

## **1 Tradename**

Tabrecta<sup>®</sup> 150 mg and 200 mg film-coated tablets

## **2 Description and composition**

### **Pharmaceutical form**

#### **Film-coated tablet**

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.

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

### **Active substance(s)**

Each 150 mg film-coated tablet contains 176.55 mg of capmatinib hydrochloride (anhydrous basis), which is equivalent to 150 mg of capmatinib as free base.

Each 200 mg film-coated tablet contains 235.40 mg of capmatinib hydrochloride (anhydrous basis), which is equivalent to 200 mg of capmatinib as free base.

### **Excipients**

**Tablet core:** Cellulose microcrystalline; mannitol; crospovidone; povidone; magnesium stearate; silica colloidal anhydrous; sodium laurilsulfate.

#### **Tablet coating:**

150 mg: Hypromellose; titanium dioxide (E171); macrogol 4000; talc; iron oxide, yellow (E172); iron oxide, red (E172); iron oxide, black (E172).

200 mg: Hypromellose; titanium dioxide (E171); macrogol 4000; talc; iron oxide, yellow (E172).

## **3 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.

## **4 Dosage regimen and administration**

### **Patient selection**

Patients should be selected for treatment with Tabrecta based on the presence of a MET exon 14 skipping mutation in tumor specimens using a validated test.

## Dosage regimen

### General target population

The recommended dose of Tabrecta is 400 mg orally twice daily with or without food (see section 11 Clinical pharmacology).

### Treatment duration

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

### Dose modifications for adverse drug reactions

The recommended dose reduction schedule for the management of adverse drug reactions (ADRs) based on individual safety and tolerability is listed in Table 4-1.

**Table 4-1 Tabrecta dose reduction schedule**

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

Tabrecta should be permanently discontinued in patients unable to tolerate 200 mg orally twice daily.

Recommendations for dose modifications of Tabrecta for ADRs are provided in Table 4-2.

**Table 4-2 Tabrecta dose modifications for the management of adverse drug reactions**

Adverse drug 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 4-1.
	Grade 4 (>20.0 x ULN)	Permanently discontinue Tabrecta.
Combined elevations in ALT and/or AST with concurrent total bilirubin increase, in the absence of cholestasis or hemolysis	If patient develops ALT and/or AST >3 x ULN along with total bilirubin >2 x ULN, irrespective of baseline grade	Permanently discontinue Tabrecta.

<b>Adverse drug reaction</b>	<b>Severity</b>	<b>Dose modification</b>
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 4-1.
	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 4-1, otherwise permanently discontinue Tabrecta.
	Grade 4 (>10.0 x ULN)	Permanently discontinue Tabrecta.
Other adverse drug reactions	Grade 2	Maintain dose level. If intolerable, consider temporarily withholding Tabrecta until resolved, then resume Tabrecta at a reduced dose as per Table 4-1.
	Grade 3	Temporarily withhold Tabrecta until resolved, then resume Tabrecta at a reduced dose as per Table 4-1.
	Grade 4	Permanently discontinue Tabrecta.

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

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

*Baseline = at the time of treatment initiation.*

## **Special populations**

### **Renal impairment**

No dose adjustment is necessary in patients with mild or moderate renal impairment based on population pharmacokinetic evaluations; Tabrecta has not been studied in patients with severe renal impairment (see section 11 Clinical pharmacology).

### **Hepatic impairment**

No dose adjustment is necessary in patients with mild, moderate, or severe hepatic impairment (see section 11 Clinical pharmacology).

### **Pediatric patients (below 18 years of age)**

The safety and efficacy of Tabrecta in pediatric patients have not been established.

### **Geriatric patients (65 years of age or older)**

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

## **Method of administration**

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

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

## **5 Contraindications**

None.

## **6 Warnings and precautions**

### **Interstitial lung disease (ILD)/pneumonitis**

ILD/pneumonitis, which can be fatal, has occurred in patients treated with Tabrecta (see section 7 Adverse drug reactions). Prompt investigation should be performed in any patient with new or worsening of pulmonary symptoms indicative of ILD/pneumonitis (e.g. dyspnea, 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 Dosage regimen and administration).

### **Hepatic effects**

Transaminase elevations have occurred in patients treated with Tabrecta (see section 7 Adverse drug reactions). Liver function tests (including ALT, AST, and total bilirubin) should be performed prior to the start of treatment, every 2 weeks during the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients who develop transaminase or bilirubin elevations. Based on the severity of the adverse drug reaction, temporarily withhold, dose reduce, or permanently discontinue Tabrecta (see section 4 Dosage regimen and administration).

### **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 fetotoxicity and teratogenicity. Pregnant women and females of reproductive potential should be advised of the potential risk to a fetus if Tabrecta is used during pregnancy or if the patient becomes pregnant while taking Tabrecta. Sexually-active females of reproductive potential should use effective contraception during treatment with Tabrecta and for at least 7 days after the last dose. Male patients with sexual partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms during treatment with Tabrecta and for at least 7 days after the last dose (see section 9 Pregnancy, lactation, females and males of reproductive potential).

## **Risk of photosensitivity**

Based on findings from animal studies, there is a potential risk of photosensitivity reactions with Tabrecta (see section 13 Non-clinical safety data). In GEOMETRY mono-1, it was recommended that patients use precautionary measures against ultraviolet exposure such as the use of sunscreen or protective clothing during treatment with Tabrecta. Patients should be advised to limit direct ultraviolet exposure during treatment with Tabrecta.

## **7 Adverse drug reactions**

### **Summary of the safety profile (data cut-off: 15-Apr-2019)**

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 = 334), regardless of prior treatment or MET dysregulation (mutation and/or amplification) status. The median duration of exposure to Tabrecta across all cohorts was 14.9 weeks (range: 0.4 to 177.0 weeks). Among patients who received Tabrecta, 31.1% were exposed for at least 6 months and 15.9% were exposed for at least one year.

Serious adverse events (AEs) regardless of causality were reported in 169 patients (50.6%) who received Tabrecta. Serious AEs regardless of causality in > 2% of patients included dyspnoea (6.9%), pneumonia (4.8%), pleural effusion (3.6%), general physical health deterioration (3.0%), vomiting (2.4%), and nausea (2.1%).

Ten patients (3.0%) died while on treatment with Tabrecta due to causes other than the underlying malignancy. One of these deaths was confirmed as treatment-related: pneumonitis.

Permanent discontinuation of Tabrecta due to an AE regardless of causality was reported in 54 patients (16.2%). The most frequent AEs ( $\geq 0.5\%$ ) leading to permanent discontinuation of Tabrecta were peripheral oedema (1.8%), pneumonitis (1.8%), fatigue (1.5%), ALT increased (0.9%), AST increased (0.9%), nausea (0.9%), vomiting (0.9%), blood bilirubin increased (0.6%), blood creatinine increased (0.6%), general physical health deterioration (0.6%), ILD (0.6%), organising pneumonia (0.6%), and pneumonia (0.6%).

Dose interruptions due to an adverse event regardless of causality were reported in 181 patients (54.2%) who received Tabrecta. Adverse events regardless of causality requiring dose interruption in > 2% of patients who received Tabrecta included peripheral edema (8.7%), blood creatinine increased (7.2%), nausea (5.4%), vomiting (5.4%), lipase increased (4.5%), ALT increased (3.9%), dyspnoea (3.9%), amylase increased (3.3%), AST increased (3.0%), blood bilirubin increased (2.1%), fatigue (2.1%), and pneumonia (2.1%).

Dose reductions due to an adverse event regardless of causality were reported in 76 patients (22.8%) who received Tabrecta. Adverse events regardless of causality requiring dose reductions in > 2% of patients who received Tabrecta included peripheral oedema (7.2%), ALT increased (3.0%), blood creatinine increased (2.1%), and nausea (2.1%).

The most common ADRs reported with an incidence of  $\geq 20\%$  (all Grades) in patients who received Tabrecta were peripheral oedema, nausea, fatigue, vomiting, blood creatinine increased, dyspnoea, and decreased appetite. The most common Grade 3 or 4 ADRs reported

with an incidence of  $\geq 5\%$  in patients who received Tabrecta were peripheral oedema, fatigue, dyspnoea, alanine aminotransferase increased and lipase increased.

### Tabulated summary of adverse drug reactions from clinical studies

Adverse drug reactions from clinical studies (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

**Table 7-1 Adverse drug reactions in patients (N = 334) who received Tabrecta in Study A2201 (GEOMETRY mono-1) (Data cut-off: 15-Apr-2019)**

Adverse drug reactions	All Grades n (%)	Frequency category	Grade 3/4 n (%)	Frequency category
<b>Infections and infestations</b>				
Cellulitis	9 (2.7)	Common	3 (0.9)*	Uncommon
<b>Metabolism and nutrition disorders</b>				
Decreased appetite	69 (20.7)	Very common	3 (0.9)*	Uncommon
Hypophosphataemia	21 (6.3)	Common	8 (2.4)	Common
Hyponatraemia	18 (5.4)	Common	11 (3.3)	Common
<b>Respiratory, thoracic, and mediastinal disorders</b>				
Dyspnoea	81 (24.3)	Very common	23 (6.9)	Common
Cough	54 (16.2)	Very common	2 (0.6)*	Uncommon
ILD / pneumonitis	15 (4.5)	Common	6 (1.8)*	Common
<b>Gastrointestinal disorders</b>				
Nausea	147 (44.0)	Very common	9 (2.7)*	Common
Vomiting	94 (28.1)	Very common	8 (2.4)*	Common
Diarrhoea	61 (18.3)	Very common	1 (0.3)*	Uncommon
Constipation	60 (18.0)	Very common	3 (0.9)*	Uncommon
Amylase increased	29 (8.7)	Common	12 (3.6)	Common
Lipase increased	26 (7.8)	Common	18 (5.4)	Common
Acute pancreatitis	1 (0.3)	Uncommon	1 (0.3)*	Uncommon
<b>Hepatobiliary disorders</b>				
Alanine aminotransferase increased	42 (12.6)	Very common	19 (5.7)	Common
Hypoalbuminaemia	38 (11.4)	Very common	4 (1.2)*	Common
Aspartate aminotransferase increased	29 (8.7)	Common	10 (3.0)*	Common
Blood bilirubin increased	11 (3.3)	Common	2 (0.6)*	Uncommon
<b>Skin and subcutaneous tissue disorders</b>				
Pruritus <sup>1</sup>	33 (9.9)	Common	1 (0.3)*	Uncommon
Urticaria	4 (1.2)	Common	2 (0.6)*	Uncommon
<b>Renal and urinary disorders</b>				
Blood creatinine increased	85 (25.4)	Very common	0	
Acute kidney injury <sup>2</sup>	5 (1.5)	Common	1 (0.3)*	Uncommon
<b>General disorders and administration-site conditions</b>				

Adverse drug reactions	All Grades n (%)	Frequency category	Grade 3/4 n (%)	Frequency category
Oedema peripheral <sup>3</sup>	173 (51.8)	Very common	29 (8.7)*	Common
Fatigue <sup>4</sup>	108 (32.3)	Very common	28 (8.4)*	Common
Non-cardiac chest pain <sup>5</sup>	50 (15.0)	Very common	7 (2.1)*	Common
Pyrexia <sup>6</sup>	48 (14.4)	Very common	2 (0.6)*	Uncommon
Back pain	47 (14.1)	Very common	3 (0.9)*	Uncommon
Weight decreased	34 (10.2)	Very common	2 (0.6)*	Uncommon

<sup>1</sup> Pruritus includes preferred terms (PTs) of pruritus, pruritus allergic, and pruritus generalized.

<sup>2</sup> Acute kidney injury includes PTs of acute kidney injury and renal failure.

<sup>3</sup> Oedema peripheral includes PTs of peripheral swelling, oedema peripheral, and fluid overload.

<sup>4</sup> Fatigue includes PTs of fatigue and asthenia.

<sup>5</sup> Non-cardiac chest pain includes PTs of chest discomfort, musculoskeletal chest pain, non-cardiac chest pain, and chest pain.

<sup>6</sup> Pyrexia includes PTs of pyrexia and body temperature increased.

\* No Grade 4 ADRs reported in Study A2201 (GEOMETRY mono-1).

## Description of selected adverse drug reactions (data cut-off: 15-Apr-2019)

### *ILD/pneumonitis*

Any Grade ILD/pneumonitis was reported in 15 of 334 patients (4.5%) treated with Tabrecta in Study A2201 (GEOMETRY mono-1). Grade 3 ILD/pneumonitis was reported in 6 patients (1.8%), with a fatal event of pneumonitis reported in 1 patient (0.3%). ILD/pneumonitis occurred in 8 of 161 patients (5.0%) with a history of prior radiotherapy and 7 of 173 patients (4.0%) who did not receive prior radiotherapy. Eight patients (2.4%) 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 6.0 weeks (range: 0.7 to 64.4 weeks).

### *Hepatic effects*

Any Grade ALT/AST elevations were reported in 43 of 334 patients (12.9%) treated with Tabrecta in Study A2201 (GEOMETRY mono-1). Grade 3 or 4 ALT/AST elevations were observed in 19 of 334 patients (5.7%) treated with Tabrecta. Three patients (0.9%) 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 6.1 weeks (range: 2.1 to 17.9 weeks).

## 8 Interactions

### Effect of other medicinal products on Tabrecta

#### *Strong CYP3A inhibitors*

In healthy subjects, coadministration of a single 200 mg capmatinib dose with the strong CYP3A inhibitor itraconazole (200 mg once daily for 10 days) increased capmatinib AUC<sub>inf</sub> by 42% with no change in capmatinib C<sub>max</sub> compared to administration of capmatinib alone. Coadministration of Tabrecta with a strong CYP3A inhibitor may increase the incidence and severity of adverse drug reactions of Tabrecta. Patients should be closely monitored for adverse

drug reactions during coadministration of Tabrecta with strong CYP3A inhibitors, including but not limited to, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, and voriconazole.

### ***Strong CYP3A inducers***

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

### ***Moderate CYP3A inducers***

Simulations using physiologically-based pharmacokinetic (PBPK) models predicted that coadministration of a 400 mg capmatinib dose with the moderate CYP3A inducer efavirenz (600 mg once daily for 20 days) would result in a 44% decrease in capmatinib AUC<sub>0-12h</sub> and 34% decrease in C<sub>max</sub> at steady-state compared to administration of capmatinib alone. Decreases in capmatinib exposure may decrease Tabrecta anti-tumor activity. Caution should be exercised during coadministration of Tabrecta with moderate CYP3A inducers.

### ***Agents that raise gastric pH***

Capmatinib demonstrates pH-dependent solubility and becomes poorly soluble as pH increases *in vitro*. Gastric acid reducing agents (e.g. proton pump inhibitors, H<sub>2</sub>-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 AUC<sub>inf</sub> by 25% and decreased C<sub>max</sub> by 38% compared to administration of capmatinib alone. Caution should be exercised during coadministration of Tabrecta with proton pump inhibitors. As an alternative, an H<sub>2</sub>-receptor antagonist or antacid can be taken. Tabrecta should be taken at least 3 hours before or 6 hours after an H<sub>2</sub>-receptor antagonist. Tabrecta should be taken at least 2 hours before or 2 hours after an antacid.

## **Effect of Tabrecta on other medicinal products**

### ***Substrates of CYP enzymes***

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

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

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

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

**Drug-food/drink interactions**

Tavegra can be administered with or without food (see section 4 Dosage regimen and administration and section 11 Clinical pharmacology).

**9 Pregnancy, lactation, females and males of reproductive potential**

**9.1 Pregnancy**

**Risk summary**

Based on findings from animal studies and its mechanism of action, Tavegra can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women to inform a product-associated risk. Oral administration of capmatinib to pregnant rats and rabbits during the period of organogenesis resulted in fetotoxicity and teratogenicity. Reduced fetal weights and increased incidences of fetal malformations were observed in rats and rabbits following prenatal exposure to capmatinib at or below the exposure in humans at the maximum recommended human dose (MRHD) of 400 mg twice daily based on area under the curve (AUC) (see Data). Pregnant women and females of reproductive potential should be advised of the potential risk to a fetus if Tavegra is used during pregnancy or if the patient becomes pregnant while taking Tavegra.

## Data

### Animal data

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

In rats, maternal toxicity (reduced body weight gain and food consumption) was observed at the dose of 30 mg/kg/day. Fetal effects included reduced fetal weights, irregular/incomplete ossification, and increased incidences of fetal malformations (e.g. abnormal flexure/inward malrotation of hindpaws/forepaws, thinness of forelimbs, lack of/reduced flexion at the humerus/ulna joints, narrowed or small tongue) at doses of  $\geq 10$  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  $\geq 5$  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).

## 9.2 Lactation

### Risk summary

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

## 9.3 Females and males of reproductive potential

### Pregnancy testing

The pregnancy status of females of reproductive potential should be verified prior to starting treatment with Tabrecta.

### Contraception

#### *Females*

Sexually-active females of reproductive 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.

### ***Males***

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

### **Infertility**

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

## **10 Overdosage**

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

## **11 Clinical pharmacology**

### **Pharmacotherapeutic group, ATC**

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

### **Mechanism of action (MOA)**

Capmatinib is a highly selective and potent inhibitor of the MET receptor tyrosine kinase. High MET selectivity of capmatinib was demonstrated in two different screening panels, indicating a selectivity factor of approximately 1000 times or greater when compared to more than 400 other kinases or mutant kinase variants. At tolerated doses, capmatinib treatment results in regression of tumor xenograft models derived from lung cancer with MET exon 14 skipping mutations or MET amplification, among others. Capmatinib inhibits MET phosphorylation (both autophosphorylation and phosphorylation triggered by the ligand hepatocyte growth factor [HGF]), MET-mediated phosphorylation of downstream signaling proteins, as well as proliferation and survival of MET-dependent cancer cells.

### **Pharmacodynamics (PD)**

#### **Pharmacodynamic properties**

Capmatinib induced regression in multiple cancer xenograft models including a lung cancer xenograft model that expressed a mutant MET variant lacking exon 14. The relationship between pharmacodynamics and efficacy was studied in the S114 mouse tumor model, where deep regression was associated with more than 90% inhibition of MET phosphorylation during most of the dosing interval.

#### **Cardiac electrophysiology**

Capmatinib did not prolong the QT interval to any clinically relevant extent following administration of Tavegra at the recommended dose. Following a dose of 400 mg twice daily

in clinical studies, no patient had a new post-baseline QTcF interval value greater than 500 msec. A concentration-QT analysis showed that the estimated mean QTcF increase from baseline was 1.33 msec with upper bound 90% confidence interval (CI) of 2.58 msec at the mean steady-state C<sub>max</sub> following 400 mg twice daily dosing.

### **Pharmacokinetics (PK)**

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

### **Absorption**

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

### **Food effect:**

Food does not alter capmatinib bioavailability to a clinically meaningful extent. Tabrecta can be administered with or without food (see section 4 Dosage regimen and administration).

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<sub>inf</sub> by 46% and C<sub>max</sub> by 15% compared to when capmatinib was administered under fasted conditions. A low-fat meal increased AUC<sub>inf</sub> by 20% and C<sub>max</sub> by 11%.

When capmatinib was administered at 400 mg twice daily in cancer patients, exposure (AUC<sub>0-12h</sub>) 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 (V<sub>ss/F</sub>) is 164 L in cancer patients.

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

Capmatinib crossed the blood-brain barrier in rats with a brain-to-blood exposure (AUC<sub>inf</sub>) ratio of approximately 9%.

### **Metabolism**

*In vitro* and *in vivo* studies indicated that capmatinib is cleared mainly through metabolism driven by cytochrome P450 (CYP) 3A4 and aldehyde oxidase. The biotransformation of capmatinib occurs essentially by Phase I metabolic reactions including C-hydroxylation, lactam formation, N-oxidation, N-dealkylation, carboxylic acid formation, and combinations thereof. Phase II reactions involve glucuronidation of oxygenated metabolites. The most abundant radioactive component in plasma is unchanged capmatinib (42.9% of radioactivity AUC<sub>0-12h</sub>).

The major circulating metabolite, M16 (CMN288), is pharmacologically inactive and accounts for 21.5% of the radioactivity in plasma AUC0-12h.

## **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 (CL<sub>ss</sub>/F) of capmatinib was 19.8 L/hr.

## **Excretion**

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

## ***In vitro* evaluation of drug interaction potential**

### **Interactions between enzymes and Tabrecta**

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

### **Interactions between transporters and Tabrecta**

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

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

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

## **Special populations**

### **Geriatric patients**

In Study A2201 (GEOMETRY mono-1), 57% of the 334 patients were 65 years of age or older, and 16% were 75 years of age or older. No overall differences in the safety or effectiveness were observed between these and younger patients.

### **Age/Gender/Race/Body weight**

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

### **Renal impairment**

Based on a population pharmacokinetic analysis that included 207 patients with normal renal function (creatinine clearance [CLcr]  $\geq 90$  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 Dosage regimen and administration).

### **Hepatic impairment**

A study was conducted in non-cancer subjects with various degrees of hepatic impairment based on Child-Pugh classification using a 200 mg single-dose of capmatinib. The geometric mean systemic exposure (AUC<sub>inf</sub>) 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<sub>max</sub> 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<sub>max</sub> was similar (increased by 2%) in subjects with severe hepatic impairment compared to subjects with normal hepatic function (see section 4 Dosage regimen and administration). Mild, moderate or severe hepatic impairment had no clinically significant effect on the exposure of capmatinib.

## **12 Clinical studies**

### **Locally advanced or metastatic NSCLC with a MET exon 14 skipping mutation (treatment-naïve and previously treated) (data cut-off: 15-Apr-2019)**

The efficacy of Tabrecta for the treatment of patients with locally advanced or metastatic NSCLC with a MET exon 14 skipping mutation was demonstrated in the pivotal, global, prospective, multi-cohort, non-randomized, open-label Phase II Study A2201 (GEOMETRY mono-1). Patients (N = 334) were enrolled into study cohorts based on their prior treatment and MET dysregulation (mutation and/or amplification) status. Patients with MET mutations (N = 97) were enrolled into the MET-mutated cohorts regardless of MET amplification. Patients without MET mutations were enrolled into the MET-amplified cohorts based on their level of MET amplification.

In the MET-mutated cohorts, eligible patients were required to have Epidermal Growth Factor Receptor (EGFR) wild-type (for exon 19 deletions and exon 21 L858R substitution mutations) and Anaplastic Lymphoma Kinase (ALK) negativestatus, and MET-mutated NSCLC 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.

In the MET-mutated cohorts, a total of 97 adult patients with locally advanced or metastatic NSCLC with a MET exon 14 skipping mutation as determined using an RNA-based clinical trial assay at a central laboratory were enrolled and treated with Tabrecta. The treatment-naïve cohort (Cohort 5b) enrolled 28 patients. The previously treated cohort (Cohort 4) enrolled 69 patients who had been treated with 1 or 2 prior lines of systemic therapy for advanced disease.

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 60% female, median age 71 years (range: 49 to 90 years), 82% aged 65 years of age or older, 75% white, 24% Asian, 0% black, 60% never smoked, 80% had adenocarcinoma, 24% had ECOG PS0, 75% had ECOG PS1, and 12% had CNS metastases. In the previously treated cohort (N = 69), 94% had prior chemotherapy, 88% had prior platinum-based chemotherapy, 28% had prior immunotherapy, and 23% 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. Additional secondary endpoints were time-to-response (TTR), progression-free survival (PFS), overall survival (OS), and disease control rate (DCR). The efficacy data for treatment-naïve and previously treated patients were analyzed independently.

Efficacy results from Study A2201 (GEOMETRY mono-1) for both treatment-naïve and previously treated MET-mutated NSCLC patients are summarized in Tables 12-1 and 12-2. The primary endpoint of ORR as assessed by BIRC was met irrespective of the line of treatment and thus demonstrated that Tabrecta is efficacious in both treatment-naïve and previously treated MET-mutated NSCLC patients. The responses in treatment-naïve MET-mutated NSCLC patients were durable with 68.4% of patients having responses of 6 months or longer and 47.4% of patients having responses of 12 months or longer (median DOR of 12.58 months (95% CI: 5.55, 25.33 by BIRC assessment). The responses in previously treated MET-mutated NSCLC patients were also durable with 64.3% of patients having responses of 6 months or longer and 32.1% of patients having responses of 12 months or longer (median DOR of 9.72 months (95% CI: 5.55, 12.98)) by BIRC assessment. In both MET-mutated cohorts, the onset of response occurred within 7 weeks of treatment in the majority of patients (68.4% of treatment-naïve patients and 82.1% of previously treated patients) as assessed by BIRC. The analyses by BIRC assessment were similar to the analyses by investigator assessment.

**Table 12-1 Treatment-naïve MET-mutated locally advanced or metastatic NSCLC: Efficacy results in patients who received Tabrecta in Study A2201 (GEOMETRY mono-1) (Data cut-off: 15-Apr-2019)**

Efficacy Parameters	Tabrecta by BIRC N = 28	Tabrecta by Investigator N = 28
<b>Overall Response Rate<sup>a</sup> (95% CI)<sup>b</sup></b>	67.9% (47.6, 84.1)	60.7% (40.6, 78.5)
Complete Response (CR), n (%)	1 (3.6)	0 (0.0)
Partial Response (PR), n (%)	18 (64.3)	17 (60.7)

Efficacy Parameters	Tabrecta by BIRC N = 28	Tabrecta by Investigator N = 28
<b>Duration of Response<sup>a, †</sup></b>		
Number of responders, n	19	17
Median, months (95% CI) <sup>c</sup>	12.58 (5.55, 25.33)	13.83 (4.27, 25.33)
Patients with DOR ≥6 months	68.4%	76.5%
Patients with DOR ≥12 months	47.4%	52.9%
<b>Disease Control Rate<sup>a</sup> (95% CI)<sup>b</sup></b>	96.4% (81.7, 99.9)	96.4% (81.7, 99.9)
<b>Progression-Free Survival<sup>a</sup></b>		
Number of events, n (%)	17 (60.7)	17 (60.7)
Progressive Disease (PD), n (%)	14 (50.0)	16 (57.1)
Deaths, n (%)	3 (10.7)	1 (3.6)
Median, months (95% CI) <sup>c</sup>	9.69 (5.52, 13.86)	11.14 (5.52, 15.24)
<b>Overall Survival</b>		
Number of events, n (%)	13 (46.4)	
Median, months (95% CI) <sup>c</sup>	15.24 (12.22, NE)	

Abbreviations: BIRC, Blinded Independent Review Committee; CI, Confidence Interval; CR, Complete Response; DCR, Disease Control Rate; MET, mesenchymal-epithelial transition; NE, Not Estimable; NSCLC, Non-Small Cell Lung Cancer; PR, Partial Response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, Stable Disease.  
ORR: CR+PR.  
DCR: CR+PR+SD+Non-CR/Non-PD.  
<sup>a</sup>Determined by RECIST v1.1.  
<sup>b</sup>Clopper and Pearson exact binomial 95% CI.  
<sup>c</sup>Based on Kaplan-Meier estimate.  
† Updated based on data cut off date 28-Oct-2019

**Table 12-2 Previously treated MET-mutated locally advanced or metastatic NSCLC: Efficacy results in patients who received Tabrecta in Study A2201 (GEOMETRY mono-1) (Data cut-off: 15-Apr-2019)**

Efficacy Parameters	Tabrecta by BIRC N = 69	Tabrecta by Investigator N = 69
<b>Overall Response Rate<sup>a</sup> (95% CI)<sup>b</sup></b>	40.6% (28.9, 53.1)	42.0% (30.2, 54.5)
Complete Response (CR), n (%)	0 (0.0)	1 (1.4)
Partial Response (PR), n (%)	28 (40.6)	28 (40.6)
<b>Duration of Response<sup>a, †</sup></b>		
Number of responders, n	28	30
Median, months (95% CI) <sup>c</sup>	9.72 (5.55, 12.98)	8.31 (5.45, 12.06)
Patients with DOR ≥6 months	64.3%	60.0%
Patients with DOR ≥12 months	32.1%	30.0%
<b>Disease Control Rate<sup>a</sup> (95% CI)<sup>b</sup></b>	78.3% (66.7, 87.3)	76.8% (65.1, 86.1)
<b>Progression-Free Survival<sup>a</sup></b>		
Number of events, n (%)	55 (79.7)	57 (82.6)
Progressive Disease (PD), n (%)	49 (71.0)	49 (71.0)
Deaths, n (%)	6 (8.7)	8 (11.6)
Median, months (95% CI) <sup>c</sup>	5.42 (4.17, 6.97)	4.80 (4.11, 7.75)
<b>Overall Survival</b>		
Number of events, n (%)	44 (63.8)	

Efficacy Parameters	Tabrecta by BIRC N = 69	Tabrecta by Investigator N = 69
Median, months (95% CI) <sup>c</sup>	13.57 (8.61, 21.19)	

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

ORR: CR+PR.

DCR: CR+PR+SD+Non-CR/Non-PD.

<sup>a</sup>Determined by RECIST v1.1.

<sup>b</sup>Clopper and Pearson exact binomial 95% CI.

<sup>c</sup>Based on Kaplan-Meier estimate.

† Updated based on data cut off date 28-Oct-2019

## 13 Non-clinical safety data

### Repeat-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  $\geq 2.2$  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<sub>max</sub> of 14000 ng/mL), about 2.9 times the human C<sub>max</sub> at the 400 mg twice daily clinical dose.

### **Reproductive toxicity**

For information on reproductive toxicity, see section 9 Pregnancy, lactation, females and males of reproductive potential.

## **14 Pharmaceutical information**

### **Incompatibilities**

Not applicable.

### **Special precautions for storage**

See folding box. Do not store above 30°C.

Store in the original package. Protect from moisture.

Tabrecta must be kept out of the reach and sight of children.

**Instructions for use and handling**

In-use period (for HDPE bottle only): Discard any unused Tabrecta remaining after 6 weeks of first opening the bottle.

**Special precautions for disposal**

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

**Manufacturer**

See folding box.

**Presentation**

For both 150 mg and 200 mg strengths: Tablets are packed in PCTFE/PVC-Alu blister, in a box of 60 tablets.

Not all presentations may be available locally.

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