▼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 – TABRECTA® (CAPMATINIB) TABLETS

1 NAME OF THE MEDICINE

Capmatinib hydrochloride.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

150 mg: Each film-coated tablet contains capmatinib hydrochloride 183.0 mg equivalent to 150 mg capmatinib.

200 mg: Each film-coated tablet contains capmatinib hydrochloride 244.0 mg equivalent to 200 mg capmatinib.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Film-coated tablet

150 mg: pale orange brown, ovaloid, curved film-coated tablet with bevelled edges, unscored, debossed with 'DU' on one side and 'NVR' on the other side.

200 mg: yellow, ovaloid, curved film-coated tablet with bevelled edges, unscored, debossed with 'LO' on one side and 'NVR' on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

TABRECTA® is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a MET exon 14 skipping mutation

4.2 DOSE AND METHOD OF ADMINISTRATION

Patient selection

Prior to the use of capmatinib to treat locally advanced or metastatic NSCLC, the presence of a MET exon 14 skipping mutation must be established. Testing used in clinical practice should be adequately comparable to the testing used in clinical studies (refer to section 5.1 Pharmacodynamic properties – clinical trials). A list of IVD companion diagnostic (CDx) tests is available on the TGA website.

Dosing regimen

The recommended dose of TABRECTA is 400 mg orally twice daily with or without food (see Section 5.2, Pharmacokinetic properties).

Treatment should be continued based on individual safety and tolerability and as long as the patient is deriving clinical benefit from therapy.

If a dose of TABRECTA is missed or vomiting occurs, the patient should not make up for the dose, but take the next dose at the scheduled time.

Dose modifications for adverse reactions

The recommended dose reduction schedule for the management of adverse reactions based on individual safety and tolerability is listed in Table 1.

Table 1 TABRECTA dose reduction schedule

Dose level	Dose and schedule	Number and strength of tablets
Starting dose	400 mg twice daily	Two 200 mg tablets / twice daily
First-dose reduction	300 mg twice daily	Two 150 mg tablets / twice daily
Second-dose reduction	200 mg twice daily	One 200 mg tablet / twice daily

TABRECTA should be permanently discontinued in patients unable to tolerate 200 mg orally twice daily. Recommendations for dose modifications of TABRECTA for adverse reactions are provided in Table 2.

Table 2 TABRECTA dose modifications for the management of adverse reactions

Adverse drug reaction	Severity	Dose modification
Interstitial lung disease (ILD)/pneumonitis	Any grade	Immediately withhold with suspected ILD/pneumonitis Permanently discontinue TABRECTA if ILD/pneumonitis is suspected or confirmed treatment-related
Isolated ALT and/or AST elevations from baseline, without concurrent total bilirubin increase	Grade 3 (>5.0 to ≤20.0 x ULN)	Temporarily withhold TABRECTA until recovery to baseline ALT/AST grade. If recovered to baseline within 7 days, then resume TABRECTA at the same dose, otherwise resume TABRECTA at a reduced dose as per Table 1.
	Grade 4 (>20.0 x ULN)	Permanently discontinue TABRECTA
Combined elevations in ALT and/or AST with concurrent total bilirubin increase, in the absence of cholestasis or hemolysis	If patient develops ALT and/or AST >3 x ULN along with total bilirubin >2 x ULN, irrespective of baseline grade	Permanently discontinue TABRECTA
Isolated total bilirubin elevation from baseline, without concurrent ALT and/or AST increase	Grade 2 (>1.5 to ≤3.0 x ULN)	Temporarily withhold TABRECTA until recovery to baseline bilirubin grade.

Adverse drug reaction	Severity	Dose modification
		If recovered to baseline within 7 days, then resume TABRECTA at the same dose, otherwise resume TABRECTA at a reduced dose as per Table 1.
	Grade 3 (>3.0 to ≤10.0 x ULN)	Temporarily withhold TABRECTA until recovery to baseline bilirubin grade.
		If recovered to baseline within 7 days, then resume TABRECTA at a reduced dose as per Table 1, otherwise Permanently discontinue TABRECTA
	Grade 4 (>10.0 x ULN)	Permanently discontinue TABRECTA
Other adverse drug reactions	Grade 2	Maintain dose level. If intolerable, consider temporarily withholding TABRECTA until resolved, then resume TABRECTA at a reduced dose as per Table 1.
	Grade 3	Temporarily withhold TABRECTA until resolved, then resume TABRECTA at a reduced dose as per Table 1.
	Grade 4	Permanently discontinue TABRECTA

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ILD, interstitial lung disease; ULN, upper limit of normal.

Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events).

Baseline = at the time of treatment initiation.

Special populations

Renal impairment

Caution should be exercised in patients with severe renal impairment (creatinine clearance [CrCl] 15 to 29 mL/min) as TABRECTA has not been studied in these patients. No dose adjustment is necessary in patients with mild (CrCl 60 to 89 mL/min) or moderate (CrCl 30 to 59 mL/min) renal impairment (see section 5.2, Pharmacokinetic properties, special populations).

Hepatic impairment

No dose adjustment is necessary in patients with mild, moderate, or severe hepatic impairment as per Child-Pugh classification (see section 5.2, Pharmacokinetic properties, special populations).

Paediatric patients (below 18 years of age)

The safety and efficacy of TABRECTA in paediatric patients have not been established.

Elderly patients (65 years of age or older)

No dose adjustment is necessary in patients 65 years of age or older.

Method of administration

TABRECTA should be taken orally twice daily with or without food. The tablets should be swallowed whole and should not be broken, chewed, or crushed.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Interstitial lung disease (ILD)/pneumonitis

ILD/pneumonitis, which can be fatal, has occurred in patients treated with TABRECTA (see section 4.8 Adverse effects, undesirable effects). Prompt investigation should be performed in any patient with new or worsening of pulmonary symptoms indicative of ILD/pneumonitis (e.g. dyspnoea, cough, fever). TABRECTA should be immediately withheld in patients with suspected ILD/pneumonitis and permanently discontinued if no other potential causes of ILD/pneumonitis are identified (see section 4.2 Dose and method of administration).

Hepatic effects

Transaminase elevations have occurred in patients treated with TABRECTA (see section 4.8 Adverse effects (undesirable effects)). Liver function tests (including ALT, AST, and total bilirubin) should be performed prior to the start of treatment, every 2 weeks during the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients who develop transaminase or bilirubin elevations. Based on the severity of the adverse drug reaction, temporarily withhold, dose reduce, or permanently discontinue TABRECTA (see section 4.2 Dose and method of administration).

Elevations of pancreatic enzymes

Elevations in amylase and lipase levels have occurred in patients treated with TABRECTA (see section 4.8 Adverse effects (Undesirable effects)). Pancreatitis (Grade 3) occurred in one patient (0.3%). Amylase and lipase should be monitored at baseline and regularly during treatment with TABRECTA. Based on the severity of the adverse drug reaction, temporarily withhold, dose reduce, or permanently discontinue TABRECTA (see section 4.2 Dose and method of administration).

Hypersensitivity reactions

No cases of serious hypersensitivity were reported in patients treated with TABRECTA in Study GEOMETRY mono-1. In other clinical studies, cases of serious hypersensitivity were reported in patients treated with TABRECTA (see section 4.8 Adverse effects (Undesirable effects)). Clinical symptoms included pyrexia, chills, pruritus, rash, blood pressure decreased, nausea and vomiting. Based on the severity of the adverse drug reaction, temporarily withhold or permanently discontinue TABRECTA.

embryo-foetal toxicity

Based on findings from animal studies and its mechanism of action, TABRECTA can cause foetal harm when administered to a pregnant patient. Oral administration of capmatinib to pregnant rats and rabbits during the period of organogenesis resulted in fetotoxicity and

teratogenicity. TABRECTA should not be used during pregnancy, unless clearly necessary, and only after careful consideration of both the patient's need and the risk to the fetus. Patients who are pregnant or could become pregnant should be advised of the potential risk to a fetus if TABRECTA is used during pregnancy or if the patient becomes pregnant while taking TABRECTA. People who could become pregnant should use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with TABRECTA and for at least 7 days after the last dose. Male patients with sexual partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms during treatment with TABRECTA and for at least 7 days after the last dose (see section 4.6 Fertility, pregnancy and lactation).

Risk of photosensitivity

Based on findings from animal studies, there is a potential risk of photosensitivity reactions with TABRECTA (see section 5.3, Preclinical safety data). In GEOMETRY mono-1, it was recommended that patients use precautionary measures against ultraviolet exposure such as the use of sunscreen or protective clothing during treatment with TABRECTA. Patients should be advised to limit direct ultraviolet exposure during treatment with TABRECTA.

Use in hepatic impairment

See section 4.2, Dose and method of administration and section 5.2, Pharmacokinetic properties, special populations.

Use in renal impairment

See section 4.2, Dose and method of administration and section 5.2, Pharmacokinetic properties, special populations.

Use in the elderly

See section 4.2, Dose and method of administration and section 5.2, Pharmacokinetic properties, special populations.

Paediatric use

The safety and efficacy of TABRECTA in paediatric patients have not been established.

Effects on laboratory tests

See Section 4.8 adverse effects, undesirable effects.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of other medicinal products on TABRECTA

Strong CYP3A inhibitors

In healthy subjects, coadministration of a single 200 mg capmatinib dose with the strong CYP3A inhibitor itraconazole (200 mg once daily for 10 days) increased capmatinib AUCinf by 42% with no change in capmatinib Cmax compared to administration of capmatinib alone. Coadministration of TABRECTA with a strong CYP3A inhibitor may increase the incidence and

severity of adverse drug reactions of TABRECTA. Patients should be closely monitored for adverse drug reactions during coadministration of TABRECTA with strong CYP3A inhibitors, including but not limited to, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, and voriconazole.

Strong CYP3A inducers

In healthy subjects, coadministration of a single 400 mg capmatinib dose with the strong CYP3A inducer rifampicin (600 mg once daily for 9 days) decreased capmatinib AUCinf by 67% and decreased Cmax by 56% compared to administration of capmatinib alone. Decreases in capmatinib exposure may decrease TABRECTA anti-tumour activity. Coadministration of TABRECTA with strong CYP3A inducers, including but not limited to, carbamazepine, phenobarbital, phenytoin, rifampicin and St. John's wort (*Hypericum perforatum*) should be avoided. An alternative medication with no or minimal potential to induce CYP3A should be considered.

Moderate CYP3A inducers

Simulations using physiologically-based pharmacokinetic (PBPK) models predicted that coadministration of a 400 mg capmatinib dose with the moderate CYP3A inducer efavirenz (600 mg once daily for 20 days) would result in a 44% decrease in capmatinib AUC0-12h and 34% decrease in Cmax at steady-state compared to administration of capmatinib alone. Decreases in capmatinib exposure may decrease TABRECTA anti-tumour activity. Caution should be exercised during coadministration of TABRECTA with moderate CYP3A inducers.

Agents that raise gastric pH

Capmatinib demonstrates pH-dependent solubility and becomes poorly soluble as pH increases *in vitro*. Gastric acid reducing agents (e.g. proton pump inhibitors, H_2-receptor antagonists, antacids) may alter the solubility of capmatinib and reduce its bioavailability. In healthy subjects, coadministration of a single 600 mg capmatinib dose with the proton pump inhibitor rabeprazole (20 mg once daily for 4 days) decreased capmatinib AUCinf by 25% and decreased Cmax by 38% compared to administration of capmatinib alone. Clinically relevant drug-drug interactions between capmatinib and gastric acid reducing agents are unlikely to occur as co-administration of rabeprazole had no clinically meaningful effect on exposure of capmatinib.

Effect of TABRECTA on other medicinal products

Substrates of CYP enzymes

In cancer patients, coadministration of caffeine (CYP1A2 probe substrate) with multiple doses of capmatinib (400 mg twice daily) increased caffeine AUCinf by 134% with no change in caffeine Cmax compared to administration of caffeine alone. Coadministration of TABRECTA with a CYP1A2 substrate may increase the incidence and severity of adverse drug reactions of these substrates. If coadministration is unavoidable between TABRECTA and CYP1A2 substrates where minimal concentration changes may lead to serious adverse drug reactions, including but not limited to, theophylline and tizanidine, decrease the CYP1A2 substrate dose in accordance with the approved prescribing information.

In cancer patients, coadministration of midazolam (CYP3A substrate) with multiple doses of capmatinib (400 mg twice daily) did not cause any clinically significant increase in midazolam exposure (9% increase in AUCinf and 22% increase in Cmax) compared to administration of midazolam alone. Clinically relevant drug-drug interactions between capmatinib and CYP3A substrates are unlikely to occur as coadministration of capmatinib had no clinically meaningful effect on exposure of midazolam (a CYP3A substrate).

P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrates

In cancer patients, coadministration of digoxin (P-gp substrate) with multiple doses of capmatinib (400 mg twice daily) increased digoxin AUCinf by 47% and increased Cmax by 74% compared to administration of digoxin alone. In cancer patients, coadministration of rosuvastatin (BCRP substrate) with multiple doses of capmatinib (400 mg twice daily) increased rosuvastatin AUCinf by 108% and increased Cmax by 204% compared to administration of rosuvastatin alone. Coadministration of TABRECTA with a P-gp or BCRP substrate may increase the incidence and severity of adverse drug reactions of these substrates. If coadministration is unavoidable between TABRECTA and P-gp or BCRP substrates where minimal concentration changes may lead to serious adverse drug reactions, decrease the P-gp or BCRP substrate dose in accordance with the approved prescribing information.

<u>*In vitro* evaluation of drug interaction potential</u>

Interactions between enzymes and TABRECTA

In vitro studies showed that capmatinib is an inhibitor of CYP2C8, CYP2C9 and CYP2C19. Capmatinib showed weak induction of CYP2B6, CYP2C9 and in cultured human hepatocytes. Simulations using PBPK models predicted that capmatinib given at a dose of 400 mg twice daily is unlikely to cause clinically relevant interaction via CYP2C8, CYP2C9, CYP2C19 and CYP2B6.

Interactions between transporters and TABRECTA

Based on *in vitro* data, capmatinib showed reversible inhibition of hepatic uptake transporters OATP1B1, OATP1B3, and OCT1. However, capmatinib is not expected to cause clinically relevant inhibition of OATP1B1, OATP1B3, and OCT1 uptake transporters based on the concentration achieved at the therapeutic dose. Capmatinib is not a multidrug resistance-associated protein (MRP2) inhibitor *in vitro*.

Based on *in vitro* data, capmatinib is not an inhibitor of renal transporters OAT1 or OAT3, but capmatinib and its major metabolite CMN288 showed reversible inhibition of renal transporters MATE1 and MATE2K. Capmatinib may inhibit MATE1 and MATE2K at clinically relevant concentrations.

Based on *in vitro* data, capmatinib is a P-gp substrate, but not a BCRP or MRP2 substrate. Capmatinib is not a substrate of transporters involved in active hepatic uptake in primary human hepatocytes.

<u>Drug-food/drink interactions</u>

TABRECTA can be administered with or without food (see section 4.2 Dose and method of administration and section 5.2 Pharmacokinetic properties).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effect of capmatinib on human fertility. Fertility studies with capmatinib were not conducted in animals.

Use in pregnancy – Pregnancy Category D

Risk summary

Based on findings from animal studies and its mechanism of action, TABRECTA can cause fetal harm when administered to a pregnant patients. There are no adequate and well-controlled studies in pregnant patients to inform a product-associated risk. Oral administration of capmatinib to pregnant rats and rabbits during the period of organogenesis resulted in fetotoxicity and teratogenicity.

TABRECTA should not be used during pregnancy, unless clearly necessary, and only after careful consideration of both the patient's need and the risk to the fetus. Patients who are pregnant or could become pregnant should be advised of the potential risk to a fetus if TABRECTA is used during pregnancy or if the patient becomes pregnant while taking TABRECTA.

Pregnancy testing

The pregnancy status of patient who could become pregnant should be verified prior to starting treatment with TABRECTA.

Contraception

People who could become pregnant should use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with TABRECTA and for at least 7 days after the last dose.

Male patients with sexual partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms during treatment with TABRECTA and for at least 7 days after the last dose.

Animal data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of capmatinib up to 30 mg/kg/day and 60 mg/kg/day, respectively, during the period of organogenesis. At 30 mg/kg/day in rats and 60 mg/kg/day in rabbits, the maternal systemic exposure (AUC) was approximately 1.4 and 1.5 times, respectively, the exposure in humans at the MRHD of 400 mg twice daily.

In rats, maternal toxicity (reduced body weight gain and food consumption) was observed at the dose of 30 mg/kg/day. Fetal effects included reduced fetal weights, irregular/incomplete ossification, and increased incidences of fetal malformations (e.g. abnormal flexure/inward malrotation of hindpaws/forepaws, thinness of forelimbs, lack of/reduced flexion at the humerus/ulna joints, narrowed or small tongue) at doses of ≥10 mg/kg/day (with maternal systemic exposure at 0.56 times the exposure in humans at the MRHD of 400 mg twice daily).

In rabbits, no maternal effects were detected at doses up to 60 mg/kg/day. Fetal effects included small lung lobe at ≥5 mg/kg/day (with systemic exposure at 0.016 times the exposure in humans at the MRHD of 400 mg twice daily), and reduced fetal weights, irregular/incomplete ossification and increased incidences of fetal malformations (e.g. abnormal flexure/malrotation of hindpaws/forepaws, thinness of forelimbs/hindlimbs, lack of/reduced flexion at the humerus/ulna joints, small lung lobes, narrowed or small tongue) at the dose of 60 mg/kg/day (with systemic exposure at 1.5 times the exposure in humans at the MRHD of 400 mg twice daily).

Use in lactation.

It is not known if capmatinib is transferred into human milk after administration of TABRECTA. There are no data on the effects of capmatinib on the breastfed child or on milk production. Because of the potential for serious adverse drug reactions in breast-fed children, breast-feeding should be paused during treatment with TABRECTA and for at least 7 days after the last dose.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (Undesirable effects)

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 www.tga.gov.au/reporting-problems.

Summary of the safety profile (data cut-off:16-May-2023)

The safety of TABRECTA was evaluated in patients with locally advanced or metastatic NSCLC in the pivotal, global, prospective, multi-cohort, non-randomised, open-label Phase II Study A2201 (GEOMETRY mono-1) across all cohorts (N = 373), regardless of prior treatment or MET dysregulation (mutation and/or amplification) status. The median duration of exposure to TABRECTA across all cohorts was 17.9 weeks (range: 0.4 to 280.4 weeks). Among patients who received TABRECTA, 39.9% were exposed for at least 6 months and 24.4% were exposed for at least one year.

Overall, the most frequently reported AEs of all grades, irrespective of study drug relationship (occurring in ≥25% of all patients) were oedema peripheral (54.7%), nausea (45.8%), vomiting (28.7%), blood creatinine increased (27.6%) and dyspnoea (25.5%).

Serious adverse events (SAEs) regardless of causality were reported in 202 patients (54.2%) who received TABRECTA. Serious AEs regardless of causality in >2% of patients included dyspnoea (7.0%), pneumonia (6.2%), pleural effusion (4.3%), general physical health deterioration (2.9%) and vomiting (2.4%).

Fourteen patients (3.8%) died while on treatment with TABRECTA due to causes other than the underlying malignancy. One of these deaths was confirmed as treatment-related: pneumonitis.

Permanent discontinuation of TABRECTA due to an AE regardless of causality was reported in 68 patients (18.2%). The most frequent AEs (≥1%) leading to permanent discontinuation of TABRECTA were peripheral oedema (2.1%), pneumonitis (1.6%), fatigue (1.6%) and AST increased (1.1%).

Dose interruptions due to an AE regardless of causality were reported in 215 patients (57.6%) who received TABRECTA. AEs regardless of causality requiring dose interruption in >2% of patients who received TABRECTA included peripheral edema (11.8%), blood creatinine increased (9.1%), nausea (6.2%), lipase increased (5.6%), vomiting (5.9%), ALT increased (4.8%), dyspnoea (4.8%), pneumonia (4.6%), amylase increased (4.0%), AST increased (3.2%), diarrhoea (2.1%), asthenia (2.4%) and blood bilirubin increased (2.1%).

Dose adjustments due to an AE regardless of causality were reported in 100 patients (26.8%) who received TABRECTA. AEs regardless of causality requiring dose adjustments in >2% of patients who received TABRECTA included peripheral oedema (10.2%), ALT increased (3.2%) and blood creatinine increased (2.1%).

Tabulated summary of adverse events from clinical studies

The most common adverse events, reported in ≥10% of all patients (N=373) treated with TABRECTA in Study A2201 (GEOMETRY mono-1), are summarised below.

Table 3 Adverse events (≥10%), regardless of study drug relationship, in patients (N = 373) who received TABRECTA in Study A2201 (GEOMETRY mono-1) (Data cut-off: 16-May-2023)

	All patients N=373	
Primary system organ class Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**
Any primary system organ class	**348 (93.3)**	**141 (37.8)**
Gastrointestinal disorders	**241 (64.6)**	**18 (4.8)**
Nausea	171 (45.8)	9 (2.4)
Vomiting	107 (28.7)	9 (2.4)
Diarrhoea	71 (19.0)	2 (0.5)
Constipation	70 (18.8)	3 (0.8)
General disorders and administration site conditions	**259 (69.4)**	**69 (18.5)**
Oedema peripheral	204 (54.7)	42 (11.3)
Fatigue	86 (23.1)	17 (4.6)
Pyrexia	53 (14.2)	3 (0.8)
Asthenia	49 (13.1)	14 (3.8)
Infections and infestations	**43 (11.5)**	**17 (4.6)**
Pneumonia	43 (11.5)	17 (4.6)
Investigations	**162 (43.4)**	**29 (7.8)**

		All patients N=373
Blood creatinine increased	103 (27.6)	1 (0.3)
Alanine aminotransferase increased	53 (14.2)	26 (7.0)
Weight decreased	41 (11.0)	2 (0.5)
Aspartate aminotransferase increased	39 (10.5)	13 (3.5)
Metabolism and nutrition disorders	**108 (29.0)**	**8 (2.1)**
Decreased appetite	81 (21.7)	4 (1.1)
Hypoalbuminaemia	38 (10.2)	4 (1.1)
Musculoskeletal and connective tissue disorders	**98 (26.3)**	**7 (1.9)**
Back pain	64 (17.2)	3 (0.8)
Arthralgia	42 (11.3)	4 (1.1)
Respiratory, thoracic and mediastinal disorders	**129 (34.6)**	**28 (7.5)**
Dyspnoea	95 (25.5)	26 (7.0)
Cough	62 (16.6)	2 (0.5)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency, as reported under 'All Patients'.
- A patient with multiple occurrences of an AE is counted only once in the AE category.
- A patient with multiple severity ratings for an AE while on a treatment, is only counted under the maximum rating.

Description of selected grouped adverse events (data cut-off: 16-May-2023)

Interstitial lung disease (ILD)/pneumonitis

In all patients (N=373), interstitial lung disease and pneumonitis grouped events were reported in 20 patients (5.4%). Grade 3/4 events occurred in 8 patients (2.1%), with no Grade 4 events reported. Suspected adverse events were reported in 12 patients (3.2%), and serious adverse events in 10 patients (2.7%); 10 patients (2.7%) required hospitalisation. Events led to permanent discontinuation in 11 patients (2.9%), and adjustment in 1 patient (0.3%). The median time to first occurrence of grade 3/4 interstitial lung disease/pneumonitis events was 1.38 months (range: 0.16-20.34) and the median duration of first occurrence of grade 3/4 interstitial lung disease/pneumonitis events was 0.61 months (range: 0.16, NE).

Hepatotoxicity

In all patients (N=373), hepatotoxicity grouped events (all grades, irrespective of study drug relationship) were reported in 120 patients (32.2%). Grade 3/4 events occurred in 43 patients (11.5%), including Grade 4 events in 8 patients (2.1%). Suspected adverse events were reported in 71 patients (19.0%), and serious adverse events in 7 patients (1.9%); 6 patients (1.6%) required hospitalisation. Events led to permanent discontinuation in 7 patients (1.9%), and dose adjustment in 15 patients (4.0%). The median time to first occurrence of Grade 3/4 hepatotoxicity events was 1.41 months (range: 0.03–46.36), and the median duration was 0.49 months (range: 0.30, 0.53).

In all patients (N=373), most had normal liver function values at baseline, and any post-baseline worsening was mostly to grade 1 or 2. Overall increases in transaminases (ALT and/or AST) > 3 × upper limit of normal (ULN) (grade 2) were seen in 52 patients (13.9%). Total bilirubin > 2 × ULN were reported for 6 patients (1.6%) and > 3 × ULN were reported for 4 patients (1.1%). Three patients had concurrent peak values of total bilirubin > 2 × ULN with peak values of ALT or AST > 3 × ULN.

Pancreatitis

In all patients (N=373), pancreatitis grouped events (all grades, irrespective of study drug relationship) were reported in 53 patients (14.2%). Grade 3/4 events occurred in 33 patients (8.8%), including Grade 4 events in 7 patients (1.9%). Suspected adverse events were reported in 49 patients (13.1%), and serious adverse events in 2 patients (0.5%); 1 patient (0.3%) required hospitalisation. Events led to permanent discontinuation in 4 patients (1.1%), and dose adjustment in 4 patients (1.1%). The median time to first occurrence of Grade 3/4 pancreatitis grouped events was 1.81 months (range: 0.03–31.05), and the median duration of first occurrence of Grade 3/4 pancreatitis grouped events was 0.26 months (range: 0.26, 0.46).

Adverse drug reactions (ADRs) from clinical studies and post-marketing experience

Hypersensitivity has been observed in other clinical studies (frequency category: Uncommon), post-marketing experience and expanded access programs with TABRECTA.

4.9 OVERDOSE

There is limited experience with overdose in clinical studies with TABRECTA. Patients should be closely monitored for signs or symptoms of adverse reactions, and general supportive measures and symptomatic treatment should be initiated in cases of suspected overdose.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EX17.

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Capmatinib is a selective inhibitor of the MET receptor tyrosine kinase. At tolerated doses, capmatinib treatment results in regression of tumour xenograft models derived from lung cancer with MET exon 14 skipping mutations or MET amplification, among others. Capmatinib inhibits MET phosphorylation (both autophosphorylation and phosphorylation triggered by the ligand hepatocyte growth factor [HGF]), MET-mediated phosphorylation of downstream signalling proteins, as well as proliferation and survival of MET-dependent cancer cells.

Pharmacodynamic effects

Cardiac electrophysiology

Capmatinib did not prolong the QT interval to any clinically relevant extent following administration of TABRECTA at the recommended dose.

Clinical trials

Study A2201 (GEOMETRY mono-1): Locally advanced or metastatic NSCLC with a MET exon 14 skipping mutation (treatment-naïve and previously treated)

The efficacy of TABRECTA for the treatment of patients with locally advanced or metastatic NSCLC with a MET exon 14 skipping mutation was demonstrated in the pivotal, global, prospective, multi-cohort, non-randomised, open-label Phase II Study A2201 (GEOMETRY mono-1). Patients (N = 373) were enrolled into study cohorts based on their prior treatment and MET dysregulation (mutation and/or amplification) status. Patients with MET mutations (N = 160) were enrolled into the MET-mutated cohorts regardless of MET amplification. Patients without MET mutations were enrolled into the MET-amplified cohorts based on their level of MET amplification.

In the MET-mutated cohorts, eligible patients were required to have Epidermal Growth Factor Receptor (EGFR) wild-type (for exon 19 deletions and exon 21 L858R substitution mutations) and Anaplastic Lymphoma Kinase (ALK) negative status, and MET-mutated NSCLC with at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, along with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 1. Patients with symptomatic central nervous system (CNS) metastases who were neurologically unstable or required increasing doses of steroids within the prior 2 weeks to manage CNS symptoms, patients with clinically significant uncontrolled cardiac disease, or patients pre-treated with any MET or HGF inhibitor were not eligible for the study.

Patients continued treatment until documented disease progression, intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit.

The primary endpoint of the study was overall response rate (ORR) as determined by a Blinded Independent Review Committee (BIRC) according to RECIST 1.1. The key secondary endpoint was duration of response (DOR) by BIRC. Additional secondary endpoints were time-to-response (TTR), progression-free survival (PFS), overall survival (OS), and disease control rate (DCR). The efficacy data for treatment-naïve and previously treated patients were analysed independently.

The demographic characteristics of the MET-mutated study population were 61% female, median age 71 years (range: 48 to 90 years), 85% aged 65 years or older, 77% white, 19% Asian, 1.3% black, 61% never smoked, 83% had adenocarcinoma, 25% had ECOG PS 0, 74% had ECOG PS 1, and 16% had CNS metastases. In the previously treated cohorts (Cohorts 4 and 6) (N=100), 91% had received prior chemotherapy, 86% had prior platinum-based chemotherapy, 32% had prior immunotherapy, and 16% had received 2 prior systemic therapies.

Study A2201 (GEOMETRY mono-1): Final analysis (last patient last visit: 16-May-2023)

At the time of GEOMETRY mono-1 final analysis (LPLV: 16-May-2023), the median duration of exposure to TABRECTA across MET-mutated cohorts was 34.9 weeks (1L patients: 43.9 weeks and 2/3L patients: 27.9 weeks).

Final efficacy results from Study A2201 (GEOMETRY mono-1) for both treatment-naïve and previously treated MET-mutated NSCLC patients are summarized in Tables 8 and 9.

Table 8: Treatment-naïve MET-mutated locally advanced or metastatic NSCLC: Efficacy results by BIRC in patients who received TABRECTA in Study A2201 (GEOMETRY mono-1) (Last patient last visit: 16-May-2023)

Efficacy Parameters	**Cohort 5b N=28**	**Cohort 7 N=32**
Overall Response Rate[a] (95% CI)[b]	67.9% (47.6, 84.1)	68.8% (50.0, 83.9)
Complete Response, n (%)	2 (7.1)	1 (3.1)
Partial Response, n (%)	17 (60.7)	21 (65.6)
Duration of Response[a]		
Number of responders, n	19	22
Median, months (95% CI)[c]	12.58 (5.55, 38.67)	16.59 (8.34, NE)
Patients with DOR ≥6 months	68.4%	72.7%
Patients with DOR ≥12 months	47.4%	50.0%

Abbreviations: BIRC, Blinded Independent Review Committee; CI, Confidence Interval; CR, Complete Response; DOR, Duration of response; MET, mesenchymal-epithelial transition; NE, Not Estimable; NSCLC, Non-Small Cell Lung Cancer; ORR, Overall Response Rate; PR, Partial Response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, Stable Disease.

ORR: CR+PR.

[a]Determined by RECIST v1.1.

[b]Clopper and Pearson exact binomial 95% CI.

[c]Based on Kaplan-Meier estimate.

Table 9: Previously treated MET-mutated locally advanced or metastatic NSCLC: Efficacy results by BIRC in patients who received TABRECTA in Study A2201 (GEOMETRY mono-1) (Last patient last visit: 16-May-2023)

Efficacy Parameters	**Cohort 4 (2/3L) N = 69**	**Cohort 6 (2L) N = 31**
Overall Response Rate[a] (95% CI)[b]	40.6% (28.9, 53.1)	51.6% (33.1, 69.8)
Complete Response, n (%)	1 (1.4)	0 (0.0)
Partial Response, n (%)	27 (39.1)	16 (51.6)
Duration of Response[a]		
Number of responders, n	28	16
Median, months (95% CI)[c]	9.72 (5.55, 12.98)	9.05 (4.17, 27.60)
Patients with DOR ≥6 months	64.3%	62.5%
Patients with DOR ≥12 months	32.1%	43.8%

Abbreviations: BIRC, Blinded Independent Review Committee; CI, Confidence Interval; CR, Complete Response; ORR, Overall Response Rate; MET, mesenchymal-epithelial transition; NSCLC, Non-Small Cell Lung Cancer; ORR, Overall Response Rate; PR, Partial Response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, Stable Disease.

ORR: CR+PR.

[a]Determined by RECIST v1.1.

[b]Clopper and Pearson exact binomial 95% CI.

[c]Based on Kaplan-Meier estimate.

5.2 PHARMACOKINETIC PROPERTIES

Capmatinib exhibited dose-proportional increases in systemic exposure (AUCinf and Cmax) across the dose range tested (200 to 400 mg twice daily). Steady-state is expected to be achieved after approximately 3 days after oral dosing of capmatinib 400 mg twice daily, with a geometric mean accumulation ratio of 1.39 (coefficient of variation (CV): 42.9%).

Absorption

In humans, absorption is rapid after oral administration of capmatinib. Peak plasma levels of capmatinib (Cmax) were reached approximately 1 to 2 hours (Tmax) after an oral 400 mg dose of capmatinib tablets in cancer patients. The absorption of capmatinib tablets after oral administration is estimated to be greater than 70%.

Food effect

Food does not alter capmatinib bioavailability to a clinically meaningful extent. TABRECTA can be administered with or without food (see section 4.2 Dose and method of administration).

When capmatinib was administered at 400 mg twice daily in cancer patients, exposure (AUC0-12h) was similar after administration of capmatinib with food and under fasted conditions.

Distribution

Capmatinib is 96% bound to human plasma proteins, independent of concentration. The apparent mean volume of distribution at steady-state (Vss/F) is 164 L in cancer patients.

The blood-to-plasma ratio was 1.5 (concentration range of 10 to 1000 ng/mL), but decreased at higher concentrations to 0.9 (concentration 10000 ng/mL), indicating a saturation of distribution into red blood cells.

Capmatinib crossed the blood-brain barrier in rats with a brain-to-blood exposure (AUCinf) ratio of approximately 9%.

Metabolism

In vitro and *in vivo* studies indicated that capmatinib is cleared mainly through metabolism driven by cytochrome P450 (CYP) 3A4 and aldehyde oxidase. The biotransformation of capmatinib occurs essentially by Phase I metabolic reactions including *C*-hydroxylation, lactam formation, *N*-oxidation, *N*-dealkylation, carboxylic acid formation, and combinations thereof. Phase II reactions involve glucuronidation of oxygenated metabolites. The most abundant radioactive component in plasma is unchanged capmatinib (42.9% of radioactivity AUC0-12h). The major circulating metabolite, M16 (CMN288), is pharmacologically inactive and accounts for 21.5% of the radioactivity in plasma AUC0-12h.

Excretion

The effective elimination half-life (calculated based on geometric mean accumulation ratio) of capmatinib is 6.54 hours. The geometric mean steady-state apparent oral clearance (CLss/F) of capmatinib was 19.8 L/hr.

Capmatinib is eliminated mainly through metabolism, and subsequent faecal excretion. Following a single oral administration of [14C]-capmatinib to healthy subjects, 78% of the total radioactivity was recovered in the faeces and 22% in the urine. Excretion of unchanged capmatinib in urine is negligible.

Special populations

Elderly patients

No overall differences in the safety or effectiveness were observed between patients aged 65 and 75 years or older and younger patients.

Age/Gender/Race/Body weight

Population pharmacokinetic analysis showed that there is no clinically relevant effect of age/gender/race/body weight on the systemic exposure of capmatinib.

Renal impairment

Based on a population pharmacokinetic analysis that included 207 patients with normal renal function (CrCl ≥90 mL/min), 200 patients with mild renal impairment (CLcr 60 to 89 mL/min), and 94 patients with moderate renal impairment (CrCl 30 to 59 mL/min), mild or moderate renal impairment had no clinically significant effect on the exposure of capmatinib. TABRECTA has not been studied in patients with severe renal impairment (CrCl 15 to 29 mL/min) (see section 4.2 Dose and method of administration).

Hepatic impairment

A study was conducted in non-cancer subjects with various degrees of hepatic impairment based on Child-Pugh classification using a 200 mg single-dose of capmatinib. The geometric mean systemic exposure (AUCinf) of capmatinib was decreased by approximately 23% and 9% in subjects with mild (N = 6) and moderate (N = 8) hepatic impairment, respectively, and increased by approximately 24% in subjects with severe (N = 6) hepatic impairment compared to subjects with normal (N = 9) hepatic function. Cmax was decreased by approximately 28% and 17% in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal hepatic function, while Cmax was similar (increased by 2%) in subjects with severe hepatic impairment compared to subjects with normal hepatic function (see section 4.2 Dose and method of administration). Mild, moderate or severe hepatic impairment had no clinically significant effect on the exposure of capmatinib.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Capmatinib was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and did not cause chromosomal aberrations in the *in vitro* chromosome aberration assay in human peripheral blood lymphocytes. Capmatinib was not clastogenic in the *in vivo* bone marrow micronucleus test in rats.

Carcinogenicity

Carcinogenicity studies with capmatinib have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core: microcrystalline cellulose; mannitol; crospovidone; povidone; magnesium stearate; colloidal anhydrous silica; sodium lauryl sulfate.

Tablet coating:

150 mg: Hypromellose; titanium dioxide; macrogol 4000; purified talc; iron oxide yellow; iron oxide red; iron oxide black.

200 mg: Hypromellose; titanium dioxide; macrogol 4000; purified talc; iron oxide yellow.

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 30°C.

Store in the original package in order to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

PCTFE/PVC (polychlorotrifluoroethylene/polyvinyl chloride) blisters backed with an aluminium lidding foil.

Packs contain 60 or 120 film-coated tablets.

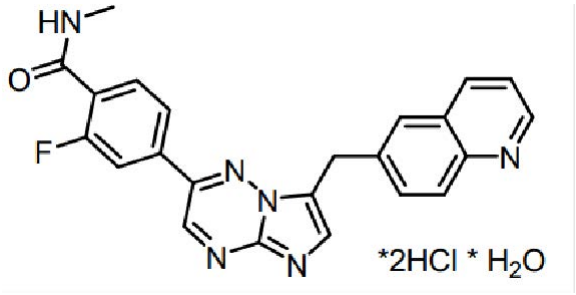
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Capmatinib is a kinase inhibitor. The chemical name is 2-Fluoro-*N*-methyl-4-[7-(quinolin-6-ylmethyl)imidazo[1,2-*b*][1,2,4]triazin-2-yl]benzamide—hydrogen chloride—water (1/2/1). The molecular formula for capmatinib dihydrochloride monohydrate is $C_{23}H_{21}Cl_2FN_6O_2$. The relative molecular mass is 503.36 g/mol for the dihydrochloride monohydrate salt and 412.43 g/mol for the free base. The chemical structure for capmatinib hydrochloride is shown below:

Chemical structure



CAS number

1865733-40-9

Capmatinib dihydrochloride monohydrate is a yellow powder with a pKa_1 of 0.9 (calculated) and pKa_2 of 4.5 (experimentally). Capmatinib dihydrochloride monohydrate is slightly soluble in acidic aqueous solutions at pH 1 and 2 and of further decreasing solubility towards neutral condition. The log of the distribution coefficient (n-octanol/acetate buffer pH 4.0) is 1.2.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

XXXXXX

10 DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
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