Summary Report of Benefit-Risk Assessment

TABRECTA FILM-COATED TABLET 150 MG, 200 MG

NEW DRUG APPLICATIONS

Active Ingredient(s)	Capmatinib
Product Registrant	Novartis (Singapore) Pte Ltd
Product Registration Number	SIN16350P, SIN16351P
Application Route	Abridged evaluation
Date of Approval	22 October 2021

Table of Contents

A INTRODUCTION

Tabrecta is indicated for the treatment of metastatic non-small cell lung cancer (NSCLC) with a MET exon 14 skipping mutation.

The active substance, capmatinib, is an oral highly selective and potent inhibitor of the MET receptor tyrosine kinase. Capmatinib inhibits MET-mediated phosphorylation and downstream signalling such as the PI3K/Akt and MAPK/ERK pathways, as well as proliferation and survival of MET-dependent cancer cells.

Tabrecta is available as film-coated tablets containing 150mg and 200mg of capmatinib as capmatinib dihydrochloride monohydrate. Other ingredients in the tablet core are microcrystalline cellulose, mannitol, crospovidone, povidone, magnesium stearate, colloidal silicon dioxide, and sodium lauril sulfate. The ingredients in the film coating are hypromellose, titanium dioxide, macrogol 4000, talc and iron oxide.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, capmatinib dihydrochloride monohydrate, is manufactured at Novartis Ringaskiddy Limited, Cork, Ireland. The drug product, Tabrecta is manufactured at Novartis Pharma Produktions GmbH, Wehr, Germany.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented for Novartis Ringaskiddy Limited was adequate to support the approved storage condition and re-test period. The packaging is a polyethylene (PE) bag or in a PE bag from continuous PE liner. The PE bag is then placed into an additional PE bag and stored in metal drum. The drug substance is approved for storage at or below 25°C with a re-test period of 18 months.

Drug product:
The tablet is manufactured using a wet granulation approach, followed by film-coating. The process is considered to be a standard process.

The manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies are conducted. It has been demonstrated that the

manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods have been appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 24 months when stored at or below 30ºC. The container closure system is a polychlorotrifluoro ethylene/ polyvinyl chloride with a heat sealable lacquered aluminium foil blister (PCTFE/PVC-Alu) containing 12 tablets/blister.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of capmatinib in the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with a MET exon 14 skipping mutation was based on 1 pivotal study (Study A2201/ Study GEOMETRY mono-1), and supported by 1 dose response study (Study CINC280X2102) as well as real-world evidence (RWE) from Study CINC280X2401.

Study CINC280X2102 was a Phase 1, open-label, multi-centre, non-randomised, single-arm, dose escalation study with an expansion phase. Based on the safety, pharmacodynamics, bioavailability and efficacy data from the escalation phase, the maximum tolerated dose of capmatinib was determined to be 400mg twice daily and was selected for further investigation in the Phase 2 study. The escalation phase was followed by an expansion phase which enrolled 55 subjects with MET-dysregulated NSCLC, out of which 4 subjects were identified with MET-mutated NSCLC. Of the 4 subjects 1 achieved complete response (CR), 2 achieved partial response (PR) and 1 had stable disease (SD). As per Blinded Independent Review Committee (BIRC) assessment, the duration of response (DOR) for the subject who achieved CR was 16.8 months, and that for the 2 subjects with PR was 2.1 months and 2.0 months, respectively. The progression free survival (PFS) was 18.6 months for the subject with CR, 3.8 months, 3.9 months for the 2 subjects with PR, and 3.0 months for the subject with SD based on Response Evaluation Criteria in Solid Tumours (RECIST) 1.1.

Study A2201 is a Phase 2, ongoing, single-arm, non-randomised, open-label, multi-cohort study conducted in patients with wild-type EGFR and ALK rearrangement negative advanced or metastatic (stage IIIB or IV) NSCLC harbouring MET mutations (detected by reverse transcriptase-polymerase chain reaction [RT-PCR]) and/or amplification (detected by fluorescent in-situ hybridisation [FISH]). Subjects with MET exon 14 skipping mutations were enrolled in Cohort 4 and Cohort 5b, and those with MET amplification without MET mutations were enrolled in Cohorts 1a, 1b, 2, 3 and Cohort 5a. All subjects in Cohorts 1a, 1b, 2, 3 and 4 must have failed 1 or 2 prior lines of systemic therapy in advanced stage, subjects in Cohort 6 must have failed one line of systemic therapy for advanced/metastatic disease, while subjects enrolled in Cohorts 5a, 5b, and 7 were treatment-naïve for advanced disease. The indication sought in the application was based on Cohorts 4 (previously treated patients) and 5b (treatment-naïve patients).

All the patients in the study were treated with capmatinib 400 mg twice daily until the subject experienced a disease progression event according to RECIST 1.1 as determined by the

investigator and confirmed by the BIRC. Dose reductions were allowed as per the dose reduction schedule, and for each subject, a maximum of 2 dose level modifications were allowed after which the subject discontinued from the treatment.

The primary efficacy endpoint was the overall response rate (ORR), defined as the proportion of subjects with a best overall response (BOR) of CR or PR by BIRC assessment. The key secondary efficacy endpoints were PFS as determined by the BIRC and investigator, time to response (TTR), overall survival (OS) and DOR calculated as the time from the date of the first documented CR or PR by the BIRC to the first documented progression or death due to any cause. In the pre-treated subjects in Cohort 4, a pre-specified ORR ≥ 35% with a lower bound of the 95% confidence limit of > 25% was considered to reflect clinically relevant efficacy. For treatment-naïve subjects in Cohort 5b, an ORR ≥ 55% with a lower bound of the 95% confidence limit > 35% was considered as clinically relevant efficacy.

The primary analysis comprised 97 subjects with 69 patients in Cohort 4 (MET mutated, pre-treated) and 28 patients in Cohort 5b (MET mutated, treatment-naïve). The median study follow-up was 22.5 months (range: 12.4 to 36.1) and 16.8 months (range: 10.3 to 24.9) for Cohorts 4 and 5b, respectively. The median age of the subjects was 71 years (range: 49-90). There was a higher proportion of women (59.8%) and 37.1% of the population were ex-smokers. The majority of subjects had good ECOG status at baseline (99.0% had ECOG PS 0 or 1). In Cohort 4, majority of the subjects (88.4%) had received platinum-based chemotherapy (irrespective of the line) prior to entering the study, whereas Cohort 5b included only subjects who had not received prior systemic chemotherapy

The primary efficacy endpoint of ORR by BIRC assessment were 40.6% (95% CI: 28.9, 53.1) in Cohort 4 and 67.9% (95% CI: 47.6, 84.1) in Cohort 5b, respectively. Consistent results were observed with the assessment by investigator, with 42.0% (95% CI: 30.2, 54.5) and 60.7% (95% CI: 40.6, 78.5) in Cohort 4 and Cohort 5b, respectively. The results met the pre-defined criteria for clinically relevant efficacy.

Similarly, for the median DOR, the BIRC assessment of 9.72 months (95% CI: 5.55, 12.98) and 12.58 months (95% CI: 5.55, 25.33) in Cohort 4 and Cohort 5b, respectively, were consistent with that by the investigator, 8.31 months (95% CI: 5.45, 12.06) and 13.83 months (95% CI: 4.27, 25.33) in Cohort 4 and Cohort 5b, respectively.

Tumour responses to capmatinib were observed with a TTR per BIRC of approximately 7 weeks, with 82.1% and 68.4% of responders achieving response within 2 months of initiating treatment in Cohort 4 and Cohort 5b, respectively. The median PFS by BIRC was 5.42 months (95% CI: 4.17, 6.97) and 9.69 months (95% CI: 5.52, 13.86) in Cohort 4 and Cohort 5b, respectively; and by the investigator was 4.80 months (95% CI: 4.11, 7.75) and 11.14 months (95% CI: 5.52, 15.24) in Cohort 4 and Cohort 5b, respectively. Median OS was 13.57 months (95% CI: 8.61, 21.19) and 15.24 months (95% CI: 12.22, NE) in Cohort 4 and Cohort 5b, respectively.

Summary of key efficacy results (15 Apr 2019 cutoff)

	Cohort 4 (MET mutated, pre-treated) N = 69	**Cohort 5b (MET mutated, treatment-naïve) N = 28**
Primary endpoint		
ORR (CR + PR), BIRC Exact binomial 95% CI	28 (40.6%) [28.9, 53.1]	19 (67.9%) [47.6, 84.1]
Complete response (CR)	0 (0.0%)	1 (3.6%)
Partial response (PR)	28 (40.6%)	18 (64.3%)

Stable disease (SD)	25 (36.2%)	8 (28.6%)
Non-CR/non-PD	1 (1.4%)	0 (0.0%)
Progressive disease (PD)	6 (8.7%)	1 (3.6%)
Not evaluable (NE)	9 (13.0%)	0 (0.0%)
Key secondary endpoints		
PFS per BIRC		
No. of events, n (%)	55 (79.7%)	17 (60.7%)
Median PFS (months) [95% CI]	5.42 [4.17, 6.97]	9.69 [5.52, 13.86]
OS		
No. of events, n (%)	44 (63.8%)	13 (46.4%)
Median OS, months [95% CI]	13.57 [8.61, 21.19]	15.24 [12.22, NE]
DOR per BIRC		
No. of events, n (%)	20 (71.4%)	10 (52.6%)
Median DOR, months [95% CI]	9.72 [5.55, 12.98]	11.14 [5.55, NE]
Median DOR, months [95% CI] *28 Oct 2019 cutoff date	9.72 [5.55, 12.98]	12.58 [5.55, 25.33]

The supporting RWE from Study CINC280X2401 was based on retrospective chart collection from 157 subjects with MET mutated advanced or metastatic NSCLC treated with MET inhibitor as compared with standard-of-care therapies including chemotherapy and immunotherapy in various lines of therapy. MET inhibiting class included drugs like cabozantinib, crizotinib, emibetuzumab, ficlatuzumab, foretinib, glesatinib, merestinib, onartuzumab, rilotumumab, sitravatinib, tepotinib, and tivantinib. The analysis showed that OS was improved in MET inhibitor-treated subjects (median OS of 25.4 months, 95% CI: 18.8, 40.9) compared to those who did not receive MET inhibitors (10.7 months, 95% CI: 7.8, 14.4). This study provided supportive evidence of the survival benefit with MET inhibitors in this patient population.

Clinical outcomes of patients receiving MET inhibitors versus patients who did not receive MET inhibitors, and standard-of-care agents

Overall survival of patients receiving MET inhibitors versus patients who did not receive MET inhibitors		
	Received MET inhibitor (N = 49)	**Did not receive MET inhibitor (N = 108)**
Median OS (months) [95% CI]	25.4 [18.8, 40.9]	10.7 [7.8, 14.4]

Clinical outcomes of patients receiving different standard-of-care agents				
	First-line		**Second- or third-line**	
	Chemotherapy (N = 61)	**Immunotherapy (N = 12)**	**Chemotherapy (N = 9)**	**Immunotherapy (N = 16)**
Median OS (months) [95% CI]	9.1 [7.5, 18.9]	18.4 [1.5, 18.4]	13.2 [3.0, 42.7]	11.9 [2.1, NE]
	Chemotherapy (N = 86)	**Immunotherapy (N = 17)**	**Chemotherapy (N = 22)**	**Immunotherapy (N = 24)**
Median PFS (months) [95% CI]	5.1 [3.3, 6.9]	2.6 [1.0, 6.9]	2.8 [1.2, 5.0]	3.1 [1.9, 4.1]
ORR (CR + PR)	25.6%	35.3%	13.6%	16.7%

Study A2201 met its primary endpoint in terms of BIRC-assessed ORR in both the pre-treated (Cohort 4) and treatment-naïve (Cohort 5b) subjects with MET-mutated NSCLC. The results of the secondary endpoints supported the primary endpoint. The ORR observed in the first-line setting of 67.9% was comparable to that seen with other approved targeted therapies, while the ORR in the second-line setting of 40.6% was numerically better than that known for the current standard of care such as docetaxel, atezolizumab, nivolumab and pembrolizumab (9 - 20%).

The benefit of treatment with MET inhibitors compared against treatment regimens without MET inhibitors in patients with MET mutated advanced or metastatic NSCLC observed in Study CINC280X2401 further supports the use of capmatinib in this patient population. While the overall data was considered promising, given the small sample size of Cohorts 4 and 5b in

Study A2201, the final results from a larger sample size of the on-going study are required to be submitted post-approval in order to confirm the observed benefit.

D ASSESSMENT OF CLINICAL SAFETY

The safety data reviewed was primarily based on the results from Study A2201 (n = 348), supplemented by data from 6 pooled studies (n=555) conducted in all solid tumour subjects who had received capmatinib monotherapy (Study A2201, Study X1101, Study X2102, Study A2108, Study A2103 and Study A2105).

Study name	Study Description
A2201	Phase II, multicentre study of capmatinib in adult subjects with EGFR wild-type, ALK-negative locally advanced or metastatic NSCLC (N=334), including also MET mutated NSCLC.
X1101	Phase I study of capmatinib in Japanese subjects with advanced solid tumours
X2102	Phase I open-label dose escalation study with expansion to assess the safety and tolerability of capmatinib in subjects with MET dependent advanced solid tumours
A2103	Phase I, multicentre, open-label, single-sequence drug-drug interaction study to assess the effect of capmatinib on the pharmacokinetics of midazolam and caffeine in subjects with MET-dysregulated advanced solid tumours
A2105	Phase I, multicentre, open-label, single-sequence drug-drug interaction study to assess the effect of capmatinib on the pharmacokinetics of digoxin and rosuvastatin in subjects with MET-dysregulated advanced solid tumours
A2108	Multicentre, open label, Phase I dose escalation study to evaluate the pharmacokinetics, safety, and tolerability of capmatinib tablet formulation with food in subjects with MET dysregulated advanced solid tumours

The median duration of exposure to capmatinib in Study A2201 as of the data cut-off date on 18 Sep 2019 was 15.4 weeks, and 34 subjects (9.8%) had received capmatinib for ≥72 weeks.

Summary of AEs (last three columns contain data with 18 Sep 2019 cutoff)

AE	Study A2201 Cohort 4 (n = 69) 15 Apr 2019 cutoff	Study A2201 Cohort 5b (n = 28) 15 Apr 2019 cutoff	Study A2201 All subjects (n = 348)	Pooled analyses All NSCLC (n = 433)	Pooled analyses All solid tumour (n = 555)
Any AE					
All grades	68 (98.6%)	28 (100%)	340 (97.7%)	425 (98.2%)	546 (98.4%)
Grade 3/4	50 (72.5%)	20 (71.4%)	231 (66.4%)	291 (67.2%)	349 (62.9%)
Treatment-related AE					
All grades	60 (87.0%)	27 (96.4%)	297 (85.3%)	371 (85.7%)	471 (84.9%)
Grade 3/4	33 (47.8%)	15 (53.6%)	128 (36.8%)	157 (36.3%)	179 (32.3%)
SAE					
All grades	35 (50.7%)	13 (46.4%)	172 (49.4%)	214 (49.4%)	263 (47.4%)
Grade 3/4	29 (42.0%)	11 (39.3%)	142 (40.8%)	175 (40.4%)	212 (38.2%)
Treatment-related SAE					
All grades	12 (17.4%)	4 (14.3%)	44 (12.6%)	54 (12.5%)	61 (11.0%)
Grade 3/4	8 (11.6%)	4 (14.3%)	30 (8.6%)	37 (8.5%)	42 (7.6%)
Discontinuations due to AE					
All grades	14 (20.3%)	6 (21.4%)	56 (16.1%)	71 (16.4%)	82 (14.8%)
Grades 3/4	8 (11.6%)	5 (17.9%)	35 (10.1%)	46 (10.6%)	52 (9.4%)
Deaths* *Due to reasons not related to study indication	2 (2.9%)	2 (7.1%)	11 (3.2%)	16 (3.7%)	26 (4.7%)

The incidences of adverse event (AE) and serious AEs observed in Study A2201 were similar between the NSCLC and all solid tumour populations.

In Study A2201, AEs were reported in 98.6% of subjects in Cohort 4 and all subjects in Cohort 5b, and the most frequently reported AEs were peripheral oedema (51.1%), nausea (43.7%),

vomiting (28.2%), and increased blood creatinine (25.0%). The most common grade 3/4 AEs (in ≥ 5% of subjects), irrespective of study drug relationship, were peripheral oedema (8.9%), dyspnoea (6.6%), increased ALT (6.0%), and increased lipase (5.7%).

The serious adverse events (SAEs) reported in ≥ 2% of all subjects were: dyspnoea (6.6%), pneumonia (4.9%), general physical health deterioration (3.7%), pleural effusion (3.4%), vomiting (2.3%), and nausea (2.0%). A total of 11 deaths were attributed to SAEs (cardiac arrest [in 2 subjects], atrial fibrillation, hepatitis, pneumonia, pneumonia bacterial, pneumonitis, organizing pneumonia, respiratory distress, sepsis, and septic shock [one subject each]). Four of these deaths (cardiac arrest, hepatitis, organizing pneumonia, pneumonitis) were reported as treatment-related by the investigator. These subjects had other confounding factors including thoracic radiotherapy prior to study entry and concomitant therapy contributing to the SAE. Fifty-six subjects (16.1%) had AEs which led to permanent discontinuation of study treatment irrespective of study drug relation, with 10.1% (35 subjects) experiencing grade 3/4 AEs leading to permanent discontinuation of study treatment.

Overview of AESI (Safety set)

	Data cutoff 15 Apr 2019						**Data cutoff 18 Sep 2019**	
	Cohort 4 (2nd/3rd line, MET mutated, n = 69)		Cohort 5b (treatment-naïve, MET mutated, n = 28)		All subjects n = 334		All subjects n = 348	
AESI	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Hepatotoxicity	17 (24.6)	8 (11.6)	8 (28.6)	3 (10.7)	94 (28.1)	32 (9.6)	101 (29.0)	35 (10.1)
Renal dysfunction	24 (34.8)	0	10 (35.7)	0	89 (26.6)	1 (0.3)	91 (26.1)	1 (0.3)
Central nervous system toxicity	14 (20.3)	0	4 (14.3)	0	62 (18.6)	3 (0.9)	64 (18.4)	3 (0.9)
Pancreatitis	9 (13.0)	8 (11.6)	5 (17.9)	3 (10.7)	41 (12.3)	26 (7.8)	43 (12.4)	28 (8.0)
Interstitial lung disease/ pneumonitis	7 (10.1)	3 (4.3)	2 (7.1)	2 (7.1)	15 (4.5)	6 (1.8)	15 (4.3)	6 (1.7)
QTc interval prolongation	1 (1.4)	0	2 (7.1)	0	10 (3.0)	3 (0.9)	10 (2.9)	3 (0.9)
Photosensitivity	0	0	0	0	1 (0.3)	0	1 (0.3)	0
Teratogenicity	0	0	0	0	0	0	0	0
Drug-drug interactions with strong CYP3A4 inducers*	0	0	0	0	0	0	0	0

A subject with multiple severity grades for an AE was only counted under the maximum grade.
*Any subject receiving treatment with strong inducers of CYP3A4 and could not be discontinued ≥1 week prior to the start of treatment with capmatinib and for the duration of the study was to be excluded from the study.
MedDRA version 22.0, CTCAE version 4.03, Case Retrieval Strategy version 17-May-2019

The AEs of special interest (AESIs) with capmatinib were hepatotoxicity (29.0%), renal dysfunction (26.1%), central nervous system toxicity (18.4%), pancreatitis (12.4%), interstitial lung disease (ILD)/pneumonitis (4.3%), QTc interval prolongation (2.9%), and photosensitivity (0.3%).

ILD/pneumonitis is a class effect for tyrosine kinase inhibitors (TKIs) including MET inhibitors. There were 15 subjects with ILD/pneumonitis-related AEs, 12 subjects had pneumonitis and 3 subjects had ILD, of which 6 were of grade 3 in severity. The remaining 9 subjects experienced grade 1/2 events and there was no grade 4 event. Most of these subjects (10 of 15 subjects) had prior immunotherapy and/or radiotherapy as confounding factors and/or had progressive disease at the onset of ILD/pneumonitis. Eight subjects discontinued study drug due to these AEs. One fatal event of ILD/pneumonitis was reported. The median time to first occurrence of

grade 3/4 ILD/pneumonitis AEs was 1.38 months and the median duration of these first occurrence of grade 3/4 ILD/pneumonitis AEs was 0.44 months.

Hepatotoxicity AEs were reported in 101 subjects, among these 6 subjects had SAEs and 35 subjects had grade 3/4 AEs. The most common were increased alanine aminotransferase, increased aspartate aminotransferase, hypoalbuminemia, increased gamma-glutamyltransferase, and increased blood alkaline phosphatase. About 2% of subjects required study drug discontinuation, 3.4% of the subjects required dose adjustment, and 7.2% subjects required dose interruption. TKIs are known to cause hepatotoxicity, and these events could be exacerbated by the underlying liver metastases seen in metastatic NSCLC.

Renal dysfunction was reported in 91 subjects, of which 68 subjects had treatment-related events, and most of the events were of grades 1/2 severity. CNS toxicity (seizures, epilepsy) was reported in 64 subjects and in 3 of the subjects the severity was grade 3. No discontinuation due to CNS toxicity was reported. Pancreatitis-grouped AEs (elevated pancreatic enzymes) were reported in 43 subjects, of which 28 reported grade 3/4 events.

The safety profile was generally consistent with the mechanism of action of TKIs. The AESIs of ILD/pneumonitis, hepatotoxicity, renal dysfunction, pancreatitis, CNS toxicity and photosensitivity were the main safety risks associated with capmatinib. Relevant information on ILD/pneumonitis and hepatotoxicity with respect to dosage modification, warnings and precautions have been included in the product label. The adverse events section has also adequately described the AESIs including those that were less commonly observed (renal dysfunction, pancreatitis, CNS toxicity, and photosensitivity). Overall safety profile of capmatinib for the treatment of patients with metastatic NSCLC with a MET exon 14 skipping mutation was considered acceptable for the intended patient population.

E ASSESSMENT OF BENEFIT-RISK PROFILE

MET-mutated NSCLC is a rare condition and is more prevalent in the elderly population with multiple related comorbidities, representing a difficult-to-treat population. MET mutation is mutually exclusive from other established molecular drivers tested and may constitute 2-3% of NSCLC patients. The prognosis with standard therapies for metastatic NSCLC population with MET-mutations is poorer compared to those without MET mutations. Capmatinib is a first-in class drug targeting MET exon 14 skipping mutations in NSCLC subjects.

The efficacy of capmatinib in the treatment of metastatic NSCLC patients with MET exon 14 skipping mutations was demonstrated in the pivotal Study A2201 with an ORR of 67.9% (95% CI: 47.6, 84.1) and 40.6% (95% CI: 28.9, 53.1) in treatment-naïve and pre-treated MET mutated metastatic NSCLC patients, respectively. The ORR observed both in the first-line setting and the second-line setting was generally higher than that observed in naïve first-line platinum recipients (30.7%) and second/third-line immunotherapy recipients (19.0%) or second/third-line single-agent chemotherapy recipients (16.7%) in metastatic NSCLC subjects with MET mutations in the RWE study. The observed ORR was also comparable to that seen with other approved targeted therapies for first-line setting, while the ORR in the second-line setting was numerically better than that known for the current standard of care and was considered clinically meaningful.

The results of the secondary endpoints supported the primary endpoint. The observed responses were durable with a median DOR of 9.72 months (95% CI: 5.55, 12.98) in the pre-

treated subjects and 12.58 months (95% CI: 5.55, 25.33) in the treatment-naïve subjects. Median PFS was 5.42 months (95% CI: 4.17, 6.97), and 9.69 months (95% CI: 5.52, 13.86) in the pre-treated and treatment-naïve cohorts, respectively. Median OS was 13.57 months (95% CI: 8.61, 21.19) in the pre-treated population and 15.24 months (95% CI: 12.22, NE) in the treatment-naïve population. Although OS and PFS could not be contextualised due to the lack of a comparator arm, they were comparable to the current available treatment options for advanced NSCLC which was reassuring.

The supporting RWE study showed that patients with MET mutated advanced or metastatic NSCLC had a greater survival benefit when treated with MET inhibitors compared against platinum-based therapy and immunotherapy, regardless of whether patients were treatment naïve or received prior lines of treatment. The findings supported the use of capmatinib in this patient population.

The safety profile of capmatinib for patients with metastatic NSCLC with a MET exon 14 skipping mutation were characterised by peripheral oedema, nausea, vomiting, and increased blood creatinine. The AESIs of ILD/pneumonitis and hepatotoxicity were the major safety risks associated with capmatinib and have been highlighted in dosage modification, warnings and precautions, and adverse events sections of the proposed product insert. Considering that the patients will be managed by oncologists with expertise in manging the treatment-related toxicities, and given the rare condition with poor prognosis with limited treatment options, the safety profile was considered acceptable for the treatment population.

Overall, the benefits in terms of improved ORR and durable response with capmatinib in the treatment of adult patients with metastatic NSCLC with MET exon 14 skipping mutations outweighed the risks associated with the treatment, subject to further results from a larger sample size and with more mature data from the pivotal Study A2201 to confirm the efficacy benefit.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Tabrecta for the treatment of patients with metastatic NSCLC with a MET exon 14 skipping mutation was deemed favourable and approval of the product registration was granted on 22 Oct 2021, subject to confirmation of clinical benefit from the updated results of the pivotal Study A2201.

APPROVED PACKAGE INSERT AT REGISTRATION

NOVARTIS

1 Tradename

Tabrecta® 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.

Adverse drug reaction	Severity	Dose modification
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 (≥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 ≥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 ≥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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

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
Infections and infestations				
Cellulitis	9 (2.7)	Common	3 (0.9)*	Uncommon
Metabolism and nutrition disorders				
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
Respiratory, thoracic, and mediastinal disorders				
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
Gastrointestinal disorders				
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
Hepatobiliary disorders				
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
Skin and subcutaneous tissue disorders				
Pruritus[1]	33 (9.9)	Common	1 (0.3)*	Uncommon
Urticaria	4 (1.2)	Common	2 (0.6)*	Uncommon
Renal and urinary disorders				
Blood creatinine increased	85 (25.4)	Very common	0	
Acute kidney injury[2]	5 (1.5)	Common	1 (0.3)*	Uncommon
General disorders and administration-site conditions				

Adverse drug reactions	All Grades n (%)	Frequency category	Grade 3/4 n (%)	Frequency category
Oedema peripheral[3]	173 (51.8)	Very common	29 (8.7)*	Common
Fatigue[4]	108 (32.3)	Very common	28 (8.4)*	Common
Non-cardiac chest pain[5]	50 (15.0)	Very common	7 (2.1)*	Common
Pyrexia[6]	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

[1] Pruritus includes preferred terms (PTs) of pruritus, pruritus allergic, and pruritus generalized.

[2] Acute kidney injury includes PTs of acute kidney injury and renal failure.

[3] Oedema peripheral includes PTs of peripheral swelling, oedema peripheral, and fluid overload.

[4] Fatigue includes PTs of fatigue and asthenia.

[5] Non-cardiac chest pain includes PTs of chest discomfort, musculoskeletal chest pain, non-cardiac chest pain, and chest pain.

[6] 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 AUCinf by 42% with no change in capmatinib Cmax compared to administration of capmatinib alone. Coadministration of Tabrecta with a strong CYP3A inhibitor may increase the incidence and severity of adverse drug reactions of Tabrecta. Patients should be closely monitored for adverse

drug reactions during coadministration of Tabrecta with strong CYP3A inhibitors, including but not limited to, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, 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 AUCinf by 67% and decreased Cmax 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 AUC0-12h and 34% decrease in Cmax 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_2-receptor antagonists, antacids) may alter the solubility of capmatinib and reduce its bioavailability. In healthy subjects, coadministration of a single 600 mg capmatinib dose with the proton pump inhibitor rabeprazole (20 mg once daily for 4 days) decreased capmatinib AUCinf by 25% and decreased Cmax by 38% compared to administration of capmatinib alone. Caution should be exercised during coadministration of Tabrecta with proton pump inhibitors. As an alternative, an H_2-receptor antagonist or antacid can be taken. Tabrecta should be taken at least 3 hours before or 6 hours after an H_2-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 AUCinf by 134% with no change in caffeine Cmax compared to administration of caffeine alone. Coadministration of Tabrecta with a CYP1A2 substrate may increase the incidence and severity of adverse drug reactions of these substrates. If coadministration is unavoidable between Tabrecta and CYP1A2 substrateswhere minimal concentration changes may lead to serious adverse drug reactions, including but not limited to, theophylline and tizanidine, decrease the CYP1A2 substrate dose in accordance with the approved prescribing information

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

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

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

Drug-food/drink interactions

Tabrecta 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, Tabrecta 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 Tabrecta is used during pregnancy or if the patient becomes pregnant while taking Tabrecta.

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 ≥10 mg/kg/day (with maternal systemic exposure at 0.56 times the exposure in humans at the MRHD of 400 mg twice daily).

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

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 Tabrecta 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 Tabrecta. 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 Tabrecta 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 Cmax following 400 mg twice daily dosing.

Pharmacokinetics (PK)

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

Absorption

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

Food effect:

Food does not alter capmatinib bioavailability to a clinically meaningful extent. Tabrecta can be administered with or without food (see section 4 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 AUCinf by 46% and Cmax by 15% compared to when capmatinib was administered under fasted conditions. A low-fat meal increased AUCinf by 20% and Cmax by 11%.

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

Distribution

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

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

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

Metabolism

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

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

Elimination

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

Excretion

Capmatinib is eliminated mainly through metabolism, and subsequent fecal excretion. Following a single oral administration of [14C]-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] ≥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 (AUCinf) of capmatinib was decreased by approximately 23% and 9% in subjects with mild (N = 6) and moderate (N = 8) hepatic impairment, respectively, and increased by approximately 24% in subjects with severe (N = 6) hepatic impairment compared to subjects with normal (N = 9) hepatic function. Cmax was decreased by approximately 28% and 17% in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal hepatic function, while Cmax was similar (increased by 2%) in subjects with severe hepatic impairment compared to subjects with normal hepatic function (see section 4 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
Overall Response Rate[a] (95% CI)[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
Duration of Response[a, †]		
Number of responders, n	19	17
Median, months (95% CI)[c]	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%
Disease Control Rate[a] (95% CI)[b]	96.4% (81.7, 99.9)	96.4% (81.7, 99.9)
Progression-Free Survival[a]		
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)[c]	9.69 (5.52, 13.86)	11.14 (5.52, 15.24)
Overall Survival		
Number of events, n (%)	13 (46.4)	
Median, months (95% CI)[c]	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.

[a]Determined by RECIST v1.1.

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

[c]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
Overall Response Rate[a] (95% CI)[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)
Duration of Response[a,†]		
Number of responders, n	28	30
Median, months (95% CI)[c]	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%
Disease Control Rate[a] (95% CI)[b]	78.3% (66.7, 87.3)	76.8% (65.1, 86.1)
Progression-Free Survival[a]		
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)[c]	5.42 (4.17, 6.97)	4.80 (4.11, 7.75)
Overall Survival		
Number of events, n (%)	44 (63.8)	

Efficacy Parameters	Tabrecta by BIRC N = 69	Tabrecta by Investigator N = 69
Median, months (95% CI)[c]	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.

[a]*Determined by RECIST v1.1.*

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

[c]*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 (Cmax of 14000 ng/mL), about 2.9 times the human Cmax 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 30ºC.

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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