

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EXKIVITY safely and effectively. See full prescribing information for EXKIVITY.

EXKIVITY® (mobocertinib) capsules, for oral use
Initial U.S. Approval: 2021

WARNING: QTc PROLONGATION AND TORSADES DE POINTES
See full prescribing information for complete boxed warning.

- EXKIVITY can cause life-threatening heart rate-corrected QT (QTc) prolongation, including Torsades de Pointes, which can be fatal, and requires monitoring of QTc and electrolytes at baseline and periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation (5.1).
- Avoid use of concomitant drugs which are known to prolong the QTc interval and use of strong or moderate CYP3A inhibitors with EXKIVITY, which may further prolong the QTc (5.1, 7.1, 7.3).
- Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of QTc prolongation (2.3).

RECENT MAJOR CHANGES
Dosage and Administration (2.3) 0x/2023

INDICATIONS AND USAGE
EXKIVITY is a kinase inhibitor indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). (1, 2.1)

DOSAGE AND ADMINISTRATION
Recommended Dosage: 160 mg orally once daily, with or without food. (2.2)

DOSAGE FORMS AND STRENGTHS
Capsules: 40 mg. (3)

CONTRAINDICATIONS
None. (4)

WARNINGS AND PRECAUTIONS

- Interstitial Lung Disease (ILD)/Pneumonitis:** Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Immediately withhold EXKIVITY in patients with suspected ILD/pneumonitis and permanently discontinue EXKIVITY if ILD/pneumonitis is confirmed. (2.3, 5.2)
- Cardiac Toxicity:** Monitor cardiac function, including left ventricular ejection fraction, at baseline and during treatment. Withhold, resume at reduced dose or permanently discontinue based on severity. (2.3, 5.3)
- Diarrhea:** Diarrhea may lead to dehydration or electrolyte imbalance, with or without renal impairment. Monitor electrolytes and advise patients to start an antidiarrheal agent at first episode of diarrhea and to increase fluid and electrolyte intake. Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity. (2.3, 5.4)
- Embryo-Fetal Toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective non-hormonal contraception. (5.5, 8.1, 8.3)

ADVERSE REACTIONS

The most common (>20%) adverse reactions are diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, and musculoskeletal pain. The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, increased amylase, increased lipase, decreased potassium, decreased hemoglobin, increased creatinine, and decreased magnesium. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals America, Inc. at 1-844-217-6468 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP3A Inhibitors:** Avoid concomitant use of EXKIVITY with strong or moderate CYP3A inhibitors. If concomitant use of a moderate CYP3A inhibitor is unavoidable, reduce the dose of EXKIVITY. (2.4, 7.1)
- CYP3A Inducers:** Avoid concomitant use of EXKIVITY with strong or moderate CYP3A inducers. (7.1)

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2023

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FULL PRESCRIBING INFORMATION

WARNING: QTc PROLONGATION AND TORSADES DE POINTES

- EXKIVITY can cause life threatening heart rate-corrected QT (QTc) prolongation, including Torsades de Pointes, which can be fatal, and requires monitoring of QTc and electrolytes at baseline and periodically during treatment. Increase monitoring frequency in patients with risk factors for QTc prolongation [see *Warnings and Precautions (5.1)*].
- Avoid use of concomitant drugs which are known to prolong the QTc interval and use of strong or moderate CYP3A inhibitors with EXKIVITY, which may further prolong the QTc [see *Warnings and Precautions (5.1), Drug Interactions (7.1, 7.3)*].
- Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of QTc prolongation [see *Dosage and Administration (2.3)*].

1 INDICATIONS AND USAGE

EXKIVITY is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test [see *Dosage and Administration (2.1)*], whose disease has progressed on or after platinum-based chemotherapy.

This indication is approved under accelerated approval based on overall response rate and duration of response [see *Clinical Studies (14)*]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients with locally advanced or metastatic NSCLC for treatment with EXKIVITY based on the presence of EGFR exon 20 insertion mutations [see *Clinical Studies (14)*]. Information on FDA-approved tests is available at: <http://www.fda.gov/CompanionDiagnostics>.

2.2 Recommended Dosage

The recommended dosage of EXKIVITY is 160 mg orally once daily until disease progression or unacceptable toxicity.

Take EXKIVITY with or without food [see *Clinical Pharmacology 12.3*], at the same time each day. Swallow EXKIVITY capsules whole. Do not open, chew or dissolve the contents of the capsules.

If a dose is missed by more than 6 hours, skip the dose and take the next dose the following day at its regularly scheduled time.

If a dose is vomited, do not take an additional dose. Take the next dose as prescribed the following day.

2.3 Dosage Modifications for Adverse Reactions

EXKIVITY dose reduction levels for adverse reactions are summarized in Table 1.

Table 1: Recommended EXKIVITY Dose Reductions

Dose Reductions	Dose Level
First dose reduction	120 mg once daily
Second dose reduction	80 mg once daily

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

Table 2: Recommended Dosage Modifications for EXKIVITY Adverse Reactions

Adverse Reaction	Severity*	EXKIVITY Dosage Modification
QTc Interval Prolongation and Torsades de Pointes <i>[see Warnings and Precautions (5.1)]</i>	Grade 2 (QTc interval 481-500 msec)	<u>First Occurrence</u> <ul style="list-style-type: none"> Withhold EXKIVITY until \leq Grade 1 or baseline. Upon recovery, resume EXKIVITY at the same dose. <u>Recurrence</u> <ul style="list-style-type: none"> Withhold EXKIVITY until \leq Grade 1 or baseline. Upon recovery, resume EXKIVITY at the next lower dose or permanently discontinue EXKIVITY.
	Grade 3 (QTc interval \geq 501 msec or QTc interval increase of $>$ 60 msec from baseline)	<u>First Occurrence</u> <ul style="list-style-type: none"> Withhold EXKIVITY until \leq Grade 1 or baseline. Upon recovery, resume EXKIVITY at the next lower dose or permanently discontinue EXKIVITY. <u>Recurrence</u> <ul style="list-style-type: none"> Permanently discontinue EXKIVITY.
	Grade 4 (Torsades de Pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia)	<ul style="list-style-type: none"> Permanently discontinue EXKIVITY.
Interstitial Lung Disease (ILD)/pneumonitis <i>[see Warnings and Precautions (5.2)]</i>	Any grade	<ul style="list-style-type: none"> Withhold EXKIVITY if ILD/pneumonitis is suspected. Permanently discontinue EXKIVITY if ILD/pneumonitis is confirmed.
Decreased Ejection Fraction or Heart Failure	Grade 2 decreased ejection fraction	<ul style="list-style-type: none"> Withhold EXKIVITY until \leq Grade 1 or baseline. If recovered to baseline within 2 weeks, resume EXKIVITY at

Adverse Reaction	Severity*	EXKIVITY Dosage Modification
[see Warnings and Precautions (5.3)]		the same dose or the next lower dose. <ul style="list-style-type: none"> If not recovered to baseline within 2 weeks, permanently discontinue EXKIVITY.
	≥ Grade 2 heart failure or Grade 3 or 4 decreased ejection fraction	<ul style="list-style-type: none"> Permanently discontinue EXKIVITY.
Diarrhea [see Warnings and Precautions (5.4)]	Intolerable or recurrent Grade 2 or Grade 3	<ul style="list-style-type: none"> Withhold EXKIVITY until ≤ Grade 1. Resume EXKIVITY at the same dose or the next lower dose.
	Grade 4	<u>First Occurrence</u> <ul style="list-style-type: none"> Withhold EXKIVITY until ≤ Grade 1. Resume EXKIVITY at the next lower dose. <u>Recurrence</u> <ul style="list-style-type: none"> Permanently discontinue EXKIVITY.
Increased Amylase or Lipase [see Adverse Reactions (6.1)]	Grade 3 without signs or symptoms	<ul style="list-style-type: none"> Withhold EXKIVITY until ≤ Grade 1. Resume EXKIVITY at the same dose or next lower dose. If not recovered to ≤ Grade 1 within 2 weeks, permanently discontinue EXKIVITY.
	Grade 3 with signs or symptoms	<ul style="list-style-type: none"> Withhold EXKIVITY until ≤ Grade 1. Resume EXKIVITY at the next lower dose. If not recovered to ≤ Grade 1 within 2 weeks, permanently discontinue EXKIVITY.
	Grade 4	<u>First Occurrence</u> <ul style="list-style-type: none"> Withhold EXKIVITY until ≤ Grade 1. Resume EXKIVITY at the next lower dose if recovery occurs within 2 weeks. Permanently discontinue EXKIVITY if recovery does not occur within 2 weeks.

Adverse Reaction	Severity*	EXKIVITY Dosage Modification
		<u>Recurrence</u> <ul style="list-style-type: none"> Permanently discontinue EXKIVITY.
Other Adverse Reactions [see Adverse Reactions (6.1)]	Intolerable or recurrent Grade 2 or Grade 3	<ul style="list-style-type: none"> Withhold EXKIVITY until \leq Grade 1. Resume EXKIVITY at the same dose or the next lower dose.
	Grade 4	<u>First Occurrence</u> <ul style="list-style-type: none"> Withhold EXKIVITY until \leq Grade 1. Resume EXKIVITY at the next lower dose if recovery occurs within 2 weeks. Permanently discontinue EXKIVITY if recovery does not occur within 2 weeks. <u>Recurrence</u> <ul style="list-style-type: none"> Permanently discontinue EXKIVITY.

ULN = upper limit of normal

* Graded per Common Terminology Criteria for Adverse Events Version 5.0

2.4 Dosage Modifications for Moderate CYP3A Inhibitors

Avoid concomitant use of moderate CYP3A inhibitors with EXKIVITY. If concomitant use of a moderate CYP3A inhibitor cannot be avoided, reduce the EXKIVITY dose by approximately 50% (i.e., from 160 to 80 mg, 120 to 40 mg, or 80 to 40 mg) and monitor the QTc interval more frequently. After the moderate CYP3A inhibitor has been discontinued for 3 to 5 elimination half-lives, resume EXKIVITY at the dose taken prior to initiating the moderate CYP3A inhibitor [see Drug Interactions (7.1)].

3 DOSAGE FORMS AND STRENGTHS

Capsules: 40 mg, white, size 2, imprinted with “MB788” on the cap and “40mg” on the body in black ink.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 QTc Prolongation and Torsades de Pointes

EXKIVITY can cause life-threatening heart rate-corrected QT (QTc) prolongation, including Torsades de Pointes, which can be fatal. In the 250 patient subset of the pooled EXKIVITY safety population who had scheduled and unscheduled electrocardiograms (ECGs) [see Adverse Reactions (6.1), Clinical Pharmacology (12.2)], 1.2% of patients had a QTc interval >500 msec and 11% of patients had a change-from-baseline QTc interval >60 msec. Grade 4 Torsades de Pointes occurred in 1 patient (0.4%). Clinical trials of EXKIVITY did not enroll patients with baseline QTc greater than 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. Increase monitoring frequency in patients with risk factors for QTc prolongation, such as patients with congenital long QT 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 [see *Drug Interactions (7.1)*], which may further prolong the QTc [see *Drug Interactions (7.3)*].

Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of the QTc prolongation [see *Dosage and Administration (2.3)*].

5.2 Interstitial Lung Disease (ILD)/Pneumonitis

EXKIVITY can cause ILD/pneumonitis, which can be fatal. In the pooled EXKIVITY safety population [see *Adverse Reactions (6.1)*], ILD/pneumonitis occurred in 4.3% of patients including 0.8% Grade 3 events and 1.2% fatal events.

Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Immediately withhold EXKIVITY in patients with suspected ILD/pneumonitis and permanently discontinue EXKIVITY if ILD/pneumonitis is confirmed [see *Dosage and Administration (2.3)*].

5.3 Cardiac Toxicity

EXKIVITY can cause cardiac toxicity (including decreased ejection fraction, cardiomyopathy, and congestive heart failure) resulting in heart failure which can be fatal. In the pooled EXKIVITY safety population [see *Adverse Reactions (6.1)*], heart failure occurred in 2.7% of patients including 1.2% Grade 3 reactions, 0.4% Grade 4 reactions, and one (0.4%) fatal case of heart failure.

EXKIVITY can cause QTc prolongation resulting in Torsades de Pointes [see *Warnings and Precautions (5.1)*]. Atrial fibrillation (1.6%), ventricular tachycardia (0.4%), first degree atrioventricular block (0.4%), second degree atrioventricular block (0.4%), left bundle branch block (0.4%), supraventricular extrasystoles (0.4%) and ventricular extrasystoles (0.4%) also occurred in patients receiving EXKIVITY.

Monitor cardiac function, including assessment of left ventricular ejection fraction at baseline and during treatment. Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity [see *Dosage and Administration (2.3)*].

5.4 Diarrhea

EXKIVITY can cause diarrhea, which can be severe. In the pooled EXKIVITY safety population [see *Adverse Reactions (6.1)*], diarrhea occurred in 93% of patients, including 20% Grade 3 and 0.4% Grade 4. The median time to first onset of diarrhea was 5 days but diarrhea has occurred within 24 hours after administration of EXKIVITY. In the 48% of patients whose diarrhea resolved, the median time to resolution was 3 days. Diarrhea may lead to dehydration or electrolyte imbalance, with or without renal impairment. Treat diarrhea promptly.

Advise patients to start an antidiarrheal agent (e.g., loperamide) at first sign of diarrhea or increased bowel movement frequency and to increase fluid and electrolyte intake.

Monitor electrolytes and withhold, reduce the dose or permanently discontinue EXKIVITY based on the severity [see *Dosage and Administration (2.3)*].

5.5 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, EXKIVITY can cause fetal harm when administered to a pregnant woman. Oral administration of mobocertinib to pregnant rats during the period of organogenesis resulted in embryoletality at maternal exposures approximately 1.7

times the human exposure based on area under the curve (AUC) at the 160 mg once daily clinical dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with EXKIVITY [see *Drug Interactions (7.2)*] and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose of EXKIVITY [see *Use in Specific Populations (8.1, 8.3)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- QTc Prolongation and Torsades de Pointes [see *Warnings and Precautions (5.1)*]
- Interstitial Lung Disease (ILD)/Pneumonitis [see *Warnings and Precautions (5.2)*]
- Cardiac Toxicity [see *Warnings and Precautions (5.3)*]
- Diarrhea [see *Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in WARNINGS AND PRECAUTIONS reflects exposure to EXKIVITY as a single agent at a dose of 160 mg orally once daily in 256 patients, including 114 patients with EGFR exon 20 insertion mutation-positive locally advanced or metastatic NSCLC from Study AP32788-15-101, and patients with other solid tumors. Forty-eight percent (48%) were exposed for 6 months or longer and 12% were exposed for greater than one year. The most common (>20%) adverse reactions were diarrhea, rash, nausea, stomatitis, vomiting, decreased appetite, paronychia, fatigue, dry skin, and musculoskeletal pain. The most common ($\geq 2\%$) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, increased amylase, increased lipase, decreased potassium, decreased hemoglobin, increased creatinine, and decreased magnesium.

EGFR Exon 20 Insertion Mutation-Positive Locally Advanced or Metastatic NSCLC Previously Treated with Platinum-Based Chemotherapy

The safety of EXKIVITY was evaluated in a subset of patients in Study AP32788-15-101 with EGFR exon 20 insertion mutation-positive locally advanced or metastatic NSCLC who received prior platinum-based chemotherapy [see *Clinical Studies (14)*]. Patients with a history of interstitial lung disease, drug-related pneumonitis, radiation pneumonitis that required steroid treatment; significant, uncontrolled, active cardiovascular disease; or prolonged QTc interval were excluded from enrollment in this trial. A total of 114 patients received EXKIVITY 160 mg once daily until disease progression or unacceptable toxicity; 60% were exposed for 6 months or longer and 14% were exposed for greater than 1 year.

Serious adverse reactions occurred in 46% of patients who received EXKIVITY. Serious adverse reactions in $\geq 2\%$ of patients included diarrhea, dyspnea, vomiting, pyrexia, acute kidney injury, nausea, pleural effusion, and cardiac failure. Fatal adverse reactions occurred in 1.8% of patients who received EXKIVITY, including cardiac failure (0.9%), and pneumonitis (0.9%).

Permanent discontinuation occurred in 17% of patients who received EXKIVITY. Adverse reactions requiring permanent discontinuation of EXKIVITY in at least $\geq 2\%$ of patients were diarrhea and nausea.

Dosage interruptions of EXKIVITY due to an adverse reaction occurred in 51% of patients. Adverse reactions which required dosage interruption in >5% of patients included diarrhea, nausea and vomiting.

Dose reductions of EXKIVITY due to an adverse reaction occurred in 25% of patients. The adverse reaction requiring dose reduction in >5% of patients was diarrhea.

Table 3 summarizes the adverse reactions in Study AP32788-15-101.

Table 3: Adverse Reactions (≥10%) in Patients with EGFR Exon 20 Insertion Mutation-Positive NSCLC Whose Disease Has Progressed on or after Platinum-Based Chemotherapy in Study AP32788-15-101

Adverse Reaction	EXKIVITY (N = 114)	
	All Grades* (%)	Grade 3 or 4 (%)
Gastrointestinal Disorders		
Diarrhea	92	22
Stomatitis ^a	46	4.4 ^{**}
Vomiting	40	2.6 ^{**}
Decreased appetite	39	0.9 ^{**}
Nausea	37	4.4 ^{**}
Decreased weight	21	0
Abdominal pain ^b	18	1.8 ^{**}
Gastroesophageal reflux disease	15	0
Dyspepsia	11	0
Skin and Subcutaneous Tissue Disorders		
Rash ^c	78	1.8 ^{**}
Paronychia ^d	39	0.9 ^{**}
Dry skin	32	0
Pruritus	24	0.9 ^{**}
Alopecia	19	0
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain ^e	34	2.6 ^{**}
General Disorders and Administration Site Conditions		
Fatigue ^f	29	3.5 ^{**}
Respiratory, Thoracic and Mediastinal Disorders		
Cough ^g	24	0
Upper respiratory tract infection ^h	16	0
Dyspnea ⁱ	15	4.4
Rhinorrhea	13	0
Eye Disorders		
Ocular Toxicity ^j	11	0
Cardiac Disorders		
QTc interval prolongation ^k	10	3.5
Hypertension ^l	10	4.4 ^{**}
Nervous System Disorders		
Headache	10	0

* Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE 5)

** Events of Grade 3 only (no Grade 4 occurred)

- a Stomatitis includes angular cheilitis, aphthous ulcer, cheilitis, mouth ulceration, mucosal inflammation, odynophagia, and stomatitis.
- b Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain upper, abdominal tenderness, and gastrointestinal pain.
- c Rash includes acne, dermatitis, dermatitis acneiform, rash, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, and urticaria.
- d Paronychia includes nail bed tenderness, nail disorder, nail infection, onycholysis, and paronychia.
- e Musculoskeletal pain includes arthralgia, back pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, and spinal pain.
- f Fatigue includes asthenia, and fatigue.
- g Cough includes cough, productive cough, and upper-airway cough syndrome.
- h Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection, rhinitis, sinusitis, and upper respiratory tract infection.
- i Dyspnea includes dyspnea, and dyspnea exertional.
- j Ocular toxicity includes dry eye, eye pruritis, abnormal sensation in eye, eye discharge, blepharitis, trichiasis, conjunctival hemorrhage, vitreous floaters, blurred vision and corneal edema.
- k QTc interval prolongation includes electrocardiogram QT prolonged, and ventricular arrhythmia.
- l Hypertension includes blood pressure increased, and hypertension.

Clinically relevant adverse reactions in <10% of patients receiving EXKIVITY included edema (9%), acute kidney injury (8%), peripheral neuropathy (7%), palmar-plantar erythrodysesthesia (4.4%), pneumonitis (2.6%) and cardiac failure (2.6%).

Table 4 summarizes the laboratory abnormalities in Study AP32788-15-101.

Table 4: Select Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients with EGFR Exon 20 Insertion Mutation-Positive NSCLC Whose Disease Has Progressed on or after Platinum-Based Chemotherapy in Study AP32788-15-101

Laboratory Abnormality	EXKIVITY** (N = 114)	
	All Grades* (%)	Grade 3 or 4 (%)
Hematology		
Decreased red blood cells	59	3.5
Decreased lymphocytes	52	15
Decreased platelets	26	0.9
Decreased leukocytes	25	0
Chemistry		
Increased creatinine	52	2.7
Increased amylase	40	13
Increased lipase	35	10
Decreased potassium	29	5.3
Increased alkaline phosphatase	25	1.8
Decreased albumin	23	1.8
Decreased magnesium	23	2.7
Increased alanine aminotransferase	22	2.7
Increased aspartate aminotransferase	21	1.8
Decreased sodium	20	0.9

* Grades per NCI CTCAE v5.0

** The denominator used to calculate the rate varied from 93 to 113 based on the number of patients with a baseline and at least one post-treatment value. The laboratory abnormalities are values that reflect worsening from baseline.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on EXKIVITY

Strong or Moderate CYP3A Inhibitors	
Clinical Impact	<ul style="list-style-type: none"> Coadministration of EXKIVITY with strong or moderate CYP3A inhibitors increased mobocertinib plasma concentrations [see <i>Clinical Pharmacology (12.3)</i>], which may increase the risk of adverse reactions, including QTc interval prolongation.
Prevention or Management	<ul style="list-style-type: none"> Avoid concomitant use of strong or moderate CYP3A inhibitors with EXKIVITY. If concomitant use of moderate CYP3A inhibitors cannot be avoided, reduce the EXKIVITY dose and monitor the QTc interval more frequently with ECGs [see <i>Dosage and Administration (2.4)</i>, <i>Warnings and Precautions (5.1)</i>].
Strong or Moderate CYP3A Inducers	

Clinical Impact	<ul style="list-style-type: none"> • Coadministration of EXKIVITY with strong or moderate CYP3A inducers decreased mobocertinib plasma concentrations [see <i>Clinical Pharmacology (12.3)</i>], which may reduce EXKIVITY anti-tumor activity.
Prevention or Management	<ul style="list-style-type: none"> • Avoid concomitant use of strong or moderate CYP3A inducers with EXKIVITY.

7.2 Effect of EXKIVITY on Other Drugs

CYP3A Substrates	
Clinical Impact	<ul style="list-style-type: none"> • Coadministration of EXKIVITY with CYP3A substrates may decrease plasma concentrations of CYP3A substrates [see <i>Clinical Pharmacology (12.3)</i>], which may reduce the efficacy of these substrates.
Prevention or Management	<ul style="list-style-type: none"> • Avoid concomitant use of hormonal contraceptives with EXKIVITY [see <i>Warnings and Precautions (5.5)</i>, <i>Use in Specific Populations (8.3)</i>]. • Avoid concomitant use of EXKIVITY with other CYP3A substrates where minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, increase the CYP3A substrate dosage in accordance with the approved product Prescribing Information.

7.3 Drugs that Prolong the QTc Interval

Drugs that Prolong the QTc Interval	
Clinical Impact	<ul style="list-style-type: none"> • EXKIVITY can cause QTc interval prolongation [see <i>Warnings and Precautions (5.1)</i>, <i>Clinical Pharmacology (12.2)</i>]. Coadministration of EXKIVITY with drugs known to prolong the QTc interval may increase the risk of QTc interval prolongation [see <i>Warnings and Precautions (5.1)</i>, <i>Clinical Pharmacology (12.2)</i>].
Prevention or Management	<ul style="list-style-type: none"> • Avoid concomitant use of other medications known to prolong the QTc interval with EXKIVITY. If concomitant use is unavoidable, monitor the QTc interval more frequently with ECGs [see <i>Warnings and Precautions (5.1)</i>].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action [see *Clinical Pharmacology (12.1)*], EXKIVITY can cause fetal harm when administered to a pregnant woman. There are no available data on EXKIVITY use in pregnant women. Oral administration of mobocertinib to pregnant rats during the period of organogenesis resulted in embryoletality (embryo-fetal death) and maternal toxicity at plasma exposures approximately 1.7 times the human exposure based on AUC at the 160 mg once daily clinical dose (see *Data*). Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study, once daily oral administration of mobocertinib to pregnant rats during the period of organogenesis resulted in maternal toxicity (reduced body weight gain and food consumption) at 10 mg/kg (approximately 1.7 times the human exposure based on AUC at the 160 mg once daily clinical dose). Adverse effects on embryo-fetal development at this dose level

included embryoletality due to post-implantation loss (embryo-fetal death) and effects on fetal growth (decreased fetal weights). There was no clear evidence of fetal malformations at the high dose level (10 mg/kg).

8.2 Lactation

Risk Summary

There are no data on the presence of mobocertinib or its metabolites in human milk or their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with EXKIVITY and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

EXKIVITY can cause fetal harm when administered to pregnant women [see *Use in Specific Populations* (8.1)].

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating EXKIVITY.

Contraception

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with EXKIVITY and for 1 month after the last dose. EXKIVITY may render hormonal contraceptives ineffective [see *Drug Interactions* (7.2)].

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose.

Infertility

Based on animal studies, EXKIVITY may impair fertility in males and females of reproductive potential [see *Nonclinical Toxicology* (13.1)].

8.4 Pediatric Use

The safety and effectiveness of EXKIVITY in pediatric patients have not been established.

8.5 Geriatric Use

Of the 114 patients [see *Clinical Studies* (14)] who received EXKIVITY in clinical studies, 37% were 65 years and over, and 7% were 75 years and over. No overall difference in effectiveness was observed between patients aged 65 and older and younger patients. Exploratory analysis suggests a higher incidence of Grade 3 and 4 adverse reactions (69% vs 47%) and serious adverse reactions (64% vs 35%) in patients 65 years and older as compared to those younger than 65 years.

8.6 Renal Impairment

No dosage adjustment of EXKIVITY is recommended for patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73 m² by Modification of Diet in Renal Disease [MDRD] equation). The recommended dosage of EXKIVITY has not been established for patients with severe renal impairment (eGFR <30 mL/min/1.73 m²) [see *Clinical Pharmacology* (12.3)].

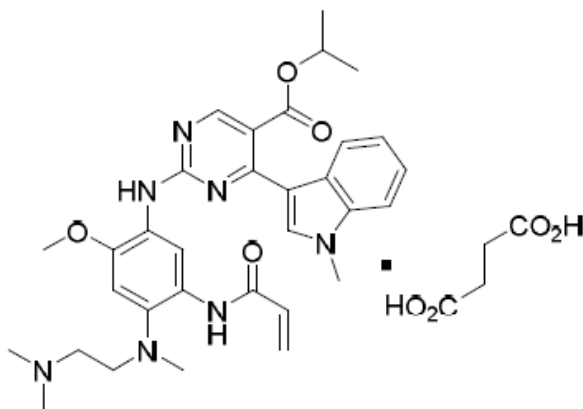
8.7 Hepatic Impairment

No dosage 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 has not been established for patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST) [see *Clinical Pharmacology* (12.3)].

11 DESCRIPTION

Mobocertinib is a kinase inhibitor. The chemical name for mobocertinib succinate is propan-2-yl 2-[5-(acryloylamino)-4-[[2-(dimethylamino)ethyl](methyl)amino]-2-methoxyanilino]-4-(1-methyl-1H-indol-3-yl)pyrimidine-5-carboxylate succinate. The molecular formula is $C_{32}H_{39}N_7O_4 + C_4H_6O_4$ (succinate salt) which corresponds to a molecular weight of 703.8 g/mol. Mobocertinib has no chiral centers. The chemical structure of mobocertinib succinate is shown below:



Mobocertinib succinate has a solubility of 152 mg/mL in pH 1.0 and >17.6 mg/mL in pH 6.8 solutions at 37°C.

EXKIVITY capsule for oral administration contains 40 mg mobocertinib equivalent to 48.06 mg mobocertinib succinate, with no inactive ingredients. The capsule shells contain gelatin and titanium dioxide. The printing ink contains shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide, potassium hydroxide, and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mobocertinib is a kinase inhibitor of the epidermal growth factor receptor (EGFR) that irreversibly binds to and inhibits 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 vitro, mobocertinib also inhibited the activity of other EGFR family members (HER2 and HER4) and one additional kinase (BLK) at clinically relevant concentrations (IC_{50} values <2 nM).

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

In animal tumor implantation models, mobocertinib exhibited anti-tumor activity against xenografts with the EGFR exon 20 insertions NPH or ASV.

12.2 Pharmacodynamics

Mobocertinib exposure-response relationships and the time course of pharmacodynamic response are unknown.

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 [see *Warnings and Precautions (5.1)*].

12.3 Pharmacokinetics

After single- and multiple-dose administration, combined molar C_{max} and AUC_{0-24h} 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 of 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 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 μ M. The mean (standard deviation) bound fraction was 99.3% (0.11%) for mobocertinib, 99.5% (0.16%) for AP32960 and 98.6% (0.36%) 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 (V_{ss}/F) of mobocertinib was 3,509 L (38%) at steady-state.

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.

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.

Excretion

Following administration of a single 160 mg oral dose of radiolabeled mobocertinib, approximately 76% of the dose was recovered in feces (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 feces and urine for AP32960 was approximately 12% and 1%, respectively. The metabolite AP32914 was below the detection limit in urine and feces.

Specific Populations

No clinically meaningful differences in the pharmacokinetics of mobocertinib were observed based on age (18 to 86 years), race (White, Black, Asian), sex, body weight (37.3 to 132 kg), mild-to-moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m² by MDRD), or 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 (eGFR <30 mL/min/1.73 m²) renal impairment and severe (total bilirubin >3 times ULN and any AST) hepatic impairment on mobocertinib pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Effect of CYP3A Inhibitors on Mobocertinib: Coadministration of EXKIVITY with multiple doses of itraconazole or ketoconazole (strong CYP3A inhibitors) is predicted to increase the steady-state combined molar AUC of mobocertinib and its active metabolites by 374 to 419%.

Coadministration of EXKIVITY with multiple doses of a moderate CYP3A inhibitor is predicted to increase the steady-state combined molar AUC of mobocertinib and its active metabolites by approximately 100-200%.

Effect of CYP3A Inducers on Mobocertinib: Coadministration of EXKIVITY with multiple doses of rifampin (a strong CYP3A inducer) is predicted to decrease the steady-state combined molar AUC of mobocertinib and its active metabolites by 92%.

Coadministration of EXKIVITY with multiple doses of efavirenz (a moderate CYP3A inducer) is predicted to decrease the steady-state combined molar AUC of mobocertinib and its active metabolites by 58%.

Effect of Mobocertinib on CYP3A Substrates: Coadministration of EXKIVITY 160 mg once daily with oral or intravenous midazolam (a CYP3A substrate) decreased the AUC of midazolam by 32% and 16%, respectively.

Effect of Mobocertinib on P-gp Substrates: No clinically meaningful differences in the pharmacokinetics of digoxin or dabigatran etexilate (P-gp substrates) are predicted when coadministered with multiple doses of EXKIVITY.

Effect of Mobocertinib on BCRP Substrates: The clinical significance of changes in the pharmacokinetics of sulfasalazine (a BCRP substrate) when coadministered with multiple doses of EXKIVITY is unknown.

In Vitro Studies

CYP Enzymes: Mobocertinib, AP32960, and AP32914 do not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, or 2D6 at clinically relevant concentrations.

Transporter Systems: Mobocertinib is an inhibitor of P-gp and BCRP. At clinically relevant concentrations, mobocertinib does not inhibit BSEP, MATE1, MATE2-K, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, or OCT2.

Mobocertinib is a substrate of P-gp. Mobocertinib is not a substrate of BCRP, OATP1B1, and OATP1B3.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were not performed with mobocertinib. Mobocertinib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay and did not induce chromosomal aberrations in an in vitro chromosome aberration assay in human peripheral blood lymphocytes. Mobocertinib was not clastogenic in an in vivo bone marrow micronucleus test in rats.

Fertility, early embryonic development, and pre- and post-natal toxicology studies were not conducted with mobocertinib; however, in 4- and 13-week repeat-dose toxicology studies in rats and dogs, 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. These effects may be reversible.

13.2 Animal Toxicology and/or Pharmacology

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 the 4-week repeat-dose study in dogs, 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 the 13-week repeat-dose study in dogs, 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.

14 CLINICAL STUDIES

The efficacy of EXKIVITY was evaluated in a pooled subset of patients with EGFR exon 20 insertion mutation-positive metastatic or locally advanced NSCLC whose disease had progressed on or after platinum-based chemotherapy enrolled in an international, open-label, multicohort clinical trial (AP32788-15-101, NCT02716116). Patients had histologically or cytologically confirmed locally advanced or metastatic disease (Stage IIIB or IV) and a documented EGFR exon 20 insertion mutation based on local testing. Patients received EXKIVITY at a dose of 160 mg once daily until disease progression or intolerable toxicity.

In the efficacy population, EGFR exon 20 insertion mutation status was determined by prospective local testing using samples from tumor tissue (87%), plasma (5%), or other specimens such as pleural fluid (8%). Of the 114 patients with EGFR exon 20 insertion mutations, 70% of patient tissue samples were tested retrospectively using Life Technologies Corporation OncoPrint Dx™ Target Test. While 75% of patients were positive for EGFR exon 20 insertion mutation, 14% did not have an EGFR exon 20 insertion mutation identified, and 11% did not generate reportable results.

The efficacy population consisted of 114 patients and had the following demographic characteristics: the median age was 60 years (range: 27 to 84 years); 66% were female; 60% were Asian, 37% were White, and 3% were Black; 71% had never smoked; at baseline, 75% had Eastern Cooperative Oncology Group (ECOG) performance status 1. At baseline, 99% of patients had metastatic disease, 98% of patients had adenocarcinoma histology and 35% of patients had brain metastases. The median number of prior therapies was 2 (range: 1 to 7) and 43% percent had received prior immunotherapy.

The major efficacy outcome measure was overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by blinded independent central review (BICR). Additional efficacy outcome measures included duration of response (DOR) by BICR. Efficacy results are summarized in Table 5.

Table 5: Efficacy Results in Patients with EGFR Exon 20 Insertion Mutation-Positive NSCLC Whose Disease Has Progressed on or after Platinum-Based Chemotherapy in Study AP32788-15-101

	EXKIVITY (n=114)
Overall Response Rate (ORR)^a (95% CI)	28% (20, 37) ^b
Duration of Response (DOR)	
Median (months) ^c , (95% CI)	17.5 (7.4, 20.3)
Patients with DOR ≥6 months ^d	59%

^a Per BICR, CI = confidence interval

^b All responses were partial responses

^c Kaplan-Meier estimate using confirmed responses only

^d Based on observed duration of response

Investigator-assessed ORR was 35% (95% CI: 26, 45) with a median DOR of 11.2 months (63% of these patients had observed responses lasting longer than 6 months).

16 HOW SUPPLIED/STORAGE AND HANDLING

EXKIVITY is supplied as 40 mg capsules: white, size 2, imprinted with “MB788” on the cap and “40mg” on the body in black ink.

Bottle of 90 capsules	NDC 63020-040-90
Bottle of 120 capsules	NDC 63020-040-12

Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

QTc Interval Prolongation and Torsades de Pointes

Inform patients of the risk of QTc prolongation. Symptoms that may be indicative of significant QTc prolongation include dizziness, lightheadedness, and syncope. Advise patients to report these symptoms and to inform their healthcare provider about the use of any heart medications [see *Warnings and Precautions (5.1)*].

Interstitial Lung Disease (ILD)/Pneumonitis

Inform patients of the risks of severe or fatal ILD/pneumonitis. Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms such as cough, shortness of breath or chest pain [see *Warnings and Precautions (5.2)*].

Cardiac Toxicity

Inform patients of the risk of heart failure. Advise patients to contact their healthcare provider immediately if they experience any signs or symptoms of heart failure such as palpitations, shortness of breath, chest pain, and syncope [see *Warnings and Precautions (5.3)*].

Diarrhea

Inform patients that EXKIVITY may cause diarrhea, which may be severe in some cases and should be treated promptly. Advise patients to have antidiarrheal medicine readily available and promptly start antidiarrheal treatment (e.g., loperamide), increase oral fluids and electrolyte intake, and contact their healthcare provider if diarrhea occurs [see *Warnings and Precautions (5.4)*].

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions (5.5), Use in Specific Populations (8.1)*].

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with EXKIVITY and for 1 month after the last dose [see *Use in Specific Populations (8.3)*].

Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for 1 week after the last dose [see *Use in Specific Populations (8.3)*].

Lactation

Advise women not to breastfeed during treatment with EXKIVITY and for 1 week after the last dose [see *Use in Specific Populations (8.2)*].

Infertility

Advise females and males of reproductive potential that EXKIVITY may impair fertility [see *Use in Specific Populations (8.3)*].

Drug Interactions

Advise patients to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see *Drug Interactions (7)*]. Inform patients to avoid grapefruit or grapefruit juice while taking EXKIVITY.

Missed Dose

Advise patients that if a dose of EXKIVITY is missed by 6 hours or if vomiting occurs, resume treatment as prescribed the next day [see *Dosage and Administration (2.2)*].

Distributed by:

Takeda Pharmaceuticals America, Inc.

Lexington, MA 02421

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