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

AUSTRALIAN PRODUCT INFORMATION

EXKIVITY® (mobocertinib)

1 NAME OF THE MEDICINE

Mobocertinib.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each EXKIVITY capsule contains mobocertinib succinate equivalent to 40 mg of mobocertinib base. For the full list of excipients, see *List of excipients* (6.1).

3 PHARMACEUTICAL FORM

Hard capsule.

Appearance

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

EXKIVITY has **provisional approval** in Australia for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that has an exon 20 insertion mutation of the epidermal growth factor receptor (EGFR), who have received prior platinum-based chemotherapy.

The decision to approve this indication has been made on the basis of objective response rate and duration of response in a single arm study. Continued approval of this indication depends on verification and description of benefit in a confirmatory study.

4.2 DOSE AND METHOD OF ADMINISTRATION

Recommended dose

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

EXKIVITY should be taken at approximately the same time each day; and can be taken with or without food.

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 on that day. Resume the usual dosing on the following day at the regularly scheduled time.

If vomiting occurs after taking a dose, do not repeat the dose. Resume the usual dosing on the following day at the regularly scheduled time.

Dose modifications for adverse reactions

EXKIVITY dose levels for dose reduction for the management of adverse reactions are summarised in *Table 1*.

Table 1: Recommended dose levels for EXKIVITY dose reduction

Dose reduction	**Dose level**
No reduction (starting dose)	160 mg once daily
First dose reduction	120 mg once daily
Second dose reduction	80 mg once daily

Recommended dose modifications of EXKIVITY for the management of adverse reactions are provided in *Table 2*.

Table 2. Recommended EXKIVITY dose modifications for adverse reactions

Adverse reaction	**Severity***	**Dose modification**
QTc interval prolongation [see *Special warnings and precautions for use* (4.4)]	Grade 2 (QTc interval 481-500 msec)	First occurrence • Withhold EXKIVITY until ≤ Grade 1 or baseline. • Upon recovery, resume EXKIVITY at the same dose. Recurrence • Withhold EXKIVITY until ≤ Grade 1 or baseline. • Upon recovery, resume EXKIVITY at the next lower dose or permanently discontinue EXKIVITY.
	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 *Special warnings and precautions for use* (4.4)]	Any grade	• Withhold EXKVITY if ILD/pneumonitis is suspected. • Permanently discontinue EXKIVITY if ILD/pneumonitis is confirmed.
Decreased ejection fraction or cardiac failure [*see Special warnings and precautions for use* (4.4)]	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 2 cardiac failure or Grade 3 or 4 decreased ejection fraction	• Permanently discontinue EXKIVITY.
Diarrhoea [see *Special warnings and precautions for use* (4.4)]	Grade 1, or first occurrence of tolerable Grade 2	• No dose modification is required. Initiate treatment with anti-diarrheal medicinal products (e.g., loperamide) at first onset of diarrhoea.
	Intolerable or recurrent Grade 2, or any Grade 3	• Withhold EXKIVITY until recovery to ≤ Grade 1. • Resume EXKIVITY at the same dose or the next lower dose.
	Grade 4	First occurrence • 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 *Adverse effects* (4.8)]	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 *Adverse effects* (4.8)*]*	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 *Adverse effects* (4.8)]	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. • 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).

Dose modifications for moderate CYP3A inhibitors

Avoid coadministration of moderate CYP3A inhibitors during treatment with EXKIVITY [see *Interactions with other medicines and other forms of interactions* (4.5) and *Pharmacological properties* (5.2)]. If coadministration of a moderate CYP3A inhibitor cannot be avoided, reduce the EXKIVITY once daily 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 discontinuation of the coadministered moderate CYP3A inhibitor, wait for 3 to 5 elimination half-lives for the moderate CYP3A inhibitor before resuming the original EXKIVITY dose.

4.3 CONTRAINDICATIONS

None.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

QTc prolongation and Torsades de Pointes

EXKIVITY can cause life-threatening prolongation of the heart rate-corrected QT (QTc) interval, including resultant arrhythmias. In the subset (n=250) of the pooled EXKIVITY safety population who had a baseline and at least one subsequent electrocardiogram (ECG), an increase of at least 60 msec from baseline QTc occurred in 11% of patients and a QTc interval longer than 500 msec occurred in 1.2% [see *Pharmacological properties* (5.1)]. Grade 4 Torsades de Pointes occurred in 1 patient (0.4%). Clinical trials of EXKIVITY did not enrol 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 coadministration of other substances which are known to

prolong the QTc interval. Avoid coadministration of strong or moderate CYP3A inhibitors with EXKIVITY, which may further prolong the QTc interval [see *Interactions with other medicines and other forms of interactions* (4.5)].

Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of the QT prolongation [see *Dose and method of administration* (4.2)].

Interstitial lung disease/pneumonitis

EXKIVITY can cause interstitial lung disease (ILD)/pneumonitis, which can be fatal. In the pooled EXKIVITY safety population [see *Adverse effects* (4.8)], ILD/pneumonitis occurred in 4.3% of patients, including a 0.8% rate of Grade 3 events, one (0.4%) Grade 4 event, and 3 (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 *Dose and method of administration* (4.2)].

Cardiac failure

EXKIVITY can cause cardiac toxicity (including decreased ejection fraction, cardiomyopathy and congestive cardiac failure), resulting in cardiac failure, which can be fatal. In the pooled EXKIVITY safety population [see *Adverse effects* (4.8)], cardiac failure occurred in 2.7% of patients, including a 1.2% rate of Grade 3 events, one (0.4%) Grade 4 event, and one (0.4%) fatal case of heart failure.

Monitor cardiac function, including left ventricular ejection fraction, at baseline and during treatment. Withhold, reduce the dose, or permanently discontinue EXKIVITY based on the severity of cardiac failure [see *Dose and method of administration* (4.2)].

Diarrhoea

EXKIVITY can cause diarrhoea, which can be severe. In the pooled EXKIVITY safety population [see *Adverse effects* (4.8)], diarrhoea occurred in 93% of patients, Grade 3 diarrhoea occurred in 20% of patients, and Grade 4 diarrhoea occurred in 1 patient (0.4%). The median time to first onset of diarrhoea was five days but could occur as soon as 24 hours after administration of EXKIVITY. In the forty-eight percent of patients whose diarrhoea resolved, the median time to resolution was three days.

To avoid dehydration, electrolyte imbalance, and renal impairment, treat diarrhoea promptly. Advise patients to start an anti-diarrhoeal agent (e.g., loperamide) at the first sign of diarrhoea or increased stool frequency, and to increase fluid and electrolyte intake.

Monitor electrolytes, and withhold, reduce the dose or permanently discontinue EXKIVITY based on diarrhoea severity [see *Dose and method of administration* (4.2)].

Embryo-fetal toxicity

Based on its mechanism of action and data from animal studies, EXKIVITY can cause fetal harm when administered during pregnancy.

Advise pregnant patients of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with EXKIVITY [see *Interactions with other medicines and other forms of interactions* (4.5)] and for one month following the final dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for one week following the final dose of EXKIVITY [see *Fertility, pregnancy and lactation* (4.6)].

Use in hepatic impairment

No dose adjustment is recommended for patients with mild hepatic impairment. Mobocertinib has not been studied in patients with moderate or severe hepatic impairment [see *Pharmacological properties* (5.2)].

Use in renal impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment. Mobocertinib has not been studied in patients with severe renal impairment [see *Pharmacological properties* (5.2)].

Use in the elderly

Of the 114 patients treated with EXKIVITY in clinical studies, 37% were at least 65 years of age, and 7% were at least 75 years of age. No overall differences in efficacy were observed for patients ≥ 65 years of age compared to younger adult 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 of age, compared to younger adult patients.

Paediatric use

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

Effects on laboratory tests

See *Adverse effects (undesirable effects)* (4.8).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of other drugs on EXKIVITY

Strong or moderate CYP3A inhibitors

Plasma concentrations of mobocertinib are increased when EXKIVITY is coadministered with a strong or moderate CYP3A inhibitor [see *Drug interaction studies*, below], which may increase the risk of adverse reactions, including QTc interval prolongation [see *Special warnings and precautions for use* (4.4)].

Avoid coadministration of strong or moderate CYP3A inhibitors with EXKIVITY. If coadministration of a moderate CYP3A inhibitor cannot be avoided, reduce the EXKIVITY dose [see *Dose and method of administration* (4.2)] and monitor the QTc interval more frequently with ECGs [see *Special warnings and precautions for use* (4.4)].

Strong or moderate CYP3A inducers

Plasma concentrations of mobocertinib are decreased when EXKIVITY is coadministered with a strong or moderate CYP3A inducer, which may decrease the efficacy of EXKIVITY [see *Drug interaction studies*, below].

Avoid coadministration of strong or moderate CYP3A inducers with EXKIVITY.

Effect of EXKIVITY on other drugs

CYP3A substrates

Plasma concentrations of CYP3A substrates may be decreased when they are coadministered with EXKIVITY, which may reduce their efficacy [see *Drug interaction studies*, below].

Avoid coadministration of hormonal contraceptives with EXKIVITY [see *Special warnings and precautions for use* (4.4), and *Fertility, pregnancy and lactation* (4.6)].

Avoid coadministration of EXKIVITY with other CYP3A substrates where minimal concentration changes may lead to serious therapeutic failures. If coadministration is unavoidable, increase the CYP3A substrate dose in accordance with the approved Product Information.

Substances that prolong the QTc interval

Coadministration of EXKIVITY with other substances known to prolong the QTc interval may increase the risk of life-threatening QTc interval prolongation [see *Special warnings and precautions for use* (4.4), and *Pharmacological properties* (5.1)].

Avoid coadministration of other substances known to prolong the QTc interval with EXKIVITY. If coadministration is unavoidable, monitor the QTc interval more frequently with ECGs [see *Special warnings and precautions for use* (4.4)].

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_{24} of mobocertinib and its active metabolites by 374 to 419%.

Coadministration of EXKIVITY with multiple doses of erythromycin or fluconazole (moderate CYP3A inhibitors) is predicted to increase the steady-state combined molar AUC_{24} of mobocertinib and its active metabolites by 116 to 135%.

Effect of CYP3A inducers on mobocertinib

Coadministration of EXKIVITY with multiple doses of rifampicin (a strong CYP3A inducer) is predicted to decrease the steady-state combined molar AUC_{24} 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_{24} 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_{inf} of midazolam by 32% and 16%, respectively.

Effect of mobocertinib on P-gp substrates

Coadministration of EXKIVITY 160 mg once daily is predicted to have no clinically meaningful effect on the pharmacokinetics of P-gp substrates (such as digoxin or dabigatran etexilate).

Effect of mobocertinib on BCRP substrates

The clinical significance of changes in the pharmacokinetics of BCRP substrates (such as sulfasalazine) when coadministered with multiple doses of EXKIVITY is unknown.

In vitro studies

CYP enzymes

Mobocertinib, AP32960, and AP32914 are time-dependent inhibitors and inducers of CYP3A, with the net effect being weak induction in vivo. 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. Given that mobocertinib exhibits high solubility and high permeability in vitro, P-gp inhibitors are unlikely to increase plasma concentrations of mobocertinib.

Mobocertinib is not a substrate of BCRP, OATP1B1, or OATP1B3.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

EXKIVITY can cause fetal harm when administered during pregnancy [see *Use in pregnancy*, below].

Pregnancy testing

Verify pregnancy status prior to initiating EXKIVITY.

Contraception

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with EXKIVITY and for at least one month following the final dose. EXKIVITY may render hormonal contraceptives ineffective [see *Interactions with other medicines and other forms of interactions* (4.5)].

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with EXKIVITY and for at least one week following the final dose.

Infertility

Based on animal data, mobocertinib may impair fertility in males and females of reproductive potential [see *Preclinical safety data* (5.3)].

Use in pregnancy

Pregnancy Category D.

There are no human data available on the use of EXKIVITY in pregnancy, however, based on its mechanism of action [see *Pharmacological properties* (5.1)] and data from animal studies, EXKIVITY can cause fetal harm when administered during pregnancy. Advise patients of the potential risk to a fetus.

In an embryo-fetal development study, oral administration of mobocertinib once daily 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 at the recommended clinical dose). Adverse effects on embryo-fetal development at this dose level, included embryo-fetal death and effects on fetal growth (decreased fetal weights). There was no clear evidence of teratogenicity (fetal malformations) at this dose level, which was the highest tested.

Use in lactation

There are no data on the presence of mobocertinib or its metabolites in human milk, or their effects on a breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with EXKIVITY and for one week following the final dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no data on the effect of mobocertinib on the ability to drive or operate machinery. Fatigue has been observed in clinical trials. Advise patients not to drive or operate machines if they experience fatigue while taking mobocertinib.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

- QTc prolongation [see Special warnings and precautions for use (4.4)]
- Interstitial lung disease/pneumonitis [see *Special warnings and precautions for use* (4.4)]
- Cardiac failure [see *Special warnings and precautions for use* (4.4)]
- Diarrhoea [see *Special warnings and precautions for use* (4.4)]

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 EXKIVITY safety population described in *Special warnings and precautions for use* (4.4) reflects exposure to EXKIVITY as a single agent at a dose of 160 mg orally once daily in 256 patients, including 114 patients from Study AP32788-15-101 with locally advanced or metastatic NSCLC harbouring an EGFR exon 20 insertion mutation, and patients with other solid tumours. 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 diarrhoea, 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 haemoglobin, increased creatinine, and decreased magnesium.

Locally advanced or metastatic NSCLC harbouring an EGFR exon 20 insertion mutation, that has been previously treated with platinum-based chemotherapy

The safety of EXKIVITY was evaluated in a subset of patients in Study AP32788-15-101 who had locally advanced or metastatic NSCLC harbouring an EGFR exon 20 insertion mutation, and who had received prior platinum-based chemotherapy [see *Pharmacodynamic properties – Clinical trials* (5.1)]. 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 enrolment 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 longer than a year.

Serious adverse reactions occurred in 46% of patients who received EXKIVITY. Serious adverse reactions in ≥2% of patients included diarrhoea, dyspnoea, 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 due to an adverse reaction occurred in 17% of patients who received EXKIVITY. Diarrhoea and nausea each led to permanent discontinuation of EXKIVITY in at least 2% of patients.

Dose interruptions of EXKIVITY due to an adverse reaction occurred in 51% of patients. Adverse reactions which necessitated dose interruption in >5% of patients included diarrhoea, nausea and vomiting.

Dose reductions of EXKIVITY due to an adverse reaction occurred in 25% of patients. The only adverse reaction that led to dose reduction in >5% of patients was diarrhoea.

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

Table 3. Adverse reactions that occurred in at least 10% of patients with NSCLC harbouring an EGFR exon 20 insertion mutation, whose disease had progressed on or after platinum-based chemotherapy, and who received mobocertinib in Study AP32788-15-101

Adverse Reaction	EXKIVITY (N = 114)	
	All Grades* (%)	Grade 3 or 4 (%)
Gastrointestinal disorders		
Diarrhoea	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
Dyspnoea[i]	15	4.4
Rhinorrhoea	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] Dyspnoea includes dyspnoea, and dyspnoea 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 oedema.

[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 oedema (9%), acute kidney injury (8%), peripheral neuropathy (7%), palmar-plantar erythrodysaesthesia (4.4%), pneumonitis (2.6%) and cardiac failure (2.6%).

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

Table 4. Select laboratory abnormalities that worsened from baseline in at least 20% of patients with NSCLC harbouring an EGFR exon 20 insertion mutation, whose disease had progressed on or after platinum-based chemotherapy, and who received mobocertinib in Study AP32788-15-101

Laboratory abnormality	EXKIVITY** (N = 114)	
	All Grades* (%)	Grade 3 or 4 (%)
Haematology		
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.

Description of selected adverse reactions

Non-QT conduction abnormalities

Other than QT prolongation [see *Warnings and special precautions for use* (4.4)], other events of cardiac conduction abnormality that occurred in patients receiving EXKIVITY in the pooled safety population (N=256) were 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%). The causality of these events to mobocertinib has not been established.

Reporting suspected adverse effects

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

4.9 OVERDOSE

There is no known specific antidote for overdose with EXKIVITY. In the event of an overdose, monitor the patient for adverse reactions *[see Adverse Effects (4.8)]* and provide appropriate supportive care.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Mobocertinib is a kinase inhibitor of the epidermal growth factor receptor (EGFR) that irreversibly binds to and inhibits EGFR harbouring an exon 20 insertion mutation 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 EGFR family members (HER2 and HER4), and one additional kinase (BLK) at clinically relevant concentrations (IC_{50} values <2 nM).

In cell culture 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 those required for WT-EGFR signalling inhibition.

In murine tumour implantation models, mobocertinib demonstrated anti-tumour activity against xenografts carrying either the [NPH] or the [ASV] EGFR exon 20 insertion mutation.

Pharmacodynamic effects

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 (upper confidence interval limit: 25.5 msec) following administration of EXKIVITY at the recommended dose of 160 mg once daily.

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

Clinical trials

Previously-treated, metastatic non-small cell lung cancer harbouring an EGFR exon 20 insertion mutation

The efficacy of EXKIVITY was evaluated in pooled subset of 114 patients with locally advanced or metastatic NSCLC harbouring an EGFR exon 20 insertion mutation, whose disease had progressed on or after platinum-based chemotherapy, and who were enrolled in an international, single-arm, open-label, multicohort study (Study AP32788-15-101; NCT02716116). Trial eligibility required 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.

The major efficacy outcome measure was confirmed objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumours (RECIST v1.1) by an independent review committee (IRC). Additional efficacy outcome measures included duration of response (DOR) per IRC.

The pooled efficacy population (n=114) had a median age of 60 years (range: 27 to 84 years), were mostly female (66%), Asian (60%) or Caucasian (37%), and had never smoked (71%). ECOG performance status was 1 (75%) or 0 (25%) and adenocarcinoma histology was predominant (98%). Local testing for EGFR exon 20 insertion mutation status was mainly performed on tumour tissue (87%) but for a small group was performed on plasma (5%), or other specimens such as pleural fluid (8%). Retrospective central analysis of 70% of patient tissue samples was conducted using the Life Technologies Corporation Oncomine Dx™ Target Test. While 75% of patients were positive for EGFR exon 20 insertion mutation by central analysis, 14% did not have an EGFR exon 20 insertion mutation identified, and 11% did not generate reportable results.

Efficacy results from this study, with a median follow-up duration of 14.2 months, are summarised in *Table 5*.

Table 5: Efficacy results in patients with NSCLC harbouring an EGFR exon 20 insertion mutation, whose disease had progressed on or after platinum-based chemotherapy, and who received mobocertinib in Study AP32788-15-101

	EXKIVITY (n=114)
Objective response rate (ORR) [95% CI]	28% [20, 37] [a]
Duration of response (DOR)	
Median (months)[b] [95% CI]	17.5 [7.4, 20.3]
Patients with DOR ≥6 months[c]	59%

CI = confidence interval

[a] All responses were partial responses

[b] Kaplan-Meier estimate in confirmed responders only

[c] 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).

5.2 PHARMACOKINETIC PROPERTIES

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

Absorption

Following administration of 160 mg EXKIVITY, the median (min, max) time to peak concentration (T_{max}) of mobocertinib was 4 (1, 8) hours. The mean (%CV) absolute bioavailability of EXKIVITY is 37% (50%).

Effect of food

Compared to administration after an overnight fast, there was no clinically meaningful effect on the combined molar C_{max} and AUC_{inf} of mobocertinib, AP32960, and AP32914 when EXKIVITY was administered with a high-fat meal (approximately 900 to 1000 calories with approximately 150, 250, and 500 to 600 calories derived from protein, carbohydrate, and fat, respectively) or a low-fat meal (approximately 336 calories with approximately 37, 253, and 46 calories derived from protein, carbohydrate, and fat, respectively).

Distribution

Mobocertinib, AP32960, and AP32914 were bound to human plasma proteins in a concentration-independent manner *in vitro* from 0.5 to 5.0 µM, with mean bound fractions of 99.3%, 99.5%, and 98.6%, respectively. The blood-to-plasma ratios were 0.763, 1.15, and 0.714 for mobocertinib, AP32960, and AP32914, respectively. The mean (%CV) apparent volume of distribution at steady-state for mobocertinib was 3509 L (38%).

Elimination

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

Metabolism

Mobocertinib is primarily metabolised by CYP3A in vitro. Following administration of a single 160 mg dose of radiolabelled mobocertinib, oxidation was the major metabolic pathway. 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 dose of radiolabelled mobocertinib, 76% of the administered dose was recovered in faeces (6% as unchanged mobocertinib) and 4% of the administered dose was recovered in urine (1% as unchanged mobocertinib). The percentage of the administered dose recovered in faeces and urine for AP32960 was 12% and 1%, respectively. The metabolite AP32914 was below the detection limit in urine and faeces.

Specific populations

Age (18 to 86 years), race (Asian, Caucasian, Black), sex, and body weight (37 to 132 kg) had no clinically meaningful effect on the pharmacokinetics of mobocertinib.

Patients with renal impairment

The pharmacokinetics of mobocertinib is similar in patients with normal renal function and in patients with mild or moderate renal impairment (estimated glomerular filtration rate between 30 and 89 mL/min/1.73 m^2 by MDRD equation). The effect of severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m^2) on mobocertinib pharmacokinetics is unknown.

Patients with hepatic impairment

The pharmacokinetics of mobocertinib is similar in patients with normal hepatic function and in patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin >1 to 1.5 times ULN and any AST). The effect of moderate or severe hepatic impairment on mobocertinib pharmacokinetics is unknown.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

Carcinogenicity studies have not been performed with mobocertinib.

Fertility in animals

Studies of fertility, early embryonic development, and pre- and postnatal toxicology were not conducted with mobocertinib; however, an evaluation of the reproductive tract was conducted in the general toxicity studies. In rats and/or dogs (≥0.3 times the human exposure based on AUC at the recommended clinical dose), there were generally reversible macroscopic changes that included decreases in organ weights affecting multiple reproductive organs (including ovaries, seminal vesicle/prostate gland, and/or uterus). There were also (at ≥0.2 times the human exposure at the recommended clinical dose) microscopic changes of decreased epithelial thickness/inflammation of the cervix/vagina and atrophy of the uterus, prostate gland, or mammary gland (males only). In a 3-month toxicity study in dogs, there were no reproductive tract effects in the sexually mature males. Based on these findings, mobocertinib may impair fertility in human males and females. These effects may be reversible.

General toxicology in animals

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 at the recommended 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 human exposure at the recommended 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 human exposure at the recommended clinical dose. The clinical relevance of these findings is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

EXKIVITY contains no inactive ingredients. The capsule shell contains gelatin, titanium dioxide and TekPrint SW-9008.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30º C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type

Blister pack (polychlorotrifluoroethylene (PCTFE)/polyvinyl chloride (PVC)/aluminium).

Pack size

112 capsules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

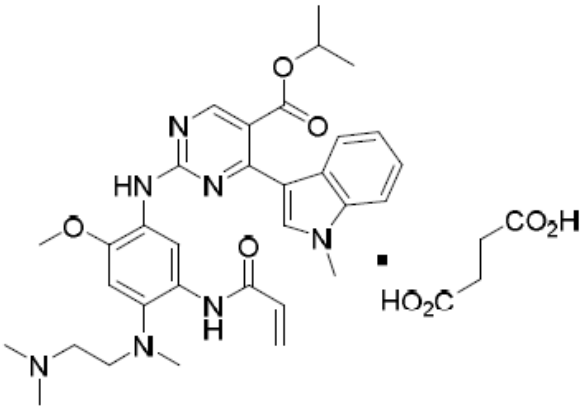
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Formula

$C_{32}H_{39}N_7O_4 + C_4H_6O_4$ (succinate salt)

Chemical structure



CAS number

Mobocertinib: 2389149-74-8

Mobocertinib (succinate salt): 1847461-43-1

Molecular weight

703.8 g/mol (succinate salt)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4).

8 SPONSOR

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9 DATE OF FIRST APPROVAL

19 July 2022

10 DATE OF REVISION

n/a.

Summary table of changes

Section Changed	Summary of new information
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