

TABRECTA 150 MG, TABRECTA 200 MG

Film coated tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

TABRECTA 150 MG: Each film-coated tablet contains 150 mg capmatinib (as capmatinib dihydrochloride monohydrate).

TABRECTA 200 MG: Each film-coated tablet contains 200 mg capmatinib (as capmatinib dihydrochloride monohydrate).

For the full list of excipients, see section 16.

1 INDICATIONS AND USAGE

TABRECTA is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an approved test.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

2.2 Select patients for treatment with TABRECTA based on the presence of a mutation that leads to MET exon 14 skipping in tumor specimens [see *Clinical Studies (14)*]. Recommended Dosage

The recommended dosage of TABRECTA is 400 mg orally twice daily with or without food, adequate hydration is recommended. 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.

2.3 Dosage Modifications for Adverse Reactions

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 <i>[see Warnings and Precautions (5.1)]</i>	Any grade	Permanently discontinue TABRECTA.

Increased ALT and/or AST without increased total bilirubin <i>[see Warnings and Precautions (5.2)]</i>	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.

Adverse Reaction	Severity	Dosage Modification
Increased ALT and/or AST with increased total bilirubin in the absence of cholestasis or hemolysis <i>[see Warnings and Precautions (5.2)]</i>	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 <i>[see Warnings and Precautions (5.2)]</i>	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 <i>[see Adverse Reactions (6.1)]</i>	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).

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 150 mg: pale orange brown, ovaloid, curved film-coated with beveled edges, unscored, debossed with ‘DU’ on one side and ‘NVR’ on the other side
- 200 mg: yellow, ovaloid, curved film-coated with beveled edges, unscored, debossed with ‘LO’ on one side and ‘NVR’ on the other side

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 16.

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease (ILD)/Pneumonitis

ILD/pneumonitis, which can be fatal, occurred in patients treated with TABRECTA [see *Adverse Reactions (6.1)*]. ILD/pneumonitis occurred in 4.5% of patients treated with TABRECTA in GEOMETRY mono-1, with 1.8% of patients experiencing Grade 3 ILD/pneumonitis and one patient experiencing death (0.3%). Eight patients (2.4%) discontinued TABRECTA due to ILD/pneumonitis. The median time-to-onset of Grade 3 or higher ILD/pneumonitis was 1.4 months (range: 0.2 months to 1.2 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 *Dosage and Administration (2.3)*].

5.2 Hepatotoxicity

Hepatotoxicity occurred in patients treated with TABRECTA [see *Adverse Reactions (6.1)*]. Increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST) occurred in 13% of patients treated with TABRECTA in GEOMETRY mono-1. Grade 3 or 4 increased ALT/AST occurred in 6% of patients. Three patients (0.9%) discontinued TABRECTA due to increased ALT/AST. The median time-to-onset of Grade 3 or higher increased ALT/AST was 1.4 months (range: 0.5 to 4.1 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 *Dosage and Administration (2.3)*].

5.3 Risk of Photosensitivity

Based on findings from animal studies, there is a potential risk of photosensitivity reactions with TABRECTA [see *Nonclinical Toxicology (13.2)*]. 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.

5.4 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 *Use in Specific Populations (8.1, 8.3)*].

6 ADVERSE REACTIONS

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

- ILD/Pneumonitis [see *Warnings and Precautions (5.1)*]
- Hepatotoxicity [see *Warnings and Precautions (5.2)*]

6.1 Clinical Trials Experience

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

Metastatic Non-Small Cell Lung Cancer

The safety of TABRECTA was evaluated in GEOMETRY mono-1 [see *Clinical Studies (14)*]. Patients received TABRECTA 400 mg orally twice daily until disease progression or unacceptable toxicity (N=334). Among patients who received TABRECTA, 31% were exposed for at least 6 months and 16% were exposed for at least one year.

Serious adverse reactions occurred in 51% of patients who received TABRECTA. Serious adverse reactions in $\geq 2\%$ of patients included dyspnea (7%), pneumonia (4.8%), pleural effusion (3.6%), general physical health deterioration (3%), vomiting (2.4%), and nausea (2.1%). A fatal adverse reaction occurred in one patient (0.3%) due to pneumonitis.

Permanent discontinuation of TABRECTA due to an adverse reaction occurred in 16% of patients. The most frequent adverse reactions ($\geq 1\%$) leading to permanent discontinuation of TABRECTA were peripheral edema (1.8%), pneumonitis (1.8%), and fatigue (1.5%).

Dose interruptions due to an adverse reaction occurred in 54% of patients who received TABRECTA. Adverse reactions requiring dosage interruption in $> 2\%$ of patients who received TABRECTA included peripheral edema, increased blood creatinine, nausea, vomiting, increased lipase, increased ALT, dyspnea, increased amylase, increased AST, increased blood bilirubin, fatigue, and pneumonia.

Dose reductions due to an adverse reaction occurred in 23% of patients who received TABRECTA. Adverse reactions requiring dosage reductions in $> 2\%$ of patients who received TABRECTA included peripheral edema, increased ALT, increased blood creatinine, and nausea.

The most common adverse reactions ($\geq 20\%$) in patients who received TABRECTA were peripheral edema, nausea, fatigue, vomiting, dyspnea, and decreased appetite.

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

Table 3: Adverse Reactions ($\geq 10\%$) in Patients Who Received TABRECTA in GEOMETRY mono-1

Adverse Reactions	TABRECTA (N = 334)	
	Grades 1 to 4 (%)	Grades 3 to 4 ^a (%)
General disorders and administration-site conditions		
Peripheral edema ^b	52	9
Fatigue ^c	32	8
Non-cardiac chest pain ^d	15	2.1
Back pain	14	0.9
Pyrexia ^e	14	0.6
Weight decreased	10	0.6
Gastrointestinal disorders		
Nausea	44	2.7
Vomiting	28	2.4
Constipation	18	0.9
Diarrhea	18	0.3
Respiratory, thoracic, and mediastinal disorders		
Dyspnea	24	7 ^a
Cough	16	0.6
Metabolism and nutrition disorders		
Decreased appetite	21	0.9

^a Only includes Grade 3 adverse reactions with exception of dyspnea. Grade 4 dyspnea was reported in 0.6% of patients.

^b Peripheral edema includes peripheral swelling, peripheral edema, and fluid overload.

^c Fatigue includes fatigue and asthenia.

^d Non-cardiac chest pain includes chest discomfort, musculoskeletal chest pain, non-cardiac chest pain, and chest pain.

^e Pyrexia includes pyrexia and body temperature increased.

Clinically relevant adverse reactions occurring in $< 10\%$ of patients treated with TABRECTA included pruritus (allergic and generalized), 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	68	1.8
Increased creatinine	62	0.3
Increased alanine aminotransferase	37	8
Increased alkaline phosphatase	32	0.3
Increased amylase	31	4.4
Increased gamma-glutamyltransferase	29	7
Increased lipase	26	7
Increased aspartate aminotransferase	25	4.9
Decreased sodium	23	6
Decreased phosphate	23	4.6
Increased potassium	23	3.1
Decreased glucose	21	0.3
Hematology		
Decreased lymphocytes	44	14
Decreased hemoglobin	24	2.8
Decreased leukocytes	23	0.9

^aThe denominator used to calculate the rate varied from 320 to 325 based on the number of patients with a baseline value and at least one post-treatment value.

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il/>

7 DRUG INTERACTIONS

7.1 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 *Clinical Pharmacology (12.3)*]. 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 *Clinical Pharmacology (12.3)*]. Avoid coadministration of TABRECTA with strong and moderate CYP3A inducers.

7.2 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 *Clinical Pharmacology (12.3)*]. 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 *Clinical Pharmacology (12.3)*]. 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 *Clinical Pharmacology (12.3)*]. 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action [see *Clinical Pharmacology (12.1)*], 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.

8.2 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.

8.3 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 *Use in Specific Populations (8.1)*].

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.

8.4 Pediatric Use

Safety and effectiveness of TABRECTA in children and adolescents under the age of 18 years have not been established.

8.5 Geriatric Use

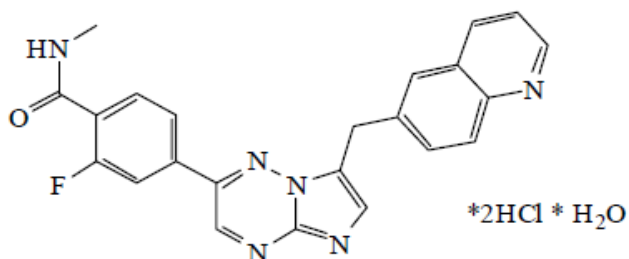
In GEOMETRY mono-1, 57% of the 334 patients were 65 years or older and 16% were 75 years or older. No overall differences in the safety or effectiveness were observed between these patients and younger patients.

8.6 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 *Clinical Pharmacology* (12.3)]. TABRECTA has not been studied in patients with severe renal impairment (CLcr 15 to 29 mL/min).

11 DESCRIPTION

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 C₂₃H₂₁Cl₂FN₆O₂. 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 dihydrochloride monohydrate is shown below:



Capmatinib dihydrochloride monohydrate is a yellow powder with a pK_{a1} of 0.9 (calculated) and pK_{a2} 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.

TABRECTA is supplied for oral use as ovaloid, curved film-coated tablets with beveled edges, unscored containing 150 mg (pale orange brown color) or 200 mg (yellow color) capmatinib (equivalent to 183.00 mg or 244.00 mg respectively of capmatinib dihydrochloride monohydrate). Each tablet strength contains colloidal silicon dioxide; crospovidone; magnesium stearate; mannitol; microcrystalline cellulose; povidone; and sodium lauryl sulfate as inactive ingredients.

The 150 mg tablet coating contains ferric oxide, red; ferric oxide, yellow; ferrosferric oxide; hypromellose; polyethylene glycol (PEG) 4000; talc; and titanium dioxide. The 200 mg tablet coating contains ferric oxide, yellow; hypromellose; polyethylene glycol (PEG) 4000; talc; and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 Pharmacodynamics

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.

12.3 Pharmacokinetics

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 CL_{cr} 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 CL_{cr} 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-INF} by 42% with no change in capmatinib C_{max} .

Strong CYP3A Inducers: Coadministration with rifampicin (a strong CYP3A inducer) decreased capmatinib AUC_{0-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_{0-12h} by 44% and decrease C_{\max} by 34%.

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

Substrates of CYP Enzymes: Coadministration of capmatinib increased caffeine (a CYP1A2 substrate) AUC_{0-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-INF} by 47% and increased C_{\max} by 74%.

BCRP Substrates: Coadministration of capmatinib increased rosuvastatin (a BCRP substrate) AUC_{0-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.

13 NONCLINICAL TOXICOLOGY

13.1 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.

13.2 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 ≥ 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.

14 CLINICAL STUDIES

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. Respectively, patients pre-treated with CRITZONIB were excluded.

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 28 treatment-naïve patients and 69 previously treated patients. The median age was 71 years (range: 49 to 90 years); 60% female; 75% White; 24% had Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 and 75% had ECOG PS 1; 60% never smoked; 80% had adenocarcinoma; and 12% had CNS metastases. Amongst previously treated patients, 88% received prior platinum-based chemotherapy.

Efficacy results are presented in Table 5.

Table 5: Efficacy Results in GEOMETRY mono-1

Efficacy Parameters	Treatment-Naïve N = 28	Previously Treated N = 69
Overall Response Rate^{a,b} (95% CI)^c	68% (48, 84)	41% (29, 53)
Complete Response	4%	0
Partial Response	64%	41%
Duration of Response (DOR)^a		
Median (months) (95% CI) ^d	12.6 (5.5, 25.3)	9.7 (5.5, 13.0)
Patients with DOR ≥ 12 months	47%	32%

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.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

TABRECTA (capmatinib) 150 mg and 200 mg tablets			
Strength	Description	Tablets per pack (blisters)	
150 mg	Pale orange brown, ovaloid, curved film-coated tablet with beveled edges, unscored, debossed with 'DU' on one side and 'NVR' on the other side.	120	
200 mg	Yellow, ovaloid, curved film-coated tablet with beveled edges, unscored, debossed with 'LO' on one side and 'NVR' on the other side.	120	

Storage

Do not store above 25°C. Store in original package to protect from moisture.

List of excipients

Core: microcrystalline cellulose, mannitol, crospovidone (type A), povidone (K30), magnesium stearate, colloidal silicon dioxide and sodium lauryl sulfate.

Film coating Tabrecta 150 mg: hypromellose, titanium dioxide (E171), talc, polyethylene glycol (PEG) 4000, ferric oxide yellow, ferric oxide red, ferric oxide black.

Film coating Tabrecta 200 mg: hypromellose, titanium dioxide (E171), talc, polyethylene glycol (PEG) 4000, ferric oxide yellow.

Shelf life

The expiry date of the product is indicated on the packaging materials.

18. REGISTRATION HOLDER

Novartis Israel Ltd., P.O.Box 7126, Tel Aviv.

19. REGISTRATION NUMBER

Revised in March 2022 according to MOHs guidelines.