1. NAME OF THE MEDICINAL PRODUCT

Tabrecta (150 mg film-coated tablets)
Tabrecta (200 mg film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tabrecta 150 mg film-coated tablets

Each film-coated tablet contains 150 mg of capmatinib (as capmatinib dihydrochloride monohydrate).

Tabrecta 200 mg film-coated tablets

Each film-coated tablet contains 200 mg of capmatinib (as capmatinib dihydrochloride monohydrate).

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 beveled edges, unscored, debossed with 'DU' on one side and 'NVR' on the other side.

Tabrecta 200 mg film-coated tablets

Yellow, ovaloid, curved film-coated tablet with beveled 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 metastatic non-small cell lung cancer (NSCLC) with a MET exon 14 skipping mutation (see section 5.1).

4.2 Posology and method of administration

Select patients for treatment with Tabrecta based on the presence of a mutation that leads to MET exon 14 skipping in tumor or plasma specimens. If a MET exon 14 skipping mutation is not detected in a plasma specimen, tumor tissue should be tested if feasible.

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

Dose modifications
The recommended dose reductions for the management of adverse reactions are listed in Table 1.

Table 1: Recommended Tabrecta Dose Reductions for Adverse Reactions

Dose reduction	Dose and schedule
First	300 mg orally twice daily
Second	200 mg orally twice daily

Permanently discontinue Tabrecta in patients who are unable to tolerate 200 mg orally twice daily.

The recommended dosage modifications of Tabrecta for adverse reactions are provided in Table 2.

Table 2: Recommended Tabrecta Dosage Modifications for Adverse Reactions

Adverse reaction	Severity	Dosage modification
Interstitial Lung Disease (ILD)/Pneumonitis *(see section 4.4)*	Any grade	Permanently discontinue Tabrecta.
Increased ALT and/or AST without increased total bilirubin *(see section 4.4)*	Grade 3	Withhold Tabrecta until recovery to baseline ALT/AST. If recovered to baseline within 7 days, then resume Tabrecta at the same dose; otherwise resume Tabrecta at a reduced dose.
	Grade 4	Permanently discontinue Tabrecta.
Increased ALT and/or AST with increased total bilirubin in the absence of cholestasis or hemolysis *(see section 4.4)*	ALT and/or AST greater than 3 times ULN with total bilirubin greater than 2 times ULN	Permanently discontinue Tabrecta.
Increased total bilirubin without concurrent increased ALT and/or AST *(see section 4.4)*	Grade 2	Withhold Tabrecta until recovery to baseline bilirubin. If recovered to baseline within 7 days, then resume Tabrecta at the same dose; otherwise resume Tabrecta at a reduced dose.
	Grade 3	Withhold Tabrecta until recovery to baseline bilirubin. If recovered to baseline within 7 days, then resume Tabrecta at a reduced dose; otherwise permanently discontinue Tabrecta.
	Grade 4	Permanently discontinue Tabrecta.
Other Adverse Reactions *(see section 4.8)*	Grade 2	Maintain dose level. If intolerable, consider withholding Tabrecta until resolved, then resume Tabrecta at a reduced dose.
	Grade 3	Withhold Tabrecta until resolved, then resume Tabrecta at a reduced dose.
	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).

Special populations
Pediatric Use
Safety and effectiveness of Tabrecta in pediatric patients have not been established.

Geriatric Use
In GEOMETRY mono-1, 61% of the 373 patients were 65 years or older and 18% were 75 years or older. No overall differences in the safety or effectiveness were observed between these patients and younger patients.

Renal Impairment
No dosage adjustment is recommended in patients with mild (baseline creatinine clearance [CLcr] 60 to 89 mL/min by Cockcroft-Gault) or moderate renal impairment (CLcr 30 to 59 mL/min) (see section 5.2). Tabrecta has not been studied in patients with severe renal impairment (CLcr 15 to 29 mL/min).

Method of administration

Swallow Tabrecta tablets whole. Do not break, crush or chew the tablets.
If a patient misses or vomits a dose, instruct the patient not to make up the dose, but to take the next dose at its scheduled time.

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, occurred in patients treated with Tabrecta (see section 4.8). ILD/pneumonitis occurred in 4.8% of patients treated with Tabrecta in GEOMETRY mono-1, with 1.9% of patients experiencing Grade 3 ILD/pneumonitis and one patient experiencing death (0.3%). Nine patients (2.4%) discontinued Tabrecta due to ILD/pneumonitis. The median time-to-onset of Grade 3 or higher ILD/pneumonitis was 1.8 months (range: 0.2 months to 1.7 years).

Monitor for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold Tabrecta in patients with suspected ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis are identified (see section 4.2).

Hepatotoxicity

Hepatotoxicity occurred in patients treated with Tabrecta (see section 4.8). Increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST) occurred in 15% of patients treated with Tabrecta in GEOMETRY mono-1. Grade 3 or 4 increased ALT/AST occurred in 7% of patients. Three patients (0.8%) discontinued Tabrecta due to increased ALT/AST. The median time-to-onset of Grade 3 or higher increased ALT/AST was 1.8 months (range: 0.5 to 46.4 months).

Monitor liver function tests (including ALT, AST, and total bilirubin) prior to the start of Tabrecta, 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 increased transaminases or bilirubin. Based on the severity of the adverse reaction, 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 drug 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.

Risk of Photosensitivity

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

Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, Tabrecta can cause fetal harm when administered to a pregnant woman. Oral administration of capmatinib to pregnant rats and rabbits during the period of organogenesis resulted in malformations at exposures less than the human exposure based on area under the curve (AUC) at the 400 mg twice daily clinical dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Tabrecta and for 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Tabrecta and for 1 week after the last dose (see section 4.6)

4.5 Interaction with other medicinal products and other forms of interaction

Effect of Other Drugs on Tabrecta

Strong CYP3A Inhibitors
Coadministration of Tabrecta with a strong CYP3A inhibitor increased capmatinib exposure, which may increase the incidence and severity of adverse reactions of Tabrecta (see section 5.2). Closely monitor patients for adverse reactions during coadministration of Tabrecta with strong CYP3A inhibitors.

Strong and Moderate CYP3A Inducers
Coadministration of Tabrecta with a strong CYP3A inducer decreased capmatinib exposure. Coadministration of Tabrecta with a moderate CYP3A inducer may also decrease capmatinib exposure. Decreases in capmatinib exposure may decrease Tabrecta anti-tumor activity (see section 5.2). Avoid coadministration of Tabrecta with strong and moderate CYP3A inducers.

Effect of Tabrecta on Other Drugs

CYP1A2 Substrates
Coadministration of Tabrecta increased the exposure of a CYP1A2 substrate, which may increase the adverse reactions of these substrates (see section 5.2). If coadministration is unavoidable between

Tabrecta and CYP1A2 substrates where minimal concentration changes may lead to serious adverse reactions, decrease the CYP1A2 substrate dosage in accordance with the approved prescribing information.

P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) Substrates
Coadministration of Tabrecta increased the exposure of a P-gp substrate and a BCRP substrate, which may increase the adverse reactions of these substrates (see section 5.2). If coadministration is unavoidable between Tabrecta and P-gp or BCRP substrates where minimal concentration changes may lead to serious adverse reactions, decrease the P-gp or BCRP substrate dosage in accordance with the approved prescribing information.

MATE1 and MATE2K Substrates
Coadministration of Tabrecta may increase the exposure of MATE1 and MATE2K substrates, which may increase the adverse reactions of these substrates (see section 5.2). If coadministration is unavoidable between Tabrecta and MATE1 or MATE2K substrates where minimal concentration changes may lead to serious adverse reactions, decrease the MATE1 or MATE2K substrate dosage in accordance with the approved prescribing information.

4.6 Fertility, pregnancy and lactation

Pregnancy
Risk Summary
Based on findings from animal studies and its mechanism of action (see section 5.1), Tabrecta can cause fetal harm when administered to a pregnant woman. There are no available data on Tabrecta use in pregnant women. Oral administration of capmatinib to pregnant rats and rabbits during the period of organogenesis resulted in malformations at maternal exposures less than the human exposure based on AUC at the 400 mg twice daily clinical dose (see Data). Advise pregnant women of the potential risk to a fetus.

Data
Animal Data
In rats, maternal toxicity (reduced body weight gain and food consumption) occurred at 30 mg/kg/day (approximately 1.4 times the human exposure based on AUC at the 400 mg twice daily clinical dose). 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, and narrowed or small tongue) at doses of ≥ 10 mg/kg/day (approximately 0.6 times the human exposure based on AUC at the 400 mg twice daily clinical dose).

In rabbits, no maternal effects were detected at doses up to 60 mg/kg/day (approximately 1.5 times the human exposure based on AUC at the 400 mg twice daily clinical dose). Fetal effects included small lung lobe at ≥ 5 mg/kg/day (approximately 0.016 times the human exposure based on AUC at the 400 mg twice daily clinical dose), 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.

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

Females and Males of Reproductive Potential
Based on animal data, Tabrecta can cause malformations at doses less than the human exposure based on AUC at the 400 mg twice daily clinical dose (see Data).

Pregnancy Testing
Verify pregnancy status for females of reproductive potential prior to starting treatment with Tabrecta.

Contraception
Females
Advise females of reproductive potential to use effective contraception during treatment with Tabrecta and for 1 week after the last dose.

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

4.7 Effects on ability to drive and use machines

No relevant studies have been conducted. Caution is advised when driving and using machines as taking Tabrecta may cause nausea or fatigue. (see section 4.8).

4.8 Undesirable effects

The following clinically significant adverse reactions are described elsewhere in the labeling:
- ILD/Pneumonitis (see section 4.4)
- Hepatotoxicity (see section 4.4)
- Pancreatic toxicity (see section 4.4)
- Hypersensitivity reactions (see section 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.

Metastatic Non-Small Cell Lung Cancer
The safety of Tabrecta was evaluated in GEOMETRY mono-1 (see section 5.1). Patients received Tabrecta 400 mg orally twice daily until disease progression or unacceptable toxicity (N=373). Among patients who received Tabrecta, 37% were exposed for at least 6 months and 22% were exposed for at least one year.

Serious adverse reactions occurred in 53% of patients who received Tabrecta. Serious adverse reactions in ≥ 2% of patients included dyspnea (7%), pneumonia (7%), pleural effusion (4.3%), musculoskeletal pain (3.8%), general physical health deterioration (2.9%), ILD/pneumonitis (2.7%), edema (2.4%), and vomiting (2.4%). Fatal adverse reactions occurred in 0.5% of patients who received Tabrecta, including pneumonitis (0.3%) and death, not otherwise specified (0.3%).

Permanent discontinuation of Tabrecta due to an adverse reaction occurred in 17% of patients. The most frequent adverse reactions (≥ 1%) leading to permanent discontinuati**o**n of Tabrecta were ILD/pneumonitis (2.4%), edema (2.4%), fatigue (1.3%), and pneumonia (1.1%).

Dose interruptions due to an adverse reaction occurred in 57% of patients who received Tabrecta. Adverse reactions requiring dosage interruption in > 2% of patients who received Tabrecta included edema, increased blood creatinine, nausea, increased lipase, vomiting, increased ALT, dyspnea, pneumonia, fatigue, increased amylase, increased AST, musculoskeletal pain, abdominal pain, and increased blood bilirubin.

Dose reductions due to an adverse reaction occurred in 26% of patients who received Tabrecta. Adverse reactions requiring dosage reductions in > 2% of patients who received Tabrecta included edema, increased ALT and increased blood creatinine.

The most common adverse reactions (≥ 20%) in patients who received Tabrecta were edema, nausea, musculoskeletal pain, fatigue, vomiting, dyspnea, cough, and decreased appetite.

Table 3 summarizes the adverse reactions in GEOMETRY mono-1.

Table 3: Adverse Reactions (≥ 10%) in Patients Who Received Tabrecta in GEOMETRY mono-1

Adverse reactions	Tabrecta (N = 373)	
	Grades 1 to 4 (%)	Grades 3 to 4 (%)
General disorders and administration-site conditions		
Edema[a]	59	13
Musculoskeletal pain[b]	40	4.3
Fatigue[c]	34	8
Pyrexia[d]	14	0.8
Weight decreased	11	0.5
Gastrointestinal disorders		
Nausea	46	2.4
Vomiting	28	2.4
Constipation	19	0.8
Diarrhea	19	0.5
Respiratory, thoracic, and mediastinal disorders		
Dyspnea	25	7
Cough[e]	21	0.5
Pneumonia[f]	13	6
Metabolism and nutrition disorders		
Decreased appetite	21	1.1
Skin and subcutaneous tissue disorders		
Rash[g]	13	0.5
Nervous system disorders		
Dizziness[h]	13	0.5

[a] Edema includes edema peripheral, generalized edema, face edema, edema, localized edema, edema genital, eyelid edema, peripheral swelling, scrotal edema, and penile edema.
[b] Musculoskeletal pain includes arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, pain in jaw, spinal pain.[c] Fatigue includes fatigue and asthenia.
[d] Pyrexia includes pyrexia and body temperature increased.
[e] Cough includes cough, upper airway cough syndrome, and productive cough.
[f] Pneumonia includes pneumonia aspiration, pneumonia, pneumonia influenzal, pneumonia bacterial, lower respiratory tract infection, and lung abscess.
[g] Rash includes rash, dermatitis acneiform, rash maculo-papular, eczema, erythema multiforme, rash macular, dermatitis, rash erythematous, rash pustular, dermatitis bullous, and rash vesicular.
[h] Dizziness includes dizziness, vertigo, and vertigo positional.

Clinically relevant adverse reactions occurring in < 10% of patients treated with Tabrecta included pruritus (allergic pruritis), ILD/pneumonitis, cellulitis, acute kidney injury (including renal failure), urticaria, and acute pancreatitis.

Table 4 summarizes the laboratory abnormalities in GEOMETRY mono-1.

Table 4: Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in Patients Who Received Tabrecta in GEOMETRY mono-1

Laboratory abnormalities	Tabrecta[a]	
	Grades 1 to 4 (%)	Grades 3 to 4 (%)
Chemistry		
Decreased albumin	72	1.9
Increased creatinine	65	0.5
Increased alanine aminotransferase	39	9
Increased amylase	34	4.7
Increased alkaline phosphatase	32	0.6
Increased gamma-glutamyltransferase	30	6
Increased lipase	29	9
Increased aspartate aminotransferase	28	6
Decreased phosphate	26	4.4
Increased potassium	25	4.1
Decreased sodium	24	6
Decreased glucose	23	0.3
Hematology		
Decreased lymphocytes	45	14
Decreased leukocytes	25	1.7
Decreased hemoglobin	24	2.8

[a] The denominator used to calculate the rate varied from 359 to 364 based on the number of patients with a baseline value and at least one post-treatment value.

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.

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).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Capmatinib is a kinase inhibitor that targets MET, including the mutant variant produced by exon 14 skipping. MET exon 14 skipping results in a protein with a missing regulatory domain that reduces its negative regulation leading to increased downstream MET signaling. Capmatinib inhibited cancer cell growth driven by a mutant MET variant lacking exon 14 at clinically achievable concentrations and demonstrated anti-tumor activity in murine tumor xenograft models derived from human lung tumors with either a mutation leading to MET exon 14 skipping or MET amplification. Capmatinib inhibited the phosphorylation of MET triggered by binding of hepatocyte growth factor or by MET amplification, as well as MET-mediated phosphorylation of downstream signaling proteins and proliferation and survival of MET-dependent cancer cells.

Exposure-Response
Capmatinib exposure-response relationships and the time course of pharmacodynamics response are unknown.

Cardiac Electrophysiology
No large mean increase in QTc (i.e. > 20 ms) was detected following treatment with Tabrecta at the recommended dosage of 400 mg orally twice daily.

Clinical efficacy and safety

Metastatic NSCLC with a Mutation that Leads to MET Exon 14 Skipping
The efficacy of Tabrecta was evaluated in GEOMETRY mono-1, a multicenter, non-randomized, open-label, multi-cohort study (NCT02414139). Eligible patients were required to have NSCLC with a mutation that leads to MET exon 14 skipping, epidermal growth factor receptor (EGFR) wild-type and anaplastic lymphoma kinase (ALK) negative status, and at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients with symptomatic CNS metastases, clinically significant uncontrolled cardiac disease, or who received treatment with any MET or hepatocyte growth factor (HGF) inhibitor were not eligible for the study.

Out of the 97 patients enrolled in GEOMETRY mono-1 following the central confirmation of MET exon 14 skipping by a RNA-based clinical trial assay, 78 patient samples were retested with the FDA-approved FoundationOne® CDx (22 treatment-naïve and 56 previously treated patients) to detect mutations that lead to MET exon 14 skipping. Out of 78 samples retested with FoundationOne® CDx, 73 samples were evaluable (20 treatment-naïve and 53 previously treated patients), 72 (20 treatment-naïve and 52 previously treated patients) of which were confirmed to have a mutation that leads to MET exon 14 skipping, demonstrating an estimated positive percentage agreement of 99% (72/73) between the clinical trial assay and the FDA-approved assay.

Patients received Tabrecta 400 mg orally twice daily until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall response rate (ORR) as determined by a Blinded Independent Review Committee (BIRC) according to RECIST 1.1. An additional efficacy outcome measure was duration of response (DOR) by BIRC.

The efficacy population included 60 treatment-naïve patients and 100 previously treated patients. The median age was 71 years (range: 48 to 90 years); 61% female; 77% White; 25% had Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 and 74% had ECOG PS 1; 61% never smoked; 83% had adenocarcinoma; and 16% had CNS metastases. Amongst previously treated patients, 81% received one, 16% received two and 3% received three prior lines of systemic therapy. Amongst previously treated patients, 86% received prior platinum-based chemotherapy.

Efficacy results are presented in Table 5.

Table 5: Efficacy Results for Treatment-Naïve and Previously Treated Patients in GEOMETRY mono-1

Efficacy parameters	**Treatment-Naïve N = 60**	**Previously treated N = 100**
Overall response rate[a,b] (95% CI)[c]	68% (55, 80)	44% (34, 54)
Complete response	5%	0
Partial response	63%	44%
Duration of response (DOR)[a]		
Median (months) (95% CI)[d]	16.6 (8.4, 22.1)	9.7 (5.6, 13.0)
Patients % with DOR ≥ 12 months	49%	36%

Abbreviations: CI = Confidence interval

[a] Blinded Independent Review Committee (BIRC) review.

[b] Confirmed response.

[c] Clopper and Pearson exact binomial 95% CI.
[d] Based on Kaplan-Meier estimate

5.2 Pharmacokinetic properties

Capmatinib exposure (AUC_{0-12h} and C_{max}) increased approximately proportionally over a dose range of 200 mg (0.5 times the recommended dosage) to 400 mg. Capmatinib reached steady-state by day 3 following twice daily dosing, with a mean (% coefficient of variation [%CV]) accumulation ratio of 1.5 (41%).

Absorption

After administration of Tabrecta 400 mg orally in patients with cancer, capmatinib peak plasma concentrations (C_{max}) were reached in approximately 1 to 2 hours (T_{max}). The absorption of capmatinib after oral administration is estimated to be greater than 70%.

Effect of Food
A high-fat meal (containing approximately 1000 calories and 50% fat) in healthy subjects increased capmatinib AUC_{0-INF} by 46% with no change in C_{max} compared to under fasted conditions. A low-fat meal (containing approximately 300 calories and 20% fat) in healthy subjects had no clinically meaningful effect on capmatinib exposure. When capmatinib was administered at 400 mg orally twice daily in cancer patients, exposure (AUC_{0-12h}) was similar after administration of capmatinib with food and under fasted conditions.

Distribution

Capmatinib plasma protein binding is 96%, independent of capmatinib concentration. The apparent mean volume of distribution at steady-state is 164 L.

The blood-to-plasma ratio was 1.5, but decreased at higher concentrations to 0.9.

Elimination

The effective elimination half-life of capmatinib is 6.5 hours. The mean (%CV) steady-state apparent clearance of capmatinib is 24 L/hr (82%).

Metabolism
Capmatinib is primarily metabolized by CYP3A4 and aldehyde oxidase.

Excretion
Following a single oral administration of radiolabeled-capmatinib to healthy subjects, 78% of the total radioactivity was recovered in feces with 42% as unchanged and 22% was recovered in urine with negligible as unchanged.

Specific Populations
No clinically significant effects on the pharmacokinetic parameters of capmatinib were identified for the following covariates assessed: age (26 to 90 years), sex, race (White, Asian, Native American, Black, unknown), body weight (35 to 131 kg), mild to moderate renal impairment (baseline CLcr 30 to 89 mL/min by Cockcroft-Gault) and mild, moderate or severe hepatic impairment (Child-Pugh classification). The effect of severe renal impairment (baseline CLcr 15 to 29 mL/min) on capmatinib pharmacokinetics has not been studied.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches
Strong CYP3A Inhibitors: Coadministration with itraconazole (a strong CYP3A inhibitor) increased capmatinib $AUC_{0\text{-}INF}$ by 42% with no change in capmatinib C_{max}.

Strong CYP3A Inducers: Coadministration with rifampicin (a strong CYP3A inducer) decreased capmatinib $AUC_{0\text{-}INF}$ by 67% and decreased C_{max} by 56%.

Moderate CYP3A Inducers: Coadministration with efavirenz (a moderate CYP3A inducer) was predicted to decrease capmatinib $AUC_{0\text{-}12h}$ by 44% and decrease C_{max} by 34%.

Proton Pump Inhibitors: Coadministration with rabeprazole (a proton pump inhibitor) decreased capmatinib $AUC_{0\text{-}INF}$ by 25% and decreased C_{max} by 38%.

Substrates of CYP Enzymes: Coadministration of capmatinib increased caffeine (a CYP1A2 substrate) $AUC_{0\text{-}INF}$ by 134% with no change in its C_{max}. Coadministration of capmatinib had no clinically meaningful effect on exposure of midazolam (a CYP3A substrate).

P-gp Substrates: Coadministration of capmatinib increased digoxin (a P-gp substrate) $AUC_{0\text{-}INF}$ by 47% and increased C_{max} by 74%.

BCRP Substrates: Coadministration of capmatinib increased rosuvastatin (a BCRP substrate) $AUC_{0\text{-}INF}$ by 108% and increased C_{max} by 204%.

In Vitro Studies
Transporter Systems: Capmatinib is a substrate of P-gp, but not a substrate of BCRP or MRP2. Capmatinib reversibly inhibits MATE1 and MATE2K, but does not inhibit OATP1B1, OATP1B3, OCT1, OAT1, OAT3, or MRP2.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were not conducted with capmatinib. Capmatinib was not mutagenic in an *in vitro* bacterial reverse mutation assay and did not cause chromosomal aberrations in an *in vitro* chromosome aberration assay in human peripheral blood lymphocytes. Capmatinib was not clastogenic in an *in vivo* bone marrow micronucleus test in rats.

Dedicated fertility studies were not conducted with capmatinib. 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.

Animal Toxicology and/or Pharmacology

In rats, capmatinib administration resulted in vacuolation of white matter of the brain in both 4- and 13-week studies at doses $\geq$ 2.2 times the human exposure (AUC) at the 400 mg twice daily clinical dose. In some cases, the brain lesions were associated with early death and/or convulsions or tremors. Concentrations of capmatinib in the brain tissue of rats was approximately 9% of the corresponding concentrations in plasma.

In vitro and *in vivo* assays demonstrated that capmatinib has some potential for photosensitization; however, the no-observed-adverse-effect level for *in vivo* photosensitization was 30 mg/kg/day (C_{max} of 14000 ng/mL), about 2.9 times the human C_{max} at the 400 mg twice daily clinical dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Cellulose microcrystalline
Crospovidone
Magnesium stearate
Mannitol
Povidone
Silica colloidal anhydrous
Sodium laurilsulfate

Film coating

Hypromellose
Iron oxide, black (E172)
Iron oxide, red (E172)
Iron oxide, yellow (E172)
Titanium dioxide (E171)
Macrogol 4000
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30ºC. Protect from moisture. Store in the original packaging.

6.5 Nature and contents of container

PVC/PCTFE/alu (polyvinylchloride/polychlorotrifluoroethylene/aluminium) blister containing 12 film-coated tablets.

Tabrecta 150 mg film-coated tablets

Packs containing 60 or 120 film-coated tablets.

Tabrecta 200 mg film-coated tablets

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

Novartis (Thailand) Limited
689 Bhiraj Tower at EmQuartier 25th fl.,
Sukhumvit Road, North Klongton, Vadhana,
Bangkok 10110
THAILAND

8. MARKETING AUTHORISATION NUMBER(S)

Tabrecta (150 mg film-coated tablets) – Reg. no. 1C 15163/64 (NC)
Tabrecta (200 mg film-coated tablets) – Reg. no. 1C 15164/64 (NC)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 December 2021

10. DATE OF REVISION OF THE TEXT

Jan 2023