-haematologic toxicity (see “Undesirable effects”)	Intolerable or Recurrent Grade 2 or Grade 3	• Withhold EXKIVITY until recovery to ≤ Grade 1. • Resume EXKIVITY at the same dose or the next lower dose.
	Grade 4	• Withhold EXKIVITY until recovery to ≤ Grade 1. • Resume EXKIVITY at the next lower dose or consider permanent discontinuation of EXKIVITY.
Haematologic toxicity (see “Undesirable effects”)	Grade 3	• Withhold EXKIVITY until recovery to ≤ Grade 2. • Resume EXKIVITY at the same dose or the next lower dose.
	Grade 4	• Withhold EXKIVITY until recovery to ≤ Grade 1.

Table 2. Recommended EXKIVITY Dose Modifications and Management for Adverse Reactions

Adverse Reaction	Severity*	Dose Modification
		• Resume EXKIVITY at the next lower dose or consider permanent discontinuation of EXKIVITY.

ULN = upper limit of normal
* Graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 5.0 (NCI CTCAE v5).

Special dosage instructions

Patients with hepatic disorders

No dose adjustment of EXKIVITY is recommended for patients with mild (total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin > 1 to 1.5 times ULN and any AST) or moderate hepatic impairment (total bilirubin > 1.5 to 3 times ULN and any AST). The recommended dosage of EXKIVITY in patients with severe hepatic impairment has not been established (see “Pharmacokinetics”). The use of EXKIVITY in patients with severe hepatic impairment is not recommended.

Patients with renal disorders

No dose adjustment of EXKIVITY is recommended for patients with mild or moderate renal impairment (estimated glomerular filtration rate ≥30 mL/min). The recommended dosage of EXKIVITY in patients with severe renal impairment (estimated glomerular filtration rate <30 mL/min) has not been established (see “Pharmacokinetics”).

Elderly patients

No dose adjustment of EXKIVITY is recommended for patients over 65 years of age.
In studies of mobocertinib, there were no clinically significant differences in efficacy between patients less than 65 years of age and patients 65 years of age or older.

Children and adolescents

The safety and efficacy of EXKIVITY in children or adolescents aged less than 18 years have not been established. No data are available.

Mode of administration

EXKIVITY is for oral use. EXKIVITY can be taken with or without food. EXKIVITY should be taken at approximately the same time each day. EXKIVITY hard capsules should be swallowed as a whole and must not be opened or chewed and contents of the hard capsules must not be dissolved.

Contraindications

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

Warnings and precautions

QTc Interval Prolongation

Heart rate-corrected QT (QTc) interval prolongation, including ventricular arrhythmias such as Torsades de Pointes, which can be fatal, have occurred in patients treated with EXKIVITY (see "Undesirable effects" and "Properties/Effects").
Clinical trials of EXKIVITY did not enrol patients with baseline QTc > 470 msec.
Assess QTc and electrolytes at baseline and correct abnormalities in sodium, potassium, calcium, and magnesium prior to initiating EXKIVITY. Monitor QTc and electrolytes periodically during treatment. Increased monitoring frequency in patients with risk factors for QTc prolongation, such as patients with congenital long QTc syndrome, heart disease or electrolyte abnormalities. Avoid use of concomitant drugs which are known to prolong the QTc interval. Avoid concomitant use of strong or moderate CYP3A inhibitors with EXKIVITY, which may further prolong the QTc interval (see "Interactions"). Permanently discontinue EXKIVITY in patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia (see "Dosage/Administration").

Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, and fatal interstitial lung disease (ILD)/pneumonitis have occurred in patients treated with EXKIVITY (see "Undesirable effects").
Withhold EXKIVITY for acute onset of new or progressive unexplained pulmonary symptoms such as dyspnoea, cough, and fever pending diagnostic evaluation and diagnosis confirmation. Permanently discontinue EXKIVITY if ILD/pneumonitis is confirmed (see "Dosage/Administration").

Heart failure

Severe, life-threatening, and fatal heart failure (including congestive heart failure, decreased ejection fraction, and cardiomyopathy) have occurred in patients treated with EXKIVITY (see "Undesirable effects").

Conduct cardiac monitoring, including assessment of left ventricular ejection fraction at baseline and during treatment. Patients who develop signs and symptoms consistent with heart failure should be treated as clinically indicated. Management of heart failure may require permanent discontinuation of EXKIVITY (see “Dosage/Administration”).

Diarrhoea

In clinical studies, most patients experienced mild to moderate diarrhoea (see “Undesirable effects”). The median time to first onset of diarrhoea was 5 days but could occur as soon as 24 hours after administration of EXKIVITY. Diarrhoea is usually transient and had a median time to resolution of 3 days. Prolonged diarrhoea may lead to dehydration or electrolyte imbalance, with or without renal impairment. Diarrhoea can be severe or life threatening.
Early and compliant diarrhoea management such as prescribed anti-diarrhoeal medicinal products (e.g., loperamide), diet, adequate fluid intake (~2L clear liquids per day), and patient education is recommended. Patients should be instructed to have anti-diarrhoeal medicinal products (e.g., loperamide) readily available. Anti-diarrhoeal treatment should be initiated at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normal. In EXKIVITY clinical studies where loperamide was used as the anti-diarrhoeal, the dosage regimen for loperamide was 4 mg at the first bout of diarrhoea and then 2 mg every 2 hours until the patient is diarrhoea-free for at least 12 hours; daily dose of loperamide did not exceed 16 mg. If using loperamide as the anti-diarrhoeal treatment, refer to loperamide product labelling for additional information.
If diarrhoea does not improve or additional signs or symptoms are reported, standard medical practice intervention, including other anti-diarrhoeal medications, are encouraged. Anti-diarrhoeal prophylaxis may be considered as needed. Electrolytes should be monitored and patients instructed to increase fluid and electrolyte intake as needed. No dose modification is necessary unless the patient does not tolerate EXKIVITY, the symptoms recur, or the diarrhoea doesn't resolve with medical intervention. EXKIVITY needs to be interrupted and subsequent doses reduced if severe diarrhoea occurs (see “Dosage/Administration”).

Embryo-Foetal Toxicity

EXKIVITY can cause harm to the embryo or foetus when administered to pregnant women. Pregnant women must be informed of the potential risk to the foetus. Women of childbearing potential should be advised to use effective non-hormonal contraception during treatment with EXKIVITY (see “Interactions”) and for 1 month following the final dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment with EXKIVITY and for 1 week following the final dose of EXKIVITY (see “Pregnancy, lactation” and “Preclinical data”).

Interactions

Effect of Other Drugs on EXKIVITY

Avoid coadministration

CYP3A inhibitors

Mobocertinib is predominantly metabolized by CYP3A. Drugs that inhibit CYP3A can therefore lead to increased mobocertinib concentrations, which may increase the risk of adverse reactions such as QTc interval prolongation. The coadministration of strong CYP3A inhibitors with EXKIVITY, 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 (see “Warnings and Precautions”).
The coadministration of moderate CYP3A inhibitors (e.g. fluconazole and erythromycin) with EXKIVITY should be avoided. If coadministration of moderate CYP3A inhibitors cannot be avoided, the dose of EXKIVITY should be reduced by approximately 50% (e.g. from 160 mg to 80 mg, 120 mg to 40 mg, or 80 mg to 40 mg) and the QTc interval closely monitored. After discontinuation of a moderate CYP3A inhibitor for 3 to 5 elimination half-lives, EXKIVITY 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 mobocertinib and should be avoided.

Coadministration of multiple 200 mg twice daily doses of itraconazole (a strong CYP3A inhibitor) with a single 20 mg mobocertinib dose increased the combined molar C_{max} of mobocertinib and its active metabolites by 186% (i.e. geometric mean ratio of 2.86) and AUC_{inf} by 527% (i.e. geometric mean ratio of 6.27) compared to a 20 mg mobocertinib dose administered alone.

Based on simulations, the coadministration of multiple doses of itraconazole and ketoconazole (strong CYP3A inhibitors) was predicted to increase the steady-state combined molar AUC_{24} of mobocertinib and its active metabolites by 374 to 419% (i.e. geometric mean ratios of 4.74 to 5.19).
Based on simulations, the coadministration of multiple doses of a moderate CYP3A inhibitor was predicted to increase the steady-state combined molar AUC_{24} of mobocertinib and its active metabolites by approximately 100 to 200% (i.e. geometric mean ratios of approximately 2.00 to 3.00).

CYP3A inducers

Mobocertinib is predominantly metabolised by CYP3A. Drugs that induce CYP3A can therefore lead to decreased mobocertinib concentrations, which may reduce the anti-tumour activity of mobocertinib. The coadministration of moderate or strong CYP3A inducers with EXKIVITY, including but not limited to rifampicin, carbamazepine, phenytoin, rifabutin, phenobarbital, St. John's wort, efavirenz, modafinil, bosentan, etravirine and nafcillin, should be avoided.

Coadministration of multiple 600 mg once daily doses of rifampicin (a strong CYP3A inducer) with a single 160 mg mobocertinib dose decreased the combined molar C_{max} of mobocertinib and its active metabolites by 92% (i.e. geometric mean ratio of 0.08) and AUC_{inf} by 95% (i.e. geometric mean ratio of 0.05) compared to a 160 mg mobocertinib dose administered alone. Based on simulations, the coadministration of multiple doses of rifampicin was predicted to decrease the steady-state combined molar AUC_{24} of mobocertinib and its active metabolites by 92% (i.e. geometric mean ratio of 0.08).

Based on simulations, the coadministration of multiple doses of efavirenz (a moderate CYP3A inducer) was predicted to decrease the steady-state combined molar AUC_{24} of mobocertinib and its active metabolites by 58% (i.e. geometric mean ratio of 0.42).

Drugs that prolong the QTc interval

Coadministration of EXKIVITY with drugs known to prolong the QTc interval (e.g. anti-arrhythmic medicines, fluoroquinolones, triazole antifungals, 5-HT_3 receptor antagonists) and moderate or strong CYP3A inhibitors may increase the risk of QTc interval prolongation. The coadministration of such drugs should be avoided. If coadministration of EXKIVITY with moderate CYP3A inhibitors or with drugs known to prolong the QTc interval is unavoidable, conduct close ECG monitoring (see "Warnings and precautions" and "Properties/Effects").

Transporter Systems

In vitro, mobocertinib is a substrate of P-gp. Given that mobocertinib exhibits high solubility and high permeability *in vitro*, P-gp inhibitors are unlikely to increase plasma concentrations of mobocertinib.

In vitro, mobocertinib was not a substrate of BCRP, OATP1B1, and OATP1B3.

Effect of EXKIVITY on Other Drugs

Avoid coadministration

CYP3A substrates

Mobocertinib is a weak inducer of CYP3A. Coadministration of EXKIVITY with CYP3A substrates may decrease plasma concentrations of CYP3A substrates, which may reduce the efficacy of these substrates.
The coadministration of hormonal contraceptives with EXKIVITY should be avoided.
The coadministration of EXKIVITY with other CYP3A substrates where minimal concentration changes may lead to serious therapeutic failures should be avoided. If coadministration is unavoidable, the CYP3A substrate dosage should be increased in accordance with the approved Prescribing Information.
Coadministration of multiple doses of EXKIVITY 160 mg once daily with oral or intravenous midazolam (a CYP3A substrate) decreased the AUC_{inf} of midazolam by 32% (i.e. geometric mean ratio of 0.68) and 16% (i.e. geometric mean ratio of 0.84), respectively.

Other interactions

In vitro, mobocertinib, AP32960, and AP32914 do not cause inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19, or 2D6 at clinically relevant concentrations.

Transporter Systems

In vitro, mobocertinib is an inhibitor of P-gp and BCRP. The clinical relevance for substrates of BCRP is not known.
Based on simulations, the coadministration of multiple doses of EXKIVITY 160 mg once daily was predicted to result in no clinically meaningful increase in systemic exposures of P-gp substrates (e.g. digoxin, dabigatran). No dose adjustment is recommended for P-gp substrates during coadministration with EXKIVITY.

In vitro, mobocertinib does not cause inhibition of BSEP, MATE1, MATE2-K, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, or OCT2 at clinically relevant concentrations.

Pregnancy, lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential being treated with EXKIVITY should be advised to avoid becoming pregnant during treatment. Women of childbearing potential should be advised to use effective non-

hormonal contraception during treatment with EXKIVITY and for 1 month following the final dose. Men with female partners of childbearing potential should be advised to use effective contraception during treatment with EXKIVITY and for 1 week following the final dose of EXKIVITY.

Pregnancy

There is no clinical experience with the use of EXKIVITY in pregnant women. Animal studies have shown effects on the developing foetus and male and female reproductive organs (see "Preclinical data").
EXKIVITY can cause foetal harm when administered to a pregnant woman based on its mechanism of action and data from animal reproduction studies. EXKIVITY should not be used during pregnancy unless the clinical condition of the woman requires treatment. Women of childbearing age or male patients with partners of childbearing age must be informed of the potential risk to the foetus.

Lactation

It is not known whether mobocertinib or its metabolites are excreted in human milk or if there are effects on the breastfed child or on milk production. A risk to the newborn/child cannot be excluded. Breast-feeding should be discontinued during treatment with EXKIVITY and for 1 week following the final dose.

Fertility

There are no data on the effect of EXKIVITY on human fertility. Although fertility studies in animals were not conducted with EXKIVITY, other animal studies showed changes in male and female reproductive organs, and therefore a risk for effects on fertility cannot be excluded (see "Preclinical data").

Effects on ability to drive and use machines

EXKIVITY has minor influence on the ability to drive and use machines. Fatigue has been observed in clinical trials. Patients should be advised not to drive or operate machines if they experience fatigue while taking EXKIVITY.

Undesirable effects

Summary of the safety profile

The most common adverse reactions (≥ 25%) in patients treated with EXKIVITY were diarrhoea (94%), rash (80%), anaemia (69%), blood creatinine increased (57%), decreased lymphocyte (51%),

nausea (49%), stomatitis (47%), amylase increased (42%), decreased appetite (37%), lipase increased (37%), vomiting (37%), paronychia (36%), dry skin (32%), fatigue (31%), hypomagnesaemia (31%), hypokalaemia (30%), decreased platelet count (29%), alanine aminotransferase increased (28%), aspartate aminotransferase increased (28%) and hyponatraemia (28%).
Serious adverse reactions occurred in 21% of patients treated with EXKIVITY. The most common serious adverse reactions (≥ 2%) were diarrhoea (4.8%), vomiting (4.5%), acute kidney injury (3.8%), decreased appetite (2.4%), cardiac failure (2.1%), dehydration (2.1%), interstitial lung disease (2.1%) and nausea (2.1%).

Permanent discontinuation occurred in 12% of patients who received EXKIVITY. Adverse reactions requiring permanent discontinuation of EXKIVITY in at least ≥ 2% of patients were diarrhoea (3.4%) and interstitial lung disease (2.8%).

Dose interruptions of EXKIVITY due to an adverse reaction occurred in 57% of patients. Adverse reactions which required dosage interruption in > 5% of patients included diarrhoea (26%), nausea (13%), rash (11%), vomiting (8%), stomatitis (6%), and decrease appetite (6%).

Dose reductions of EXKIVITY due to an adverse reaction occurred in 33% of patients. The adverse reaction requiring dose reduction in > 5% of patients was diarrhoea (15%), rash (7%), and nausea (6%).

Fatal cases of respiratory failure and heart failure occurred in 3 (1.0%) and 2 (0.7%) patients, respectively.

List of adverse reactions

The safety data described reflect exposure to EXKIVITY in clinical trials TAK-788-1003 and AP32788-15-101, at the recommended dose of 160 mg once daily in 290 patients with advanced solid malignancies, including 285 patients with NSCLC. Patients with a history of interstitial lung disease, drug-related pneumonitis, radiation pneumonitis that required steroid treatment, or significant, uncontrolled, active cardiovascular disease, or prolonged QTc interval were excluded from enrolment in these trials. The median duration of exposure to EXKIVITY was 6.5 months. Among the 290 patients who received EXKIVITY, 52% were exposed for 6 months or longer and 26% were exposed for greater or equal to one year.

The adverse reactions are listed according to MedDRA system organ classes and the conventional frequencies as follows:

"very common" (≥1/10)

"common" (≥1/100, <1/10),

"uncommon" (≥1/1,000, <1/100)

"rare" (≥1/10,000, <1/ 1,000)

"very rare" (<1/10,000)

Within each system organ class, the Adverse Drug Reactions (ADRs) are ranked by frequency, with the most frequent reactions first.

Table 3 Adverse reactions in patients treated with EXKIVITY

System organ class/adverse reaction	All grades Adverse reactions	Grade 3 Adverse reactions	Grade 4 Adverse reactions
Blood and lymphatic system disorders			
Anaemia*	Very common (69%)	Common	
Decreased lymphocyte	Very common (51%)	Very common (15%)	Common
Decreased platelet count	Very common (29%)	Common	Uncommon
Decreased leukocyte	Very common (24%)	Uncommon	
Metabolism and nutrition disorders			
Decreased appetite	Very common (37%)	Common	
Hypomagnesaemia*	Very common (31%)	Common	Uncommon
Hypokalaemia*	Very common (30%)	Common	Uncommon
Hyponatraemia*	Very common (28%)	Common	
Weight decreased	Very common (23%)	Common	
Dehydration	Very common (11%)	Common	
Eye disorders			
Ocular toxicity[a]	Very common (12%)		
Cardiac disorders			
QT interval prolongation[b]	Very common (12%)	Common	Uncommon
Heart failure[c]	Common	Common	Uncommon
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea	Very common (10%)		
Interstitial lung disease[d]	Common	Uncommon	
Gastrointestinal disorders			
Diarrhoea	Very common (94%)	Very common (20%)	Uncommon
Nausea	Very common (49%)	Common	
Stomatitis[e]	Very common (47%)	Common	
Amylase increased*	Very common (42%)	Common	Common

Lipase increased*	Very common (37%)	Common	Common
Vomiting	Very common (37%)	Common	
Gastroesophageal reflux disease	Very common (13%)	Uncommon	
Hepatobiliary disorders			
Alanine aminotransferase increased*	Very common (28%)	Common	Uncommon
Aspartate aminotransferase increased*	Very common (28%)	Common	
Skin and subcutaneous tissue disorders			
Rash[f]	Very common (80%)	Common	
Dry skin[g]	Very common (32%)	Uncommon	
Paronychia[h]	Very common (36%)	Uncommon	
Alopecia	Very common (14%)		
Renal and urinary disorders			
Blood creatinine increased*	Very common (57%)	Common	Uncommon
Acute kidney injury[i]	Common	Common	Uncommon
General disorders and administration site conditions			
Fatigue[j]	Very common (31%)	Common	

ADRs included as preferred terms are based on MedDRA version 23.0.
* For the frequencies of the adverse reaction terms associated with laboratory changes, a patient is counted once for the highest treatment emergent adverse event grade or laboratory result.

a. Includes abnormal sensation in eye, blepharitis, conjunctival haemorrhage, corneal oedema, dry eye, eye discharge, eye pruritus, trichiasis, vision blurred, and vitreous floaters.
b. Includes electrocardiogram QT prolonged and ventricular arrhythmia
c. Includes heart failure, heart failure congestive, ejection fraction decreased, and cardiomyopathy. Grade 5 heart failure occurred in 2 (0.7%) patients.
d. Includes interstitial lung disease, pneumonitis and respiratory failure. Grade 5 respiratory failure occurred in 3 (1.0%) patients.
e. Includes stomatitis, mouth ulceration, aphthous ulcer, mucosal inflammation, cheilitis, angular cheilitis, and odynophagia.
f. Includes rash, rash maculo-papular, rash papular, rash pruritic, rash pustular, dermatitis acneiform, pruritus, dermatitis, eczema, palmar-plantar erythrodysaesthesia syndrome, erythema, urticaria, and folliculitis.
g. Includes dry skin, skin fissures, and skin exfoliation.
h. Includes paronychia, nail bed tenderness, nail disorder, nail infection, and onycholysis.
i. Includes acute kidney injury, creatinine renal clearance decreased, glomerular filtration rate decreased, renal failure, and renal impairment.
j. Includes fatigue and asthenia.

Description of selected adverse reactions

Interstitial lung disease/ Pneumonitis

In patients treated with EXKIVITY at the recommended dosage of 160 mg once daily, ILD/pneumonitis occurred in 4.5% (13/290) of patients; of these, 0.7% (2/290) were Grade 3 events. The median time

to onset of ILD/pneumonitis was 88.5 days and the median time to resolution was 17.0 days. Fatal cases of respiratory failure occurred in 3 (1.0%) patients (see “Warnings and precautions”).

Heart failure

In patients treated with EXKIVITY, heart failure (including congestive heart failure, decreased ejection fraction, and cardiomyopathy) occurred in 3.4% (10/290) of patients. Grade 3 heart failure occurred in 1.0% (3/290) of patients. Grade 4 heart failure occurred in 1 patient (0.3%). The median time to onset of heart failure was 87.5 days and the median time to resolution was 14.5 days. Fatal events of heart failure occurred in 2 (0.7%) patients. (see “Warnings and precautions”).

QTc Interval Prolongation

In patients treated with EXKIVITY, QTc interval prolongation occurred in 12% (35/290) of patients. Grade 3 QTc interval prolongation occurred in 4.5% (13/290) of patients and Grade 4 QTc interval prolongation occurred in 1 patient (0.3%).
The median time to onset of QTc interval prolongation was 58.0 days and the median time to resolution was 29.0 days.
In the 286 patient subset of the pooled EXKIVITY safety population who had scheduled and unscheduled ECGs, 2.8% of patients had a QTc interval > 500 msec and 13% of patients had a change-from-baseline QTc interval > 60 msec. On treatment ECGs were not routinely performed in cycle 1 (first 28 days of treatment) (see “Warnings and precautions” and “Properties/Effects”).

Diarrhoea

In clinical studies, 73% (213/290) of patients experienced Grade 1 or 2 diarrhoea. Grade 3 diarrhoea occurred in 20% (59/290) of patients and Grade 4 diarrhoea occurred in 1 patient (0.3%). The median time to onset of diarrhoea was 5.0 days and the median time to resolution was 3.0 days. (see “Warnings and precautions”). For Grade 3 or Grade 4 diarrhoea, the incidence was higher in patients ≥ 65 years (26% [30/114]) compared to younger patients (17% [30/176]).

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 known specific antidote for overdose with EXKIVITY. In the event of an overdose, monitor the patient for adverse reactions (see “Undesirable effects”) and provide appropriate supportive care.

Properties/Effects

ATC code

L01EB10

Mechanism of action

Mobocertinib is a kinase inhibitor of the EGFR that selectively inhibits and irreversibly binds to *EGFR* exon 20 insertion mutations at lower concentrations than Wild type (WT)-*EGFR*. Two pharmacologically active metabolites, AP32960 and AP32914, with similar inhibitory profiles to mobocertinib, have been identified in the plasma after oral administration of mobocertinib.

In cultured cells models, mobocertinib inhibits proliferation of cells driven by different *EGFR* exon 20 insertion mutation variants at 1.5- to 10-fold lower concentrations than WT-*EGFR* signalling inhibition.

In mouse tumour implantation models, mobocertinib demonstrates tumour regression of human NSCLC xenografts with the *EGFR* exon 20 insertion [NPH]. Tumour growth inhibition was observed in an engineered model expressing the *EGFR* exon 20 insertion mutation [ASV].

Pharmacodynamics

Please refer to “*Mechanism of action*”.

Cardiac Electrophysiology

The largest mean increase in QTc was 23.0 msec (UCI: 25.5 msec) following administration of EXKIVITY 160 mg once daily. The increase in QTc interval was concentration-dependent.

The largest mean increase in the PR interval was 12.4 msec (UCI: 15.0 msec). PR interval prolongation >220 msec occurred in 5% of patients taking EXKIVITY 160 mg once daily.

Clinical efficacy

Previously Treated EGFR Exon 20 Insertion Mutation-Positive locally advanced or metastatic Non-Small Cell Lung Cancer

The efficacy and safety of EXKIVITY for the treatment of patients with *EGFR* exon 20 insertion mutation-positive locally advanced or metastatic NSCLC was demonstrated in a multicentre, single-arm, open-label study (AP32788-15-101). A total of 114 patients with NSCLC who had previously been treated with platinum-based chemotherapy received EXKIVITY at a dose of 160 mg once daily until disease progression or intolerable toxicity. Eligible patients were required to have histologically or cytologically confirmed locally advanced or metastatic disease (Stage IIIB or IV), a documented *EGFR* exon 20 insertion mutation by a local test, and adequate organ and bone marrow function. Of the 114 patients with *EGFR* exon 20 insertion mutations, 70% of patient tissue samples were available and tested retrospectively using Next Generation Sequencing (NGS) by a central laboratory. Patients excluded from the study were those with active metastases in central nervous system; radiotherapy (≤14 days) or had not recovered from radiotherapy-related toxicities; significant, uncontrolled, or active cardiovascular disease; prolonged QTc interval, or use of medications associated with Torsades de Pointes; interstitial lung disease, radiation pneumonitis that required steroid treatment, or drug-related pneumonitis; disease progression following response to an *EGFR*-TKI.

The primary efficacy endpoint was confirmed objective response rate (cORR) according to Response Evaluation Criteria in Solid Tumours (RECIST v1.1) by an independent review committee (IRC). Additional efficacy endpoints included investigator-assessed cORR, duration of response (DOR), time to response, progression-free survival (PFS) and overall survival (OS). Intracranial efficacy was not assessed in the pivotal population.

The study population characteristics were: median age 60 years (range: 27 to 84 years), age 75 years or older (7%), female (66%), White (37%), Asian (60%), never smokers (71%), ECOG performance status 0 (25%) or 1 (75%) and adenocarcinoma histology (98%).
At baseline, 113 (99%) patients had metastatic disease (including brain metastases 35 %), and 1 (0.9%) patient had locally advanced disease; 43% of patients had received immunotherapy, and 22% patients had received *EGFR*-TKI.

The median duration of follow-up was 25.8 months. Efficacy results from this study are summarised in Table 4.

Table 4: Study AP32788-15-101 Efficacy Results (N = 114)		
Efficacy Parameter	**IRC Assessment**	**Investigator Assessment**
Confirmed Objective Response Rate (cORR) (95% CI)	28% (20%, 37%	35% (26%, 45%)
Complete Response	0.9%	0.9%
Partial Response	27%	34%
Duration of Response (DOR)[a]		
Median (months), (95% CI)	15.8 (7.4, 19.4)	13.9 (5.6, 19.4)
Patients with DOR ≥6 months	74%	66%
Patients with DOR ≥12 months	56%	53%
Progression-Free Survival (PFS)[b]		
Number of patients with event n (%)	76 (67%)	79 (69%
Median (months), (95% CI)	7.3 (5.5, 9.2)	7.3 (5.6, 8.8)
Overall Survival (OS)[b]		
Number of patients with event n (%)	66 (58%)	
Median (months), (95% CI)	20.2 (14.9, 25.3)	

IRC = independent review committee, CI = confidence interval,

a. Kaplan-Meier estimate in confirmed responders only

b. Kaplan-Meier estimate

Paediatrics

No studies have been conducted with EXKIVITY in paediatric population.

Temporary authorisation

The medicinal product “EXKIVITY” has been granted temporary authorisation as the clinical data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be transformed into an ordinary authorisation.

Pharmacokinetics

After single- and multiple-dose administration, combined molar C_{max} and AUC_{24} of mobocertinib and its active metabolites, AP32960 and AP32914, was dose-proportional over the dose range of 5 to 180 mg once daily (0.03 to 1.1 times the approved recommended dosage). No clinically meaningful accumulation was observed after administration of EXKIVITY 160 mg once daily based on the AUC ratio of mobocertinib.

Absorption

The median (min, max) time to peak concentration (T_{max}) of mobocertinib is 4 hours (1, 8 hours). The mean (%CV) absolute bioavailability is 37% (50%).

Effect of Food

No clinically meaningful differences in the combined molar AUC and C_{max} of mobocertinib, AP32960, and AP32914 were observed following administration with a high-fat meal (approximately 900 to 1000 calories, with 150 calories from protein, 250 calories from carbohydrate, and 500 to 600 calories from fat) or with a low-fat meal (approximately 336 calories, with 37 calories from protein, 253 calories from carbohydrate, and 46 calories from fat) compared to administration after an overnight fast.

Distribution

Mobocertinib was bound to human plasma proteins in a concentration independent manner in vitro from 0.5 to 5.0 µM. The mean (standard deviation) bound fraction was 99.3% (0.11%) for mobocertinib, 99.5% (0.16%) for AP32960 and 98.6% (1.36%) for AP32914 in vitro.

The blood-to-plasma ratio was 0.76 for mobocertinib, 1.2 for AP32960 and 0.71 for AP32914.

The mean (%CV) apparent volume of distribution (Vss/F) of mobocertinib was 3,509 L (38%) at steady-state.

Metabolism

Mobocertinib is primarily metabolized by CYP3A. The two active metabolites, AP32960 and AP32914, are equipotent to mobocertinib and account for 36% and 4% of the combined molar AUC, respectively.

Elimination

The mean (%CV) plasma elimination half-life of mobocertinib was 18 hours (21%) at steady-state. The mean apparent oral clearance (CL/F) (%CV) of mobocertinib was 138 L/hr (47%) at steady-state.

The mean (%CV) plasma elimination half-life of AP32960 was 24 hours (20%) at steady-state. The mean apparent oral clearance (CL/F) (%CV) of AP32960 was 149 L/hr (36%) at steady-state.

The mean (%CV) plasma elimination half-life of AP32914 was 18 hours (21%) at steady-state. The mean apparent oral clearance (CL/F) (%CV) of AP32914 was 159 L/hr (52%) at steady-state.

Excretion

Following administration of a single 160 mg oral dose of radiolabelled mobocertinib, approximately 76% of the dose was recovered in faeces (approximately 6% as unchanged mobocertinib) and approximately 4% was recovered in urine (approximately 1% as unchanged mobocertinib). The percentage of the administered dose recovered in faeces and urine for AP32960 was approximately 12% and 1%, respectively. The metabolite AP32914 was below the detection limit in urine and faeces.

Kinetics in specific patient groups

Hepatic impairment

No clinically meaningful differences in the pharmacokinetics of mobocertinib were observed based on mild (total bilirubin ≤ ULN and AST > ULN or total bilirubin >1 to 1.5 times ULN and any AST)-to-moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment. The effect of severe (total bilirubin >3 times ULN and any AST) hepatic impairment on mobocertinib pharmacokinetics is unknown.

Renal impairment

No clinically meaningful differences in the pharmacokinetics of mobocertinib were observed based on mild-to-moderate renal impairment (estimated glomerular filtration rate 30 to 89 mL/min). The effect of severe (estimated glomerular filtration rate <30 mL/min) renal impairment on mobocertinib pharmacokinetics is unknown.

Effects of age, body weight, race and sex

No clinically meaningful differences in the pharmacokinetics of mobocertinib were observed based on age (18 to 86 years), race (White, Black, Asian), sex, or body weight (37.3 to 132 kg).

Preclinical data

Repeated dose toxicity

In rats, mobocertinib administration resulted in histological findings of decreased corneal epithelial thickness in the 4-and 13-week repeat-dose toxicology studies at doses ≥0.8 times the human exposure (AUC) at the 160 mg once daily clinical dose.
In dogs, in the 4-week repeat-dose study, mobocertinib administration resulted in discharge from the eye, sclera injection, partial or complete closure of the eye and histological findings of corneal epithelial atrophy at doses ≥0.3 times the AUC at the 160 mg once daily clinical dose. In dogs, in the

13-week repeat-dose study, mobocertinib administration resulted in discharge, conjunctival hyperemia, and corneal opacity correlating histologically with decreased corneal epithelial thickness at doses ≥0.2 times the AUC at the 160 mg once daily clinical dose.
The clinical relevance of these findings is unknown.

Genotoxicity

Mobocertinib was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay, and does not induce chromosomal damage in an *in vitro* chromosome aberration assay, or in an *in vivo* bone marrow micronucleus assessment in Sprague-Dawley rats.

Carcinogenicity

Carcinogenicity studies have not been performed with mobocertinib.

Reproductive toxicity

Studies of fertility and early embryonic development and pre- and postnatal toxicology were not conducted with mobocertinib. In rats and dogs in the 4- and 13-week repeat-dose toxicology studies, there were generally reversible changes that included decreases in organ weights affecting multiple reproductive organs (including ovaries, seminal vesicle/prostate gland, and/or uterus) at exposures ≥0.3 times the AUC observed at the recommended clinical dose of 160 mg once daily, as well as microscopic changes of decreased epithelial thickness/inflammation of the cervix/vagina and atrophy of the uterus, prostate gland, or mammary gland (males only) at exposures ≥ 0.2 times the AUC at the 160 mg once daily clinical dose in rats and/or dogs. Based on these findings, mobocertinib may impair fertility in males and females of reproductive potential.

In a GLP-compliant preliminary dose range-finding embryo-foetal development study in pregnant rats, at doses of 1.25, 2.5, 5, or 10 mg/kg, daily oral administration of mobocertinib during organogenesis (Days 6 to 20 post coitum) resulted in maternal and foetal toxicity at 10 mg/kg (exposures approximately 1.7 times above the maximum recommended human dose of 160 mg/day). Maternal toxicity was evidenced by an adverse decrease in food consumption and body weight throughout the dosing period. There were adverse effects on embryo-foetal development, including embryolethality (embryo-foetal death) and effects on foetal growth (decreased foetal weight). No maternal or foetal toxicity was observed at ≤ 5 mg/kg (PD 20 plasma AUC_{24} of 787 h•ng/mL; approximately 0.8 times human exposure based on AUC at clinical dose of 160 mg once daily). There was no clear evidence of teratogenicity (dysmorphogenesis) at any dose.

Other information

Incompatibilities

Not applicable.

Shelf life

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

Special precautions for storage

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

Authorisation number

68147 (Swissmedic)

Packs

Pack of 112 hard capsules [A]

Marketing authorisation holder

Takeda Pharma AG, 8152 Opfikon

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