SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Tabrecta 150 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tabrecta 150 mg film-coated tablets

Each film-coated tablet contains capmatinib dihydrochloride monohydrate equivalent to 150 mg capmatinib.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Tabrecta 150 mg film-coated tablets

Pale orange brown, ovaloid, curved film-coated tablet with bevelled edges, unscored, debossed with “DU” on one side and “NVR” on the other side. Approximate size: 18 mm (length) x 7 mm (width).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tabrecta, as monotherapy, is indicated for the treatment of adult patients with unresectable locally advanced or metastatic non-small cell lung cancer (NSCLC) with a MET exon 14 skipping mutation.

4.2 Posology and method of administration

Treatment with Tabrecta should be initated by a physician experienced in the use of anticancer therapies.

Patients should be selected for treatment with Tabrecta based on the presence of genetic alterations leading to a METex14 skipping mutation in tumour tissue or plasma specimens using a validated test. If a genetic alteration is not detected in a plasma specimen, tumour tissue should be tested if feasible (see sections 4.4 and 5.1).

Posology

The recommended dose of Tabrecta is 400 mg orally twice daily with or without food.

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

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

Table 1Tabrecta 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 2Tabrecta dose modifications for the management of adverse reactions

Adverse reaction	Severity	Dose modification
Interstitial lung disease (ILD)/pneumonitis	Any grade treatment-related	Permanently discontinue Tabrecta.
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 haemolysis	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. 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.

Adverse reaction	Severity	Dose modification
Other adverse 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

Elderly

No dose adjustment is necessary in patients 65 years of age or older (see section 5.2).

Renal impairment

Caution should be exercised in patients with severe renal impairment as Tabrecta has not been studied in these patients. No dose adjustment is necessary in patients with mild or moderate renal impairment (see section 5.2).

Hepatic impairment

No dose adjustment is necessary in patients with mild, moderate or severe hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of Tabrecta in children aged 0 to 18 years have not been established. No data are available.

Method of administration

Tabrecta should be taken orally with or without food. The tablets should be swallowed whole with a glass of water and should not be broken, crushed or chewed to ensure that the full dose is administered.

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

Assessment of METex14 skipping alterations status

When detecting the presence of alterations leading to METex14 skipping using tissue-based or plasma-based specimens, it is important that a well-validated and robust test is chosen to avoid false negative or false positive results. For the characteristics of tests used in clinical studies see section 5.1.

Interstitial lung disease (ILD)/pneumonitis

ILD/pneumonitis, which can be fatal, has occurred in patients treated with Tabrecta (see section 4.8). 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).

Hepatic effects

Transaminase elevations have occurred in patients treated with Tabrecta (see section 4.8). 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 reaction, temporarily withhold, dose reduce, or permanently discontinue Tabrecta (see section 4.2).

Elevations of pancreatic enzymes

Elevations in amylase and lipase levels have occurred in patients treated with Tabrecta (see section 4.8). Amylase and lipase should be monitored at baseline and regularly during treatment with Tabrecta. Based on the severity of the adverse reaction, temporarily withhold, dose reduce, or permanently discontinue Tabrecta (see section 4.2).

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). 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 woman due to its foetotoxicity and teratogenicity (see section 4.6). Pregnant women and women of childbearing potential should be advised of the potential risk to a foetus if Tabrecta is used during pregnancy or if the patient becomes pregnant while taking Tabrecta. Sexually active women of childbearing potential should use effective contraception during treatment with Tabrecta and for at least 7 days after the last dose. The pregnancy status of women of childbearing potential should be verified prior to starting treatment with Tabrecta.

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).

Risk of photosensitivity

Based on findings from animal studies, there is a potential risk of photosensitivity reactions with Tabrecta (see section 5.3). In Study GEOMETRY mono-1, it was recommended that patients limit direct ultraviolet exposure during treatment with Tabrecta and adopt the following protective measures: use of sunscreen on exposed parts of the body, wearing of protective clothing and sunglasses. These measures should be continued for at least 7 days after the last dose.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Capmatinib undergoes metabolism through CYP3A4 enzyme and aldehyde oxidase. The risk of a drug-drug interaction via aldehyde oxidase has not been evaluated as there are no confirmed clinically relevant inhibitors.

Effect of other medicinal products on Tabrecta

Strong CYP3A inhibitors

In healthy subjects, co-administration of a single 200 mg capmatinib dose with the strong CYP3A inhibitor itraconazole (200 mg once daily for 10 days) increased capmatinib AUC_{inf} by 42% with no change in capmatinib C_{max} 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 reactions during co-administration of Tabrecta with strong CYP3A inhibitors, including but not limited to, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole and any grapefruit containing products such as grapefruit juice.

Strong CYP3A inducers

In healthy subjects, co-administration of a single 400 mg capmatinib dose with the strong CYP3A inducer rifampicin (600 mg once daily for 9 days) decreased capmatinib AUC_{inf} by 67% and decreased C_{max} by 56% compared to administration of capmatinib alone. Decreases in capmatinib exposure may decrease Tabrecta anti-tumour activity. Co-administration 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 medicinal product with no or minimal potential to induce CYP3A should be considered.

Moderate CYP3A inducers

Simulations using physiologically-based pharmacokinetic (PBPK) models predicted that co-administration of a 400 mg capmatinib dose with the moderate CYP3A inducer efavirenz (600 mg daily for 20 days) would result in a 44% decrease in capmatinib AUC_{0-12h} and 34% decrease in C_{max} at steady-state compared to administration of capmatinib alone. Decreases in capmatinib exposure may decrease Tabrecta anti-tumour activity. Caution should be exercised during co-administration 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 C_{max} 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 enyzmes

Moderate inhibition of CYP1A2 was observed when capmatinib was co-administered with the sensitive CYP1A2 substrate caffeine. Co-administration of capmatinib (400 mg twice daily) with caffeine increased caffeine AUC_{inf} by 134%. If capmatinib is co-administered with narrow therapeutic index CYP1A2 substrates, such as theophylline and tizanidine, dose reduction of the co-administered medicinal product may be required.

Clinically relevant drug-drug interactions between capmatinib and CYP3A substrates are unlikely to occur as co-administration 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, co-administration of digoxin (P-gp substrate) with multiple doses of capmatinib (400 mg twice daily) increased digoxin AUC_{inf} by 47% and increased C_{max} by 74% compared to administration of digoxin alone. In cancer patients, co-administration of rosuvastatin (BCRP substrate) with multiple doses of capmatinib (400 mg twice daily) increased rosuvastatin AUC_{inf} by 108% and increased C_{max} by 204% compared to administration of rosuvastatin alone. Co-administration of Tabrecta with a P-gp or BCRP substrate may increase the incidence and severity of adverse reactions of these substrates. Caution should be exercised during co-administration of Tabrecta with P-gp (digoxin, dabigatran etexilate, colchicine, sitagliptin, saxagliptin and posaconazole) or BCRP (methotrexate, rosuvastatin, pravastatin, mitoxantrone and sulfasalazine) substrates. If capmatinib is co-administered with narrow therapeutic index P-gp or BCRP substrates, dose reduction of the co-administered medicinal product may be required.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Sexually-active women of childbearing potential 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.

Pregnancy

There are no data from the use of capmatinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Based on findings from animal studies and its mechanism of action, capmatinib is suspected to cause congenital malformations when administered during pregnancy. Tabrecta should not be used during pregnancy unless the clinical condition of the woman requires treatment with capmatinib.

The pregnancy status of women of childbearing potential should be verified prior to starting treatment with Tabrecta.

Breast-feeding

It is unknown whether capmatinib or its metabolites are excreted in human milk after administration of Tabrecta. There is insufficient information on the excretion of capmatinib or its metabolites in animal milk. A risk to the breast-fed infant cannot be excluded. Because of the potential for serious adverse reactions in breast-fed infants, breast-feeding should be discontinued during treatment with Tabrecta and for at least 7 days after the last dose.

Fertility

No human fertility data on capmatinib are available. Fertility studies with capmatinib were not conducted in animals.

4.7 Effects on ability to drive and use machines

Tabrecta may have minor influence on the ability to drive and use machines. During treatment with Tabrecta, fatigue and asthenia have been reported.

4.8 Undesirable effects

Summary of the safety profile

The safety of Tabrecta was evaluated in patients with locally advanced or metastatic NSCLC in the pivotal, global, prospective, multi-cohort, non-randomized, 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 281.0 weeks). Among patients who received Tabrecta, 36.7% were exposed for at least 6 months and 21.7% were exposed for at least one year.

The frequencies of adverse reactions are based on all-cause adverse event frequencies identified in 373 patients exposed to capmatinib at the recommended dose.

The most common adverse drug reactions (ADRs) reported with an incidence of ≥20% (all Grades) in patients who received Tabrecta were peripheral oedema (56.8%), nausea (45.6%), fatigue (34.0%), vomiting (28.4%), blood creatinine increased (27.1%), dyspnoea (24.9%), and decreased appetite (21.4%).

The most common Grade 3 or 4 ADRs reported with an incidence of ≥5% in patients who received Tabrecta were peripheral oedema (10.5%), fatigue (8.0), dyspnoea (7.0%), ALT increased (7.0%), and lipase increased (6.7%).

Serious adverse events (AEs) regardless of causality were reported in 198 patients (53.1%) who received Tabrecta. Serious AEs regardless of causality in > 2% of patients included dyspnoea (6.7%), pneumonia (5.9%), 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.

Dose interruptions due to an adverse event regardless of causality were reported in 211 patients (56.6%) who received Tabrecta. Adverse events regardless of causality requiring dose interruption in > 2% of patients who received Tabrecta included peripheral oedema (11.0%), blood creatinine increased (8.3%), nausea (6.2%), lipase increased (5.6%), vomiting (5.6%), ALT increased (4.8%), dyspnoea (4.6%), pneumonia (4.3%), amylase increased (3.8%), AST increased (3.2%), asthenia (2.4%) and blood bilirubin increased (2.1%).

Dose reductions due to an adverse event regardless of causality were reported in 98 patients (26.3%) who received Tabrecta. Adverse events regardless of causality requiring dose

reductions in > 2% of patients who received Tabrecta included peripheral oedema (9.1%), ALT increased (3.2%) and blood creatinine increased (2.1%).

Permanent discontinuation of Tabrecta due to an AE regardless of causality was reported in 65 patients (17.4%). The most frequent AEs (≥0.5%) leading to permanent discontinuation of Tabrecta were peripheral oedema (2.1%), pneumonitis (1.6%), fatigue (1.3%), ALT increased (0.8%), AST increased (0.8%), blood creatinine increased (0.8%), nausea (0.8%), pneumonia (0.8%), vomiting (0.8%), blood bilirubin increased (0.5%), breast cancer (0.5%), cardiac failure (0.5%), general physical health deterioration (0.5%), ILD (0.5%), lipase increased (0.5%), organising pneumonia (0.5%) and pleural effusion (0.5%).

Tabulated list of adverse reactions

Adverse reactions from clinical studies (Table 3) are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3 Adverse drug reactions in patients (N = 373) who received Tabrecta in Study A2201 (GEOMETRY mono-1) (Data cut-off: 30-Aug-2021)

Adverse reaction	**All grades Frequency category**	**All grades %**	**Grade 3/4 %**
Infections and infestations			
Cellulitis	Common	2.9	1.1*
Metabolism and nutrition disorders			
Decreased appetite	Very common	21.4	1.1*
Respiratory, thoracic, and mediastinal disorders			
Dyspnoea	Very common	24.9	7.0
Cough	Very common	16.6	0.5*
ILD/pneumonitis	Common	4.6	1.9*
Gastrointestinal disorders			
Nausea	Very common	45.6	2.4*
Vomiting	Very common	28.6	2.4*
Constipation	Very common	18.8	0.8*
Diarrhoea	Very common	18.5	0.5*
Acute pancreatitis	Uncommon	0.3	0.3*
Skin and subcutaneous tissue disorders			
Pruritus[1]	Common	9.7	0.3*
Rash[2]	Common	8.6	0.5*
Urticaria	Common	1.3	0.5*
Renal and urinary disorders			

Acute kidney injury[3]	Common	3.8	0.8*
General disorders and administration site conditions			
Oedema peripheral[4]	Very common	56.8	10.5*
Fatigue[5]	Very common	34	8.0*
Back pain	Very common	16.9	0.8*
Non-cardiac chest pain[6]	Very common	14.2	1.9*
Pyrexia[7]	Very common	14.2	0.8*
Weight decreased	Common	11.0	0.5*
Investigations†			
Albumin decreased	Very common	72.0	1.9*
Creatinine increased	Very common	65.0	0.5*
Alanine aminotransferase increased	Very common	39.1	9.4
Amylase increased	Very common	33.6	4.7
Lipase increased	Very common	28.7	9.2
Aspartate aminotransferase increased	Very common	27.5	5.8
Phosphate decreased	Very common	25.9	4.4
Sodium decreased	Very common	23.6	6.0
Bilirubin increased	Common	8.0	1.1*

1 Pruritus includes preferred terms (PTs) of pruritus and pruritus allergic.
2 Rash includes PTs of rash, rash macular, rash maculopapular, rash erythematous and rash vesicular.
3 Acute kidney injury includes PTs of acute kidney injury and renal failure.
4 Oedema peripheral includes PTs of peripheral swelling, oedema peripheral, and fluid overload.
5 Fatigue includes PTs of fatigue and asthenia.
6 Non-cardiac chest pain includes PTs of chest discomfort, musculoskeletal chest pain, non-cardiac chest pain and chest pain.
7 Pyrexia includes PTs of pyrexia and body temperature increased.
* No grade 4 adverse reactions reported in Study A2201 (GEOMETRY mono-1).
† Grading according to CTCAE Version 4.03. Frequency is based on worsening from baseline laboratory values.

Adverse drug reactions 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 (see section 4.4)

Description of selected adverse reactions

ILD/pneumonitis

Any Grade ILD/pneumonitis was reported in 17 of 373 patients (4.6%) treated with Tabrecta in Study A2201 (GEOMETRY mono-1). Grade 3 ILD/pneumonitis was reported in 7 patients (1.9%), with a fatal event of pneumonitis reported in 1 patient (0.3%). ILD/pneumonitis occurred in 9 of 173 patients (5.2%) with a history of prior radiotherapy and 8 of 200 patients (4.0%) who did not receive prior radiotherapy. Eight patients (2.1%) discontinued Tabrecta due to ILD/pneumonitis. ILD/pneumonitis mostly occurred within approximately the first 3

months of treatment. The median time-to-onset of Grade 3 or higher ILD/pneumonitis was 7.9 weeks (range: 0.7 to 88.4 weeks).

Hepatic effects
Any Grade ALT/AST elevations were reported in 55 of 373 patients (14.7%) treated with Tabrecta in Study A2201 (GEOMETRY mono-1). Grade 3 or 4 ALT/AST elevations were observed in 26 of 373 patients (7.0%) treated with Tabrecta. Three patients (0.8%) discontinued Tabrecta due to ALT/AST elevations. ALT/AST elevations mostly occurred within approximately the first 3 months of treatment. The median time-to-onset of Grade 3 or higher ALT/AST elevations was 7.6 weeks (range: 2.1 to 201.6 weeks).

Elevations of pancreatic enzymes
Any Grade amylase/lipase elevations were reported in 52 of 373 patients (13.9%) treated with Tabrecta in Study A2201 (GEOMETRY mono 1). Grade 3 or 4 amylase/lipase elevations were reported in 32 of 373 patients (8.6%) treated with Tabrecta. Three patients (0.8%) discontinued Tabrecta due to amylase/lipase elevations. The median time to onset of Grade 3 or higher amylase/lipase elevations was 8.5 weeks (range: 0.1 to 135.0 weeks).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Capmatinib is an inhibitor of the MET receptor tyrosine kinase. Capmatinib inhibits MET phosphorylation (both autophosphorylation and phosphorylation triggered by the ligand hepatocyte growth factor [HGF]), MET-mediated phosphorylation of downstream signaling 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.

Detection of METex14 skipping status

In GEOMETRY mono-1, MET exon 14 skipping mutations were determined using a qualitative realtime PCR test (RT-PCR) designed to detect exon 14-deleted MET mRNA derived from formalin-fixed, paraffin-embedded human tissue. The test is indicated as an aid in selecting non-small cell lung cancer (NSCLC) patients whose tumours carry a MET mutation that causes in-frame deletion of the entire exon 14 (141 bases) in mRNA for treatment with capmatinib.

Clinical efficacy and safety

The efficacy of Tabrecta for the treatment of patients with locally advanced or metastatic NSCLC with a MET exon 14 skipping mutation was studied in a prospective, multi-cohort, non-randomized, open-label Phase II GEOMETRY mono-1 (Study A2201). Patients (N = 373) were enrolled into study cohorts based on their prior treatment and MET dysregulation (mutation and/or amplification) status, of whom 160 had MET exon 14 skipping mutation regardless of MET amplification. The MET-mutated cohorts consisted of 60 treatment-naïve patients (Cohorts 5b and 7) and 100 previously-treated patients (Cohorts 4 and 6). The efficacy data for treatment-naïve and previously-treated patients were analyzed independently.

In the MET-mutated cohorts, eligible NSCLC 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-exon 14 skipping mutation with at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (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 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.

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.

Efficacy results from GEOMETRY mono-1 for both treatment-naïve and previously-treated MET-mutated NSCLC patients are summarized in Tables 4 and 5.

Table 4Efficacy results by BIRC in treatment-naïve NSCLC patients with a METex14 skipping mutation who received Tabrecta in GEOMETRY mono-1 (data cut-off: 30-Aug-2021)

Efficacy parameters	**Overall treatment-naïve population (N=60)**	**Cohort 5b N=28**	**Cohort 7 N=32**
Overall response rate[a] (95% CI)[b]	68.3% (55.0, 79.7)	67.9% (47.6, 84.1)	68.8% (50.0, 83.9)
Complete response (CR), n (%)	3 (5.0)	2 (7.1)	1 (3.1)
Partial response (PR), n (%)	38 (63.3)	17 (60.7)	21 (65.6)
Duration of response[a]			
Number of responders, n	41	19	22
Median, months (95% CI)[c]	16.59 (8.41, 22.11)	12.58 (5.55, NE)	16.59 (8.34, NE)
Patients with DOR ≥6 months	70.7%	68.4%	72.7%
Patients with DOR ≥12 months	48.8%	47.4%	50.0%
Disease Control Rate[a] (95% CI)[b]	98.3 (91.1, 100.0)	96.4% (81.7,99.9)	100.0% (89.1, 100.0)
Progression-Free Survival[a]			
Number of events, n (%)	37 (61.7)	18 (64.3)	19 (59.4)
Progressive Disease, n (%)	30 (50.0)	15 (53.6)	15 (46.9)
Deaths, n (%)	7 (11.7)	3 (10.7)	4 (12.5)
Median, months (95% CI)[c]	12.45 (8.31, 17.97)	12.42 (8.21, 23.39)	12.45 (6.87, 20.50)
Overall Survival			
Number of events, n (%)	30 (50.0)	17 (60.7)	13 (40.6)
Median, months (95% CI)[c]	25.49 (15.24, NE)	20.76 (12.42, NE)	NE (12.85, NE)

Abbreviations: CI, confidence interval; NE, not estimable.
ORR: CR+PR.
[a] Determined by RECIST v1.1.
[b] Clopper and Pearson exact binomial 95% CI.
[c] Based on Kaplan-Meier estimate.

Table 5Efficacy results by BIRC in previously-treated NSCLC patients with a METex14 skipping mutation who received Tabrecta in GEOMETRY mono-1 (data cut-off: 30-Aug-2021)

Efficacy parameters	Overall previously-treated population (N=100)	Cohort 4 (2/3L) N=69	Cohort 6 (2L) N=31
Overall response rate[a] (95% CI)[b]	44.0% (34.1, 54.3)	40.6% (28.9, 53.1)	51.6% (33.1, 69.8)
Complete response (CR), n (%)	1 (1.0)	1 (1.4)	0 (0.0)
Partial response (PR), n (%)	43 (43.0)	27 (39.1)	16 (51.6)
Duration of response[a]			
Number of responders, n	44	28	16
Median, months (95% CI)[c]	9.72 (5.62, 12.98)	9.72 (5.55, 12.98)	9.05 (4.17, NE)
Patients with DOR ≥6 months	63.6%	64.3%	62.5%
Patients with DOR ≥12 months	36.4%	32.1%	43.8%
Disease Control Rate[a] (95% CI)[b]	82.0% (73.1, 89.0)	78.3% (66.7, 87.3)	90.3% (74.2, 98.0)
Progression-Free Survival[a]			
Number of events, n (%)	83 (83.0)	60 (87.0)	23 (74.2)
Progressive Disease, n (%)	75 (75.0)	54 (78.3)	21 (67.7)
Deaths, n (%)	8 (8.0)	6 (8.7)	2 (6.5)
Median, months (95% CI)[c]	5.49 (4.17, 8.11)	5.42 (4.17, 6.97)	6.93 (4.17, 13.34)
Overall Survival			
Number of events, n (%)	70 (70.0)	53 (76.8)	17 (54.8)
Median, months (95% CI)[c]	14.85 (11.63, 23.82)	13.57 (8.61, 22.24)	24.28 (13.54, NE)

Abbreviations: CI, confidence interval; NE, not estimable.
ORR: CR+PR.
[a] Determined by RECIST v1.1.
[b] Clopper and Pearson exact binomial 95% CI.
[c] Based on Kaplan-Meier estimate.

Paediatric population

The licensing authority has waived the obligation to submit the results of studies with Tabrecta in all subsets of the paediatric population in the treatment of lung malignant neoplasm (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Capmatinib exhibited dose-proportional increases in systemic exposure (AUC_{inf} and C_{max}) 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%). Inter-individual variability of C_{max} and AUC_{tau} was estimated to be 38% and 40%, respectively.

Absorption

In humans, absorption is rapid after oral administration of capmatinib. Under fasted conditions, peak plasma levels of capmatinib (C_{max}) were reached approximately 1 to 2 hours (T_{max}) after an oral 400 mg dose of capmatinib tablets in cancer patients. Under fed conditions, T_{max} is approximately 4-6 hours. 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).

When capmatinib was administered with food in healthy subjects, oral administration of a single 600 mg dose with a high-fat meal increased capmatinib AUC_{inf} by 46% and no change in C_{max} compared to when capmatinib was administered under fasted conditions. A low-fat meal in healthy subjects had no clinically meaningful effect on capmatinib exposure.

When capmatinib was administered at 400 mg twice daily in cancer patients, exposure (AUC_{0-12h}) 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 litres 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 crosses the blood-brain barrier (see section 5.3).

Biotransformation

In vitro and *in vivo* studies indicated that capmatinib is cleared mainly through metabolism driven by cytochrome P450 (CYP) 3A4 (40-50%) and aldehyde oxidase (40%). 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 AUC_{0-12h}). The major circulating metabolite, M16 (CMN288), is pharmacologically inactive and accounts for 21.5% of the radioactivity in plasma AUC_{0-12h}.

Elimination

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 litres/hour.

Capmatinib is eliminated mainly through metabolism, and subsequent faecal excretion. Following a single oral administration of [14C]-capmatinib capsule 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

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

Effect of age, gender, race and body weight

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

Renal impairment

Based on a population pharmacokinetic analysis that included 207 patients with normal renal function (creatinine clearance [CLcr] ≥90 ml/min), 200 patients with mild renal impairment (CLcr 60 to 89 ml/min), and 94 patients with moderate renal impairment (CLcr 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 (CLcr 15 to 29 ml/min) (see section 4.2).

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 (AUC_{inf}) 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. C_{max} was decreased by approximately 28% and 17% in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal hepatic function, while C_{max} was similar (increased by 2%) in subjects with severe hepatic impairment compared to subjects with normal hepatic function. Mild, moderate or severe hepatic impairment had no clinically significant effect on the exposure of capmatinib.

Pharmacokinetic/pharmacodynamic relationship

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

In vitro evaluation of medicinal product interaction potential

Interactions between enzymes and Tabrecta

In vitro studies showed that capmatinib is an inhibitor of CYP2C8, CYP2C9 and CYP2C19. Capmatinib also showed weak induction of CYP2B6 and CYP2C9 in cultured human hepatocytes. Simulations using PBPK models predicted that capmatinib given at a dose of 400 mg twice daily may have a weak interaction with CYP2C8. Caution should be exercised when capmatinib is co-administered with sensitive CYP2C8 substrates with narrow therapeutic index. Capmatinib is unlikely to cause clinically relevant interaction via CYP2B6, CYP2C9 or CYP2C19.

Interactions between transporters and Tabrecta

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

Based on *in vitro* data, 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. MATE1 substrates include, among others, acyclovir, cephalexin, cimetidine, dofetilide, ganciclovir, fexofenadine, metformin, pindolol and ranitidine. MATE2K substrates include, among others, acyclovir, cimetidine, ganciclovir, metformin, pindolol, pilsicainide and ranitidine.

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 an inhibitor of renal transporters OAT1 or OAT3. Capmatinib is not a MRP2 inhibitor *in vitro*.

5.3 Preclinical safety data

Repeated-dose toxicity

Repeat-dose toxicity studies conducted in rats and cynomolgus monkeys revealed the following target organs or systems: pancreas, brain/central nervous system (CNS), liver, and potentially the kidney.

Reversible findings in the pancreas were observed in rats and monkeys in 28-day and 13-week studies, including pancreatic acinar cell vacuolation and/or apoptosis without inflammation, occasionally accompanied by increased amylase or lipase. In rats, the doses of 60 mg/kg/day or higher in males and 30 mg/kg/day or higher in females showed reversible low-grade pancreatic changes in 28-day and/or 13-week studies. In monkeys, pancreatic findings included reversible low-grade acinar cell

apoptosis in all groups with higher serum amylase at the high dose of 150 mg/kg/day in the 28-day study, and increases in amylase and lipase in a small number of animals at 75 mg/kg/day in the 13-week study.

Signs indicative of CNS toxicity (such as tremors and/or convulsions), and histopathological findings of white matter vacuolation in the thalamus were observed in rats at a dose of 60 mg/kg/day for females and 120 mg/kg/day for males in a 28-day toxicity study (at doses ≥ 2.2 times the human exposure based on AUC at the 400 mg twice daily clinical dose). Additionally, results from a 13-week rat toxicity study reproduced the CNS effects and histopathological findings in the brain, and also demonstrated that the CNS effects and brain lesions were reversible. No signs of CNS toxicity or brain abnormalities were observed in cynomolgus monkey studies.

Slight changes in serum liver enzymes (ALT, AST, and/or SDH) were observed in several different studies in rats and monkeys. These changes were restricted to highly variable, minimal-to-mild elevations lacking a clear dose response. These liver enzyme elevations were mostly observed in the absence of any histological correlate within the liver, with the exception of a 13-week monkey study, which showed a reversible, minimal-to-mild subcapsular neutrophilic infiltration associated with single cell necrosis in males at 75 mg/kg/day.

Histopathologic changes were observed in the kidneys in a 28-day monkey study where mild-to-moderate deposits of amphophilic, crystalline-like material surrounded by multinucleated giant cells within the renal interstitium and/or tubular lumen were present at a dose of 75 mg/kg/day and higher. However, in a 13-week monkey study, renal precipitates or kidney toxicity was not observed at any doses tested (up to 75 mg/kg/day). Follow-up investigations on the identity of the crystalline-like material indicated that the material is not capmatinib or its metabolites, but rather calcium phosphate precipitates.

No effects on male and female reproductive organs occurred in general toxicology studies conducted in rats and monkeys at doses resulting in exposures of up to approximately 3.6 times the human exposure based on AUC at the 400 mg twice daily clinical dose.

Safety pharmacology

Safety pharmacology studies with capmatinib indicated no significant effects on CNS and respiratory functions in rats, and no effects on cardiovascular function in monkeys. Capmatinib inhibited hERG potassium current by 50% at 18.7 microM.

Carcinogenicity and mutagenicity

Carcinogenicity studies with capmatinib have not been conducted.

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.

Photosensitivity

In vitro and *in vivo* photosensitization assays with capmatinib suggested that capmatinib has the potential for photosensitization. The no-observed-adverse-effect-level (NOAEL) for *in vivo* photosensitization was 30 mg/kg/day (C_{max} of

14,000 ng/mL), about 2.9 times the human C_{max} at the 400 mg twice daily clinical dose.

Reproductive toxicity

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).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Mannitol
Crospovidone
Povidone
Magnesium stearate
Colloidal anhydrous silica
Sodium laurilsulfate

Film-coating

Tabrecta 150 mg film-coated tablets

Hypromellose
Titanium dioxide (E171)
Macrogol

Talc
Iron oxide, yellow (E172)
Iron oxide, red (E172)
Iron oxide, black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

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 containing 60 or 120 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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White City Place

195 Wood Lane

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8 MARKETING AUTHORISATION NUMBER(S)

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10 DATE OF REVISION OF THE TEXT

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