Date: 24 June 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Tabrecta

International non-proprietary name: capmatinib

Pharmaceutical form: film-coated tablets

Dosage strength(s): 200 mg and 150 mg

Route(s) of administration: oral

Marketing Authorisation Holder: Novartis Pharma Schweiz AG

Marketing Authorisation No.: 67648

Decision and Decision date: approved (temporary authorisation in accordance with Art. 9a TPA) on 26 April 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical Classification System
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutical Classification System
BID	Twice daily
BIRC	Blinded Independent Review Committee
CAP	Capmatinib
CI	Confidence interval
CL/F	Apparent total body clearance
Cmax	Maximum observed plasma/serum concentration of drug
cMET	Mesenchymal-epithelial transition factor
CMN288	Main metabolite of capmatinib
CNS	Central nervous system
CSR	Clinical study report
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
EGFR	Epidermal growth factor receptor
ERA	Environmental Risk Assessment
GCN	gene copy number
GLP	Good Laboratory Practice
HGF	Hepatocyte growth factor
HPLC	High-performance liquid chromatography
ICH	International Council for Harmonisation
Ig	Immunoglobulin
ILD	Interstitial lung disease
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
MATE	Multidrug and toxin extrusion
Max	Maximum
MET	Mesenchymal Epithelial Transition
METex14 mut	MET exon 14 skipping mutation
Min	Minimum
N/A	Not applicable
NE	Not estimable
NIRS	Near infrared spectroscopy
NO(A)EL	No Observed (Adverse) Effect Level
NSCLC	Non-small cell lung cancer
OATP	Organic anion transporting polypeptide
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamics

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PFS	Progression-free survival
P-gp	P-glycoprotein
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PPI	Proton-pump inhibitor
PSP	Pediatric Study Plan (US-FDA)
Q1	First quarter of year
QD	Once daily
RMP	Risk Management Plan
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SOC	System organ class
SwissPAR	Swiss Public Assessment Report
TKI	Tyrosine kinase inhibitor
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
UV	Ultraviolet spectrometry
Vc/F	Apparent central volume of distribution
V/F	Apparent volume of distribution

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance capmatinib of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA.
The Orphan Status was granted on 26 November 2019.

Temporary authorisation for human medical products
The applicant requested a temporary authorisation in accordance with Art. 9a TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication

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

2.2.2 Approved Indication (temporary authorisation in accordance with Art. 9a TPA)

Tabrecta is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with a MET exon 14 skipping mutation.
The efficacy and safety of Tabrecta have not been studied in patients with other oncogenic driver mutations, including EGFR or ALK tumour aberrations (see "Warnings and precautions").

2.2.3 Requested Dosage

400 mg orally twice daily (with or without food).

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	16 July 2020
Formal control completed	17 July 2020
List of Questions (LoQ)	18 September 2020
Answers to LoQ	3 December 2020
Predecision	18 January 2021
Answers to Predecision	16 March 2021
Labelling corrections	6 April 2021
Answers to Labelling corrections:	12 April 2021
Final Decision	26 April 2021
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical Context

Lung cancer is the leading cause of cancer death in men and the second leading cause of cancer death in women in the Western world. In Switzerland, approximately 4,400 new patients are diagnosed each year with lung cancer (www.nicer.org). Non-small cell lung cancer (NSCLC) accounts for 80%-90% of lung cancers, and approximately 2% (squamous cell carcinoma) to 3% (adenocarcinoma) of patients with NSCLC have tumours containing mesenchymal epithelial transition (MET) gene alterations. A total prevalence of about 100 to 200 patients with MET-mutated NSCLC is estimated in Switzerland.

The receptor tyrosine kinase mesenchymal-epithelial transition factor (cMET) and its ligand hepatocyte growth factor (HGF) play an important role in embryogenesis, during which this signalling pathway is necessary for the migration of myogenic precursor cells, the correct formation of lymph and blood vessels, and the mitosis of hepatocytes. In adults, cMET activation is mainly involved in wound healing, in which it stimulates cell migration and mitosis. During cancer growth, cMET is involved in vasculogenesis, migration, and invasion.

In patients with lung cancer, mutations that disrupt MET exon 14 splicing tend to occur in older individuals (median age of 73), with a lower proportion of never-smokers relative to patients with other oncogene-driven lung cancers, and they are enriched in sarcomatoid histology, with a prevalence ranging from 8 to 22%. MET exon 14 alterations in lung cancer have been identified as poor prognostic factors for overall disease-specific survival independent of stage.

Capmatinib is an oral ATP-competitive MET tyrosine kinase inhibitor (TKI).

The treatment of NSCLC in both first line and second line has evolved significantly with the introduction of immune-checkpoint inhibitors, either alone or in combination with chemotherapy. These treatments have brought meaningful increases in overall survival for NSCLC patients, with median overall survival (OS) of 17-22 months in first line and 9-14 months in second line. Nevertheless, it remains unclear whether this benefit also extends to patients with specific oncogenic mutations such as MET exon 14 skipping mutations, and metastatic NSCLC remains a deadly disease.

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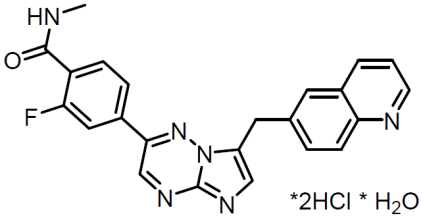
4 Quality Aspects

4.1 Drug Substance

INN: Capmatinib
Chemical name: 2-Fluoro-N-methyl-4-[7-(6-quinolinylmethyl)imidazo[1,2-b][1,2,4]triazin-2-yl] benzamide hydrochloride hydrate (1:2:1)
Molecular formula: Salt form on monohydrate basis = $C_{23}H_{17}FN_6O \cdot 2HCl \cdot H_2O$
Molecular mass: Salt form on monohydrate basis = 503.36
Molecular structure:



Capmatinib hydrochloride drug substance is a dihydrochloride salt in monohydrate form. It is a yellow crystalline powder. The drug substance is slightly hygroscopic and its solubility is pH dependent.

The drug substance is manufactured by a multiple-step chemical synthesis with final crystallisation, followed by a sieving step. The synthesis of the drug substance and the necessary in-process controls are described in detail.

The specifications are in line with the recommendations of the relevant ICH guidelines and are considered appropriate in order to ensure a consistent quality of capmatinib hydrochloride. Appropriate stability data have been generated, resulting in a suitable retest period.

4.2 Drug Product

The capmatinib film-coated tablet is an immediate release dosage form for oral administration. The 150 mg strength is a pale orange brown, ovaloid, curved tablet with bevelled edges, unscored, debossed with ‘DU’ on one side and ‘NVR’ on the other side. The 200 mg strength is a yellow, ovaloid, curved tablet with bevelled edges, unscored, debossed with ‘LO’ on one side and ‘NVR’ on the other side.

Capmatinib 150 mg and 200 mg film-coated tablet manufacturing involves standard unit operations, high-shear wet granulation, milling, drying, blending, compression and film coating.

For the control of the finished product, adequate tests and acceptance criteria for release and shelf-life have been established. The specifications include the parameters appearance, identity (NIRS, HPLC, UV), assay (HPLC), uniformity of dosage units (NIRS, HPLC), degradation products (HPLC), water content, dissolution and microbial tests. Analytical methods have been described and validated according to ICH requirements.

Appropriate stability data have been generated for 150 mg and 200 mg primary batches in the packaging material intended for commercial use and according to the relevant international guidelines.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

Regarding the marketing authorisation application for Tabrecta, Swissmedic conducted an abridged evaluation, which was based on the FDA assessment report (April 30, 2020) provided by the applicant.
Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Tabrecta in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. The low safety margins are acceptable considering the proposed indication. The adverse effects in animals generally correlate with findings in the clinical trials. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

ADME

Absorption

Capmatinib was classified as a BCS II substance due to its low solubility at higher pH values.

Fed administration of the 200 mg final market image tablet to healthy subjects resulted in an increase of capmatinib tmax from 1.5 h after fasted administration to 2 h and 3 h after administration with a low- and high-fat meal, respectively. The inter-individual variability of the capmatinib PK parameters was slightly lower after fed administration. The effect of both meal types on capmatinib Cmax and AUC was small (Cmax up to 15% ↑, AUC up to 47%↑). The capmatinib exposure was similar after fed and fasted administration of 400 mg twice daily (BID) to cancer patients. Capmatinib can be administered independently of food intake.

Dose Proportionality

There was a dose proportional increase of capmatinib exposure after fasted administration of single doses between 200 mg and 600 mg in healthy subjects. The pop PK analysis did not indicate major deviations from linearity across a dose range of 100 mg to 800 mg once daily (QD) and 100 mg to 600 mg BID in cancer patients.

Pharmacokinetics after multiple Dosing

The estimated capmatinib accumulation after BID dosing was 1.22. Time to steady state was estimated to be 48 h.

Distribution

The capmatinib mean blood/plasma AUC-ratio was 1.14 (range: 0.96 – 1.43). The mean in vitro blood to plasma ratio was about 1.5 up to capmatinib concentrations of 1000 ng/mL. At 10 000 ng/mL it decreased to 0.9, indicating a saturation of the distribution into red blood cells.

The in vitro plasma protein binding of capmatinib and its main metabolite CMN288 was approximately 96% and > 90%, respectively. Across the investigated range it was independent of the capmatinib/CMN288 concentration. The ex vivo capmatinib fraction unbound increased from 2.9% in subjects with normal hepatic function to 4.2% in subjects with severe hepatic impairment.

The capmatinib V/F was 163.8 L.

Metabolism - In vitro Data

Capmatinib was mainly metabolised by CYP3A4. The main metabolites CMN288 and M19 were formed by molybdenum-containing hydroxylase (AO). Together with human ADME data, the estimated fraction of metabolism through CYP3A4 was 40-50%, through AO it was up to 40%. However, the results of the itraconazole interaction study indicated a lower contribution of CYP3A4 to capmatinib metabolism.

Metabolism - Clinical Data

After administration of a ^{14}C-labelled capmatinib dose to healthy subjects, capmatinib represented the main proportion of radioactivity in plasma (42.9 % of the plasma AUC0-12h). The metabolite M16 (=> CMN288, formed by imidazo-triazinone formation) was the most prominent metabolite in plasma and amounted to 21.5% of the plasma AUC0-12h. It is not pharmacologically active.

Overall, more than 90% of detected radioactive components of the plasma AUC0-12h could be accounted for by capmatinib and structurally characterised metabolites.

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The metabolite profiles in urine consisted of one abundant metabolite (M16, CMN288) and numerous other metabolites. Unchanged capmatinib in urine was only detected in trace amounts (0.07% of the dose). The metabolite M16 (imidazo-triazinone formation) amounted to 2.9% of the dose. All other metabolites accounted for less than 2% of the dose. More than 19.2% of the dose (89% of total radioactivity in the 0-96 h urine pool) could be covered by capmatinib and structurally characterised metabolites.

Unchanged capmatinib amounted to 42.1% of the dose excreted in faeces. The most abundant metabolite in faeces was M16 (CMN288, 5.1%). More than 65.9% of dose (86.4% of total radioactivity in the 0-96 h faeces pool) could be covered by capmatinib and structurally characterised metabolites.

Elimination
After administration of a ^{14}C-labelled capmatinib dose, 21.8% and 77.9% of the administered dose were excreted in urine and faeces, respectively. The excretion of radioactivity was almost complete within 96 h postdose.

The capmatinib half-life was approximately 10 h in healthy subjects.

Special Populations / Intrinsic Factors

Hepatic function had a small effect on capmatinib pharmacokinetics. Compared to subjects with normal hepatic function, capmatinib total AUCinf was 23.3% lower in subjects with mild hepatic impairment, unchanged in subjects with moderate hepatic impairment and 24% higher in subjects with severe hepatic impairment. Capmatinib Cmax was 28% lower in subjects with mild hepatic impairment and unchanged in subjects with moderate or severe hepatic impairment.

Because of the increased fraction unbound, the half-life estimated from total capmatinib plasma concentration was shorter in subjects with impaired hepatic function. The unbound capmatinib AUCinf was about 20% lower in subjects with mild hepatic impairment, unchanged in subjects with moderate hepatic impairment and 78% higher in subjects with severe hepatic impairment. Unbound capmatinib Cmax was 24% lower in subjects with mild hepatic impairment, unchanged in subjects with moderate hepatic impairment and 46% higher in subjects with severe hepatic impairment. There was no statistically significant relationship between hepatic function parameters and capmatinib exposure. The CMN288 exposure and the metabolite/parent ratio were lower in subjects with impaired hepatic function.

The potential impact of race, sex, age, weight, renal and hepatic function on capmatinib PK was investigated in a pop PK analysis. The analysis included pharmacokinetic data of cancer patients only. The dataset included a total of 501 patients, with a sufficient number of patients ≥ 65 years, patients with mild hepatic impairment, or patients with mild or moderate renal impairment.
The dataset included only four patients with moderate and none with severe hepatic impairment. It included no patients with severe renal impairment.

The final pop PK model included the following covariate relationships:

- Asian origin as covariate of CL/F
- Body weight as covariate of CL/F and Vc/F

The effects of food and formulation on the capmatinib absorption parameters were implemented in the base model already and were also included in the final model.

The final pop PK model described the capmatinib (CAP) data reasonably well.

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The effect of age, gender, weight, Asian origin, mild hepatic impairment, mild or moderate renal impairment on CAP PK was small. Body weight had the highest impact. Compared to the reference weight range of 60 – 80 kg, capmatinib AUCtau,ss and Cmax,ss were 13% and 21% higher in a subject < 60 kg, respectively. For a subject > 80 kg, CAP AUCtau,ss and Cmax,ss were 11% and 17% lower, respectively.

The available pharmacokinetic data supported the dosing recommendations for the respective special populations.

Interactions

EFFECT OF OTHER DRUGS ON CAPMATINIB

In vitro Data
Capmatinib (CAP) was a substrate for CYP3A4 and P-gp. Based on the available in vitro data, its interaction potential as victim appeared to be low.

Clinical Data

Interacting Compound	GMR (90% CI)
Rabeprazole (PPI)	CAP AUCinf: 0.748 (0.637, 0.878) CAP Cmax: 0.625 (0.533, 0.734)
Itraconazole (CYP3A4 & P-gp inhibitor)	CAP AUCinf: 1.42 (1.33, 1.52) CAP Cmax: 1.03 (0.866, 1.22)
	CMN288 AUCinf: 17.9% ↑ CMN288 Cmax: ↔ Metabolite/Parent Ratio: ↓
Rifampicin (Inducer of CYPs & Transporters & Others)	CAP AUCinf: 0.335 (0.300, 0.374) CAP Cmax: 0.441 (0.387, 0.502)
	CMN288 AUCinf: 30% ↓ CMN288 Cmax: ↔ Metabolite/Parent Ratio: ↑

The clinical data were in agreement with the expectations based on the *in vitro* data. The effect of rabeprazole on capmatinib was due to capmatinib's pH-dependent solubility. Itraconazole had no major effect on capmatinib exposure, supporting the assumption of high permeability and limited contribution of P-gp to the capmatinib disposition. In addition, capmatinib was only partially metabolised by CYP3A4. Rifampicin appeared to induce both elimination pathways of capmatinib, resulting in a profound reduction of its exposure.

The available data supported the dosing recommendations for the co-administration of drugs affecting capmatinib.

EFFECT ON CAPMATINIB ON OTHER DRUGS

In vitro Data

All required CYPs and transporters were investigated at sufficiently high concentrations.

Based on the static DDI risk assessment, capmatinib was likely to interact with CYP1A2 (inhibition and induction), CYP2C8 (inhibition) and CYP3A4 (inhibition and induction) at therapeutic exposure. Furthermore, the inhibition of MATE1, MATE2K, as well as intestinal Pgp, BCRP and CYP3A4, could not be excluded. CMN288 was not likely to interact with CYPs or transporters at therapeutic exposure.

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Clinical Data

Interacting Compound	GMR (90% CI)
Midazolam (CYP3A4 substrate)	MID AUCinf: 1.09 (0.976, 1.22) MID Cmax: 1.22 (1.07, 1.38)
Caffeine (CYP1A2 substrate)	CAF AUCinf: 2.34 (2.08, 2.63) CAF Cmax: 1.04 (0.964, 1.13)
Digoxin (P-gp substrate)	DIG AUClast: 1.63 (1.42, 1.89) DIG Cmax: 1.74 (1.43, 2.13)
Rosuvastatin (BCRP and OATP1B1 substrate)	ROS AUCinf: 2.08 (1.56, 2.76) ROS Cmax. 3.04 (2.36, 3.92)

The expected inhibition of CYP1A2, P-gp and BCRP by capmatinib was confirmed by the clinical data. The capmatinib *in vitro* effects on CYP3A4 appeared to cancel each other out *in vivo*.

The available data supported the dosing recommendations for the co-administration of drugs affected by capmatinib.

Pharmacodynamics

An exposure-response analysis, but not a dedicated tQT study, was conducted for capmatinib. The results indicated that capmatinib did not prolong QTcF at therapeutic exposure. No data were available for supra-therapeutic exposure.

6.2 Dose Finding and Dose Recommendation

The applicant submitted study CINC280X2102 (EudraCT no. 2010-024101-12), a Phase I open-label dose escalation study with expansion to assess the safety and tolerability of capmatinib in patients with c-MET dependent advanced solid tumours. This study enrolled 38 patients in the dose-escalation phase and 93 in the dose-expansion phase.

A two-parameter Bayesian logistic regression model (BLRM) employing the escalation with overdose control (EWOC) principle was used during the escalation phase for dose level selection and for determination of the maximum tolerated dose/recommended phase 2 dose (MTD/RP2D). Dose-limiting toxicities were evaluated during the first cycle (28 days), but significant toxicities observed later in treatment could also influence further dose-escalation.

The study investigated two formulations of capmatinib: hard gelatin capsules and film-coated tablets.

The RP2D dose was determined to be 600 mg twice daily (BID) for the capsule formulation and 400 mg BID for the tablet formulation.

In total, 55 patients were included in the study with NSCLC, and the overall response rate in these patients was approximately 20% (13 responders according to the Blinded Independent Review Committee (BIRC)). Median progression-free survival (PFS) was 3.5 months according to the investigators and 3.7 months according to the BIRC.

6.3 Efficacy

One pivotal single-arm, multi-cohort phase 2 study is submitted, study CINC280A2201. This is an open-label study with capmatinib in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) wild type for EGFR and without an ALK translocation. The study started on 11 June 2015 and is ongoing and still enrolling new cohorts. At the time of data cut-off on 15 April 2019, 6 cohorts had enrolled 334 patients. Cohort 7 completed enrolment (32 patients) in the first quarter of

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2020. Data for cohort 7 will become available in the first quarter (Q1) of 2021, and the clinical study report (CSR) for the primary analysis is expected in Q1 2022. Cohorts were defined according to gene copy number (GCN) of MET, as well as the presence or absence of MET exon 14 skipping mutation (METex14 mut) regardless of GCN. The submitted CSR presents efficacy data on cohorts 4 and 5b. Cohort 4 enrolled 69 patients with METex14 mut NSCLC who had previously received one or two systemic treatments for advanced disease. Cohort 5b enrolled 28 METex14 mut NSCLC patients who were treatment-naïve. Cohort 6 enrolled patients with METex14 mut NSCLC who took capmatinib independent of food, while all other cohorts took capmatinib in a fasting state. Capmatinib was administered as film-coated tablets at a dosage of 400 mg (2 tablets of 200 mg) twice daily (bid) until progressive disease, intolerable toxicity, withdrawal of consent, investigator decision or death.

The statistical assumptions were that an objective response rate (ORR) of ≥35% with a lower bound of the 95% confidence interval (CI) >25% for pre-treated patient cohorts was chosen. If this ORR was not reached at interim analysis when the cohort was fully enrolled, it would be closed for futility. For treatment-naïve patients the ORR was set at ≥55% with a lower bound of the 95% CI >35%.

These assumptions seem reasonable in the context of the disease. In comparison, response rates for second-line immune checkpoint inhibitors in NSCLC range from 14% to 30%. The NSCLC response rates for first-line immune checkpoint inhibitors in combination with chemotherapy are around 50%.

At the time of data cut-off the median study follow-up was 22.5 months for cohort 4 (pre-treated) and 16.8 months for cohort 5b (treatment-naïve).

Patient disposition at data cut-off shows that the primary reason for treatment discontinuation was progressive disease (PD) in 55% of previously treated patients (cohort 4) and 40% of first-line treated patients (cohort 5b). One in five patients (20%) discontinued treatment due to adverse events (AEs) in cohorts 4 and 5b.

More than one third of patients in cohorts 4 and 5b were 75 years and older. This corresponds to the population described in the literature for METex14 mutant patients as being of older age with a median age of 73 years. There was also a predominance of women, while in the overall population there were more male patients. Finally, the majority of patients in cohorts 4 and 5b were non-smokers, which contrasts with what has been described in the literature, where METex14 mutant patients had a lower never-smoker proportion than other genetically defined subpopulations. Most patients had adenocarcinoma, 76.8% in cohort 4 and 89.3% in cohort 5b. Less than 10% of patients presented squamous cell carcinoma (6 patients [8.7%] in cohort 4, and 2 patients [7.1%] in cohort 5b). Nearly all patients presented metastatic disease at the time of study enrolment (only 2 patients in cohort 4 [1.8%] had locally advanced disease).

In cohort 4, the primary endpoint of ORR by the BIRC was met, with 28/69 (40.6%) patients presenting a partial response to capmatinib with a lower bound of the 95% CI of 28.9%.

The primary endpoint was also met in cohort 5b of treatment-naïve patients, with an ORR of 67.9% including one complete response and 18 partial responses out of 28 patients with the lower bound of 95% CI of 47.6%. In cohort 6 (one prior line of treatment, METex14 mut), ORR was 48.4%, confirming the ORR found in cohort 4 (one or two prior lines) of 40.6%. Data for cohort 7 (treatment-naïve, confirmatory cohort of cohort 5b) is not yet available.

The key secondary endpoint was duration of response (DOR). The estimated median DOR for cohort 4 (pre-treated patients, one or two prior lines) was 9.72 months (95% CI: 5.55, 12.98). In cohort 5b (treatment-naïve patients), the estimated median DOR was 12.58 months (95% CI: 5.55, NE). DOR for cohort 6 (one prior line of treatment) was also provided and was 6.93 months (95% CI: 4.17, NE) with a short median follow up of 5.6 months.

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Median OS (68.1% of events) for cohort 4 (second and third line) is 13.6 months (95% CI: 8.61, 22.24) with a median follow up of 11.5 months. Median OS for cohort 5b (first line) is 20.8 months (95% CI: 12.42, NE) with a median follow up of 18.8 months and 53.6% of events. In cohort 6 (second line), with a median follow up of 9.2 months, the median OS has not been reached. However, the data are not mature with 25.8% of events. To put these results in context, median OS with first-line immune checkpoint inhibitors in combination with chemotherapy in unselected NSCLC patients ranges from 18 to 22 months. Median OS in unselected NSCLC patients with second-line immune checkpoint inhibitors ranges from 9 to 14 months.

Median PFS is 5.4 months (4.17 to 6.97) in cohort 4 (second and third line) and 12.4 months (95% CI: 8.21, NE) months in cohort 5b (treatment-naïve). In cohort 6 (second line), median PFS is 8.1 months (95% CI: 4.17, 9.86). In first-line studies of unselected NSCLC patients with chemotherapy and immune checkpoint inhibitors, median PFS ranged from 7 to 9 months. In second line, treatment with immune checkpoint inhibitors in unselected NSCLC patients resulted in a median PFS of 2.8 to 4 months.

6.4 Safety

The summary of clinical safety was mainly based on the 334 patients with NSCLC enrolled in study A2201. In addition, there was a cohort of all NSCLC subjects, including patients from other studies treated at recommended dose comprising 419 patients as well as a cohort of 541 all patients with solid tumours.

Safety is discussed based on data from the A2201 study, given that the pooled data from the all-NSCLC population and the all-solid-tumour population vary only slightly.

Exposure
Mean exposure in all patients of the study A2201 safety cohort was 25.8 weeks. In cohort 4, the exposure was longer than in the all-patient cohort and was 33.0 weeks. In cohort 5b, it was 44.0 weeks. The median duration of exposure was lower than the mean duration of exposure in the overall safety population, at 14.9 weeks, due to the wide range (0.4 to 177 weeks). This difference was smaller in cohort 4 where the mean duration of exposure was 33.0 weeks and the median duration was 22.1 weeks. In cohort 5b, the median duration was actually higher than the mean duration of exposure, at 47.9 weeks versus 44.0 weeks.

Only slightly more than half of patients achieved a relative dose intensity of >90% in cohorts 4 and 5b. The mean actual dose was between 670 mg and 710 mg per day.

A majority of patients experienced dose reductions (59.4% in cohort 4 and 50% in cohort 5b) and dose interruptions (70% in cohort 4 and 77% in cohort 5b). The median time to first dose interruption was different between the 2 cohorts, at 6.7 weeks in cohort 4 and 17.9 weeks in cohort 5b. However, mean time to first dose interruption was more similar, at 10.8 weeks in cohort 4 and 15.6 weeks in cohort 5b.

Nearly all patients experienced at least one adverse event (AE), and the vast majority of AEs were considered treatment-related. Approximately 50% of patients experienced serious AEs, and approximately one third of serious adverse events (SAEs) (15-17%) were considered treatment-related. There were two fatal SAEs in each cohort, one of which – in cohort 4 – was considered treatment-related. Approximately two thirds of patients experienced AEs leading to dose adjustment or interruption, and 70% required additional therapy due to treatment-related AEs.

Adverse events
AEs were frequent and concerned many system organ classes (SOCs), including grade 3 and 4 toxicities. In the all-patients safety population, 14 SOCs showed an AE incidence of >20%. This listing

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is irrespective of treatment-relatedness, and a number of AEs were likely due to the underlying disease and comorbidities of an elderly patient population. Nevertheless, in the SOC investigations, 60% of patients presented AEs of any grade and 25-27% presented grade 3-4 AEs.

The most frequently observed AEs were **peripheral oedema** (50 and 75%), including approximately 10% with grade 3-4 events. Other most frequent AEs were **nausea**, **vomiting**, **blood creatinine increased**, **fatigue**, **decreased appetite**, all with an incidence of >20%. Frequent grade 3-4 AEs observed particularly in cohorts 4 and 5b were increased amylase and lipase levels. Liver transaminases were also increased to grade 3-4 in 3-4% of patients.

84.4% of all patients presented AEs considered treatment-related, and 35.6% presented treatment-related grade 3-4 AEs. The majority of the most frequently observed AEs were considered treatment-related, in particular peripheral oedema (41.6%, 7.5% grade 3-4), nausea (33.2%, 1.8% grade 3-4), blood creatinine increased (19.5%, no grade 3-4), vomiting (18.9%, 1.8% grade 3-4), fatigue (13.8%, 3.0% grade 3-4), amylase increased (8.1%, 3.0% grade 3-4) and lipase increased (7.5%, 5.1% grade 3-4).

Grade 3 and 4 adverse events
Grade 3-4 AEs were observed in 65.6% of all patients. The most frequently reported grade 3/4 AEs were: peripheral oedema (8.4%), dyspnoea (6.9%), alanine aminotransferase (ALT) increased (5.7%), and lipase increased (5.4%), fatigue (4.8%), asthenia (3.6%), amylase increased (3.6%), pulmonary embolism (3.3%), and aspartate transaminase (AST) increased (3.0%). In addition to pulmonary embolism, observed in 5.5% of patients (3.3% grade 3-4), there were deep vein thromboses in 1.8% of patients and embolism in 1.5% of patients, giving a total of nearly 9% thromboembolic events.

Deaths
There were 54 on-treatment deaths in the total group of 334 patients (15.5%), 43 of which were due to the underlying disease. Of the 11 remaining deaths due to other causes, four were considered treatment-related by the investigators. One of these four deaths occurred in cohort 4 (1/69 [1.4%]) and was due to pneumonitis.

Serious adverse events (SAEs)
Approximately 50% of patients experienced an SAE and approximately 40% an SAE of grade 3 or 4. However, only about one quarter of these (12.9%) were considered treatment-related. Dyspnoea, pneumonia, pleural effusion, deterioration of general health were the most frequently observed SAEs, and these were likely due to the underlying disease. Vomiting (2.4%), nausea (2.1%), pulmonary embolism (1.8%), and peripheral oedema (1.2%) were likely related to treatment.

Treatment interruption and discontinuation due to AEs
One in eight (16.2%) patients discontinued treatment permanently due to an AE. The most frequent AEs leading to permanent discontinuation were peripheral oedema (1.8%), pneumonitis (1.8%), fatigue (1.5%), increased AST and ALT (0.9% each), nausea (0.9%), and vomiting (0.9%).
AEs leading to dose interruptions or reductions were similar to the AEs leading to treatment discontinuation. The most frequent ones were peripheral oedema, increased blood creatinine, nausea, and vomiting. Ninety percent (90%) of patients experienced AEs requiring additional therapy and 50% experienced grade 3-4 AEs requiring additional therapy. The most frequent AE requiring additional therapy was peripheral oedema.

Adverse events of special interest
Hepatotoxicity was observed in 28.1% of all patients, with nearly 10% presenting grade 3-4 toxicity. Renal dysfunction was also observed frequently, as were CNS toxicity and pancreatitis. All of these events occurred in more than 10% of the safety population. Pneumonitis was observed in 4.5% of patients (1.8% with grade 3, no grade 4 – but one grade 5) and QTc interval prolongation in 3.0%. Teratogenicity was not observed, but there were no pregnancies.

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Hepatotoxicity was mostly due to AST and ALT increased, hypoalbuminemia, gamma GT increased, alkaline phosphatase increased. Only 6 patients (1.8%) discontinued treatment due to hepatotoxicity.

Renal dysfunction was mostly due to increased blood creatinine which, according to the applicant, is due to potent inhibition of renal transporter MATE1 and MATE2k. Three patients presented renal failure and acute kidney injury.

CNS toxicity was mostly due to dizziness, but also seizures and epilepsy (although the last two occurred in patients with baseline brain metastases).

Pancreatitis was mostly due to elevated pancreatic enzymes. Only one patient presented acute clinical pancreatitis.

Pneumonitis/interstitial lung disease (ILD) occurred in 15 patients (4.5%) and was of grade 3 in 6 (1.8%) patients. There were no grade 4 events. Seven (7) patients developed an SAE of pneumonitis/ILD, and one patient experienced a fatal event (in cohort 4). Eight (8) patients discontinued treatment due to pneumonitis/ILD and 4 had dose adjustments.

QTc interval prolongation of > 30 ms and ≤ 60 ms from baseline occurred in 11 patients (3.4%), and of > 60 ms from baseline in one. No patient discontinued treatment due to AE QTc prolongation.

Clinical chemistry
A decrease in albumin was observed in 71.6% of patients, and while there were only a few grade 3-4 events, it is important to bear in mind that grade 2 hypoalbuminemia refers to an albumin concentration of 20 g/l to <30 g/l. Grade 3 is <20 g/l. This could possibly explain the high incidence of peripheral oedema. Also of note was the very high proportion of patients showing an increase in blood creatinine, possibly due to the inhibition of renal transporters. Finally, a significant proportion of patients showed an increase in the potassium level, which needs to be monitored in order to avoid cardiac rhythm problems.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Lung cancer is the leading cause of cancer death in men and the second leading cause of cancer death in women in the Western world. In Switzerland, approximately 4’400 new patients are diagnosed each year with lung cancer (www.nicer.org). Non-small cell lung cancer (NSCLC) accounts for 80%-90% of lung cancers, and approximately 2% (squamous cell carcinoma) to 3% (adenocarcinoma) of patients with NSCLC have tumours containing MET gene alterations. A total prevalence of about 100 to 200 patients with MET-mutated NSCLC is estimated in Switzerland. While progress has been made in the past few years in treating lung cancer, metastatic non-small cell lung cancer remains a deadly disease with survival measured in months. Therefore, there is a medical need for improved treatment.

Clinical Pharmacology
Capmatinib can be administered independently of food. Its exposure increased proportionally to the administered dose in the therapeutic dose range. There was no indication of major pharmacokinetic nonlinearities. From a pharmacokinetic point of view, no dose adjustments are required for subjects with hepatic impairment of all degrees, mild or moderate renal impairment or elderly subjects. No pharmacokinetic data in patients with severe renal impairment are available. The interaction potential of capmatinib as victim appeared to be low. Capmatinib caused no QTc prolongation at therapeutic exposure. No data regarding QTc prolongation at supratherapeutic capmatinib exposure are available.

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Capmatinib should not be co-administered with strong or moderate CYP inducers. Capmatinib showed a pH-dependent solubility. Therefore, caution is required during the co-administration with PPIs. Capmatinib has an interaction potential as perpetrator. Dose adjustments of substrates for CYP1A2, Pgp or BCRP/OATP1B1 with narrow therapeutic index are most likely required.

Conclusions: Clinical Pharmacology
There were no major pharmacokinetic problems associated with capmatinib.

Clinical
The pivotal single-arm, multi-cohort phase 2 study A2201 reached its primary endpoint of overall response rate (ORR) in cohorts of pre-treated and treatment-naïve non-small cell lung cancer patients whose tumours harboured a MET exon 14 skipping mutation. ORR was 40.6% (cohort 4) and 48.4% (cohort 6) in pre-treated patients and 67.9% in treatment-naïve patients, which is numerically higher than for other approved therapies in Switzerland. In addition, a median PFS of 5-12 months depending on treatment line and a median OS of 14 to 21 months are clinically meaningful in these patient populations.

The pivotal study A2201 is a single-arm trial that has enrolled 69 pre-treated patients in cohort 4 and 28 treatment-naïve patients in cohort 5b. Since there is no comparator arm, there is a possibility of selection bias. It is unclear how capmatinib would compare to standard of care, particularly because the literature on prognosis for this specific genetically defined subpopulation is conflicting. In addition, follow-up is short and the number of patients limited.

Only slightly more than half of patients had a relative dose intensity of >90%. Nearly all patients experienced adverse events, and approximately 50% experienced serious adverse events. Nevertheless, this incidence of SAEs is similar to other standard treatments, particularly first-line chemotherapy in combination with immune checkpoint inhibitors. The most frequent AEs considered treatment-related were peripheral oedema, nausea, vomiting, fatigue, asthenia, blood creatinine increased, and pancreatic enzymes increased. Overall, the safety profile seems manageable in a patient population with age- and disease-related comorbidities.

The number of patients in the safety cohort, particularly for first-line treatment, is limited, as is the follow-up.

Conclusions: Clinical
A response rate of 41% to 48% in the second- and third-line treatment of NSCLC with a manageable safety profile is an alternative for a defined elderly population with metastatic NSCLC with the given molecular MET exon 14 skipping mutation. The risk-benefit evaluation is positive for the requested temporary authorisation in accordance with Art. 9a TPA.

For first-line treatment, an overall response rate of 68% is clinically relevant although the safety data remain limited. However, with the enrolment of an additional 32 treatment-naïve patients for whom primary analyses will be available during the first quarter of 2021, the risk-benefit evaluation is currently positive for the requested temporary authorisation in accordance with Art. 9a TPA.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Tabrecta, film-coated tablets was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This allows quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse effects. See “Adverse effects” for information on reporting adverse effects. Tabrecta is subject to a temporary marketing authorisation (see “Properties/Actions”).

Tabrecta®

Composition

Active substances

Capmatinib as capmatinib hydrochloride monohydrate

Excipients

Tabrecta 150 mg

Film-coated tablet core: Microcrystalline cellulose, mannitol (E421), crospovidone, povidone K30, magnesium stearate, colloidal anhydrous silica, sodium lauryl sulfate.

Tablet coating: Hypromellose, E171, macrogol 4000, talc, E172 (yellow), E172 (red), E172 (black).

Contains 0.12 mg sodium.

Tabrecta 200 mg

Film-coated tablet core: Microcrystalline cellulose, mannitol (E421), crospovidone, povidone K30, magnesium stearate, colloidal anhydrous silica, sodium lauryl sulfate.

Tablet coating: Hypromellose, E171, macrogol 4000, talc, E172 (yellow).
Contains 0.16 mg sodium.

Pharmaceutical form and quantity of active substance per unit

Tabrecta 150 mg

Each 150 mg film-coated tablet contains 183 mg, capmatinib hydrochloride monohydrate, equivalent to 150 mg capmatinib as free base.
Pale orange-brown, ovaloid, curved film-coated tablet with bevelled edges, unscored, debossed with “DU” on one side and “NVR” on the other side.

Tabrecta 200 mg

Each 200 mg film-coated tablet contains 244 mg, capmatinib hydrochloride monohydrate, equivalent to 200 mg capmatinib as free base.
Yellow, ovaloid, curved film-coated tablet with bevelled edges, unscored, debossed with “LO” on one side and “NVR” on the other side.

Indications/Potential uses

Tabrecta is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with a MET exon 14 skipping mutation.
The efficacy and safety of Tabrecta have not been studied in patients with other oncogenic driver mutations, including EGFR or ALK tumour aberrations (see “Warnings and precautions”).

Dosage/Administration

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

Usual dosage

The recommended dose of Tabrecta is 400 mg orally twice daily with or without food (see “Pharmacokinetics”).

Treatment duration

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

Dose modification due to adverse effects/interactions

The recommended dose reduction schedule in the event of adverse drug reactions (ADRs) based on individual safety and tolerability is provided in Table 1.

Table 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 discontinued in patients unable to tolerate 200 mg twice daily.

Recommendations for dose modifications of Tabrecta due to ADRs are provided in Table 2 (see also “Adverse effects”).

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

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

Hepatotoxicity	
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. If recovered to baseline within 7 days, resume Tabrecta treatment at the same dose, otherwise resume Tabrecta treatment at a reduced dose as per Table 1.
	Grade 4 (>20.0 x ULN): Permanently discontinue Tabrecta.
Combined elevations in ALT and/or AST with concurrent total bilirubin increase, in the absence of cholestasis or haemolysis	If ALT and/or AST >3.0 x ULN occurs along with total bilirubin >2.0 x ULN, irrespective of baseline grade, permanently discontinue Tabrecta.
Isolated total bilirubin elevation from baseline, without concurrent ALT and/or AST increase.	**Grade 2 (>1.5 to ≤3.0 x ULN):** Temporarily withhold Tabrecta until recovery to baseline bilirubin. If recovered to baseline within 7 days, resume Tabrecta treatment at the same dose, otherwise resume Tabrecta treatment at a reduced dose as per Table 1.
	Grade 3 (>3.0 to ≤10.0 x ULN): Temporarily withhold Tabrecta until recovery to baseline bilirubin. If recovered to baseline within 7 days, resume Tabrecta treatment at a reduced dose as per Table 1, otherwise permanently discontinue Tabrecta.
	Grade 4 (>10.0 x ULN): Permanently discontinue Tabrecta.
Other adverse drug reactions	
	Grade 2: Maintain dose. If the adverse drug reaction is intolerable, consider temporarily withholding Tabrecta until resolved, then resume Tabrecta treatment at a reduced dose as per Table 1.
	Grade 3: Temporarily withhold Tabrecta until the adverse drug reaction is resolved, then resume Tabrecta treatment at a reduced dose as per Table 1.
	Grade 4: Permanently discontinue Tabrecta.

List of abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ILD, interstitial lung disease; ULN, upper limit of normal.
Grading is based on CTCAE criteria version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events).
Baseline = at the time of treatment initiation.

Special populations

Patients with hepatic impairment

No dose adjustment is necessary in patients with mild, moderate or severe hepatic impairment (see “Pharmacokinetics”).

Patients with renal impairment

Caution is required in patients with severe renal impairment as Tabrecta has not been studied in these patients. No dose adjustment is necessary in patients with mild or moderate renal impairment (see “Pharmacokinetics”).

Elderly patients

No dose adjustment is required in patients over 65 years of age.

Children and adolescents

The safety and efficacy of Tabrecta in children and adolescents have not been established. No data are available.

Method of administration

Tabrecta should be taken twice daily with or without food. Tabrecta should be swallowed whole and must 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.

Contraindications

Hypersensitivity to the active substance or any of the excipients of the medicinal product.

Warnings and precautions

Interstitial lung disease (ILD)/pneumonitis

ILD/pneumonitis, which can be fatal, has occurred in patients treated with Tabrecta (see “Adverse effects”). In patients with worsening of pulmonary symptoms indicative of ILD/pneumonitis (e.g. dyspnoea, cough, fever) a relevant investigation should be performed. Tabrecta should be immediately temporarily withheld in patients with suspected ILD/pneumonitis. The medicinal product must be permanently discontinued if no other potential causes of ILD/pneumonitis are identified (see “Dosage/Administration”).

Hepatotoxicity

Transaminase elevations have occurred in patients treated with Tabrecta (see “Adverse effects”). 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. In patients in whom transaminase or bilirubin elevations are determined, more frequent testing should be performed. Based on the severity of the adverse drug reaction, Tabrecta must be temporarily withheld, the dose reduced or permanently discontinued as described in Table 2 (see “Dosage/Administration”).

Embryo-fetal toxicity

Findings from animal studies and its mechanism of action suggest that Tabrecta can cause fetal harm when administered to pregnant women. Oral administration of capmatinib to pregnant rats and rabbits during organogenesis resulted in fetotoxicity and teratogenicity. Pregnant women and women of child-bearing potential should be advised of the potential risk to the fetus if Tabrecta is used during pregnancy or if the patient becomes pregnant while taking Tabrecta. Sexually active females of child-bearing 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 could become pregnant should use condoms during treatment with Tabrecta and for at least 7 days after the last dose (see “Pregnancy/Breast-feeding” and “Preclinical data”).

Photosensitivity

Based on findings from animal studies there is a potential risk of photosensitivity reactions with Tabrecta (see “Preclinical data”). In clinical studies it was recommended that patients take precautionary measures against ultraviolet exposure such as the use of sunscreen or protective clothing during treatment with Tabrecta. Patients should be advised to minimise direct ultraviolet exposure while taking Tabrecta.

Concomitant oncogenic driver mutations

The efficacy and safety of Tabrecta have not been studied in patients with other oncogenic driver mutations, including EGFR or ALK tumour aberrations.

Sodium

This medicinal product contains less than 1 mmol (23 mg) of sodium per film-coated tablet, making it practically “sodium-free”.

Interactions

Effect of Tabrecta on other medicinal products

Substrates of CYP enzymes

In cancer patients co-administration of caffeine (CYP1A2 probe substrate) with multiple doses of capmatinib (400 mg twice daily) increased caffeine AUC_{inf} by 134% with no increase in caffeine C_{max} compared to administration of caffeine alone. Caution is required during concomitant use of Tabrecta with sensitive CYP1A2 substrates with a narrow therapeutic index, particularly theophylline and tizanidine. Decrease the dose of CYP1A2 substrates as per the relevant prescribing information.

In cancer patients co-administration 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_{inf} and 22% increase in C_{max}) compared to administration of midazolam alone. Therefore, clinically relevant drug interactions between capmatinib and CYP3A substrates are unlikely to occur.

Substrates of transporters

In cancer patients co-administration of digoxin (P-gp substrate) with multiple doses of capmatinib (400 mg twice daily) increased digoxin AUC_{inf} by 47% and C_{max} by 74% compared to administration of digoxin alone. In cancer patients co-administration of rosuvastatin (BCRP substrate) with multiple doses of capmatinib (400 mg twice daily) increased AUC_{inf} by 108% and C_{max} by 204% compared to administration of rosuvastatin alone. Caution is required during concomitant use of Tabrecta with P-gp and BCRP substrates. Decrease the dose of P-gp and/or BCRP substrates as per the relevant prescribing information.

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 or induction of CYP2C8, CYP2C9, CYP2C19 and CYP2B6.

Interactions between transporters and Tabrecta

Capmatinib and its major metabolite, CMN288, showed reversible inhibition of renal transporters MATE1 and MATE2K at clinically relevant concentrations. Based on *in vitro data* 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*.

Capmatinib is not an inhibitor of renal transporters OAT1 or OAT3. Based on *in vitro* data capmatinib is a P-gp substrate and not a BCRP and MRP2 substrate. Capmatinib is not a substrate of transporters involved in active hepatic uptake in primary human hepatocytes.

Effect of other medicinal products on Tabrecta

Strong CYP3A inhibitors

In healthy subjects co-administration of a single 200 mg capmatinib dose with the strong CYP3A inhibitor itraconazole (200 mg once daily for 10 days) increased capmatinib AUC_{inf} by 42% with no increase in capmatinib C_{max} compared to administration of capmatinib alone. Caution is required during concomitant use of Tabrecta with strong CYP3A inhibitors, particularly clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil and voriconazole.

Strong CYP3A inducers

In healthy subjects co-administration of a single 400 mg capmatinib dose with the strong CYP3A inducer rifampicin (600 mg once daily for 9 days) decreased capmatinib AUC_{inf} by 67% and C_{max} by 56% compared to administration of capmatinib alone. Concomitant use of Tabrecta with strong CYP3A inducers, particularly carbamazepine, phenobarbital, phenytoin, rifampicin and St. John's wort (*Hypericum perforatum*) should be avoided. An alternative concomitant medication with no or minimal potential to induce CYP3A should be considered.

Moderate CYP3A inducers

Simulations using physiologically based pharmacokinetic (PBPK) models predicted that co-administration of a 400 mg capmatinib dose with the moderate CYP3A inducer efavirenz (600 mg once daily for 20 days) would result in a 44% decrease in capmatinib AUC_{0-12h} and 34% decrease in C_{max} at steady state compared to administration of capmatinib alone. Co-administration of Tabrecta with moderate CYP3A inducers should be avoided. An alternative concomitant medication with no or minimal potential to induce CYP3A should be considered.

Medicinal products that increase gastric pH

Capmatinib demonstrates pH-dependent solubility and becomes poorly soluble as pH increases *in vitro*. Medicinal products that reduce gastric acid (e.g. proton pump inhibitors, H_2 receptor antagonists, antacids) may alter the solubility of capmatinib and reduce its bioavailability. In healthy subjects co-administration of a single 600 mg capmatinib dose with proton pump inhibitor rabeprazole (20 mg once daily for 4 days) decreased capmatinib AUC_{inf} by 25% and C_{max} by 38% compared to administration of capmatinib alone. Caution is required during concomitant use 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.

Drug-food/drink interactions

Tabrecta may be taken with or without food (see “Dosage/Administration” and “Pharmacokinetics”).

Pregnancy/Breast-feeding

Women of childbearing potential and men of reproductive potential

Pregnancy testing

A pregnancy test must be performed on women of childbearing potential prior to the start of treatment with Tabrecta.

Contraception

Females
Sexually active females of child-bearing 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.

Pregnancy

There are no studies in pregnant women to inform a medicinal product-associated risk. Embryo-fetal toxicity occurred in animal studies (see “Preclinical data”). Pregnant women and women of childbearing potential should be advised of the potential risk to the fetus. Tabrecta should not be used during pregnancy unless clearly necessary.

Breast-feeding

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

Fertility

There are no data on the effect of capmatinib on human fertility. Fertility studies with capmatinib were not conducted in animals. Animal studies at clinically relevant human exposure did not indicate any effect of capmatinib on female or male reproductive organs (see “Preclinical data”).

Effects on ability to drive and use machines

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

Adverse effects

Summary of the safety profile

The safety of Tabrecta was evaluated in patients with locally advanced or metastatic NSCLC in the pivotal, global, prospective, multi-cohort, non-randomised, 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 safety of Tabrecta was also assessed in a pool of all NSCLC patients (N=419; of whom N=334 patients from study A2201).

The median duration of exposure to Tabrecta across all cohorts was 13.1 weeks (range: 0.1 to 187.0 weeks). Dose reductions due to adverse events (AEs), regardless of cause, occurred in 78 of all Tabrecta-treated NSCLC patients (18.6%) and treatment interruptions due to AEs, regardless of cause, occurred in 231 of all Tabrecta-treated NSCLC patients (55.1%). No negative effects on treatment efficacy were determined in patients whose dose was reduced or treatment interrupted due to AEs. Permanent discontinuation of Tabrecta due to AEs, regardless of cause, was reported in 69 of all Tabrecta-treated NSCLC patients (16.5%). The most frequent AEs (≥0.5%) leading to permanent discontinuation of Tabrecta were peripheral oedema (1.9%), pneumonitis (1.4%), fatigue (1.2%), increased ALT (1.0%), increased AST (0.7%), nausea (0.7%), vomiting (1.0%), increased blood bilirubin (0.5%), increased blood creatinine (0.7%), general physical health deterioration (0.7%), ILD (0.5%), organising pneumonia (0.5%), pneumonia (0.5%), hypoalbuminaemia (0.5%) and hypersensitivity reactions (0.5%).

Serious AEs due to any cause were reported in 211 of all Tabrecta-treated NSCLC patients (50.4%). Serious AEs due to any cause occurring in ≥2% of patients included dyspnoea (6.7%), pneumonia (4.8%), pleural effusion (3.3%), general physical health deterioration (3.1%), vomiting (2.6%), nausea (2.4%) and pulmonary embolism (2.1%). Serious treatment-related AEs were reported in 53 of all Tabrecta-treated NSCLC patients (12.6%). The most frequent serious treatment-related AEs (≥1.0%) in Tabrecta-treated patients were nausea (1.4%) and vomiting (1.7%).

15 of all Tabrecta-treated NSCLC patients (3.6%) died while on treatment with Tabrecta due to causes other than the underlying malignancy. 4 on-treatment deaths were assessed by the investigator as suspected to be related to treatment (pneumonitis, cardiac arrest, hepatitis, organising pneumonia).

The most commonly reported ADRs with an incidence of ≥20% (any grade) in all Tabrecta-treated NSCLC patients were peripheral oedema, nausea, fatigue, vomiting, dyspnoea, increased blood creatinine and decreased appetite. The most commonly reported grade 3/4 ADRs with an incidence of ≥5% in all Tabrecta-treated NSCLC patients were fatigue, peripheral oedema, dyspnoea, increased alanine aminotransferase and increased lipase.

Adverse drug reactions from clinical studies are listed by MedDRA system organ class (Table 3). Within each system organ class the adverse drug reactions are listed by frequency, with the most frequent adverse drug 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 3 Adverse drug reactions in all Tabrecta-treated NSCLC patients (n=419)

Adverse drug reactions	All grades n (%)	Frequency category	Grade 3/ 4 n (%)	Frequency category
Infections and infestations				
Cellulitis	11 (2.6)	Common	3 (0.7)*	Uncommon
Metabolism and nutrition disorders				
Decreased appetite	91 (21.7)	Very common	5 (1.2)*	Common
Hypophosphataemia	27 (6.4)	Common	11 (2.6)	Common
Hyponatraemia	22 (5.3)	Common	14 (3.3)	Common
Vascular disorders				
Embolism[7]	28 (6.7)	Common	17 (4.1)	Common
Deep vein thrombosis	7 (1.7)	Common	1 (0.2)*	Uncommon
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	106 (25.3)	Very common	28 (6.7)	Common
Cough	68 (16.2)	Very common	2 (0.5)*	Uncommon
ILD/pneumonitis	15 (3.6)	Common	6 (1.4)*	Common
Gastrointestinal disorders				
Nausea	190 (45.3)	Very common	12 (2.9)*	Common
Vomiting	124 (29.6)	Very common	11 (2.6)*	Common
Diarrhoea	80 (19.1)	Very common	3 (0.7)*	Uncommon
Constipation	73 (17.4)	Very common	4 (1.0)*	Common
Increased amylase	39 (9.3)	Common	18 (4.3)	Common
Increased lipase	35 (8.4)	Common	22 (5.3)	Common
Acute pancreatitis	2 (0.5)	Uncommon	1 (0.2)*	Uncommon
Hepatobiliary disorders				
Increased alanine aminotransferase	52 (12.4)	Very common	24 (5.7)	Common
Hypoalbuminaemia	56 (13.4)	Very common	8 (1.9)*	Common
Increased aspartate aminotransferase	36 (8.6)	Common	13 (3.1)*	Common
Increased blood bilirubin	13 (3.1)	Common	2 (0.5)*	Uncommon
Skin and subcutaneous tissue disorders				
Pruritus[1]	41 (9.8)	Common	1 (0.2)*	Uncommon
Rash	35 (8.4)	Common	4 (1.0)	Common
Urticaria	4 (1.0)	Common	2 (0.5)*	Uncommon

Renal and urinary disorders				
Increased blood creatinine	102 (24.3)	Very common	0	--
Acute kidney injury[2]	8 (1.9)	Common	1 (0.2)*	Uncommon
General disorders and administration site conditions				
Peripheral oedema[3]	212 (50.6)	Very common	32 (7.6)*	Common
Fatigue[4]	148 (35.3)	Very common	34 (8.1)*	Common
Non-cardiac chest pain[5]	60 (14.3)	Very common	8 (1.9)*	Common
Back pain	60 (14.3)	Very common	4 (1.0)*	Common
Pyrexia[6]	59 (14.1)	Very common	4 (1.0)*	Common
Decreased weight	37 (8.8)	Common	3 (0.7)	Uncommon

[1] Pruritus includes preferred terms pruritus, allergic pruritus and generalised pruritus.
[2] Acute kidney injury includes preferred terms acute kidney injury and renal failure.
[3] Peripheral oedema includes preferred terms peripheral swelling, peripheral oedema and fluid overload.
[4)] Fatigue includes preferred terms fatigue and asthenia.
[5] Non-cardiac chest pain includes preferred terms chest discomfort, musculoskeletal chest pain, non-cardiac chest pain and chest pain.
[6)] Pyrexia includes preferred terms pyrexia and increased body temperature.
[7)] Embolism includes preferred terms pulmonary embolism and embolism.
[8)] Rash includes preferred terms rash, maculopapular rash, macular rash, erythematous rash.
** No grade 4 ADRs reported in all Tabrecta-treated NSCLC patients.*

Description of selected adverse effects

ILD/pneumonitis

Any grade ILD/pneumonitis was reported in 15 of all 419 Tabrecta-treated NSCLC patients (3.6%). Grade 3 ILD/pneumonitis was reported in 6 of all Tabrecta-treated NSCLC patients (1.4%), with a fatal event of pneumonitis reported in 1 patient (0.2%). ILD/pneumonitis occurred in 8 of 208 Tabrecta-treated NSCLC patients (3.8%) with a history of prior radiotherapy and 7 of 211 Tabrecta-treated NSCLC patients (3.3%) who did not receive prior radiotherapy. 8 of all Tabrecta-treated NSCLC patients (1.9%) discontinued Tabrecta due to ILD/pneumonitis. ILD/pneumonitis mostly occurred within 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).

Hepatoxicity

Any grade ALT/AST elevations were reported in 54 of all 419 Tabrecta-treated NSCLC patients (12.9%). Grade 3/4 ALT/AST elevations were observed in 24 of all 419 Tabrecta-treated NSCLC patients (5.7%). 4 of all Tabrecta-treated NSCLC patients (1.0%) discontinued Tabrecta due to ALT/AST elevations. ALT/AST elevations mostly occurred within 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 36.0 weeks).

Reporting suspected adverse effects after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse effects via the online portal EIViS (Electronic Vigilance System). You can find further information at www.swissmedic.ch.

Overdose

There is only limited experience of overdose with Tabrecta in clinical studies. 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.

Properties/Actions

ATC code

L01EX17

Mechanism of action

Capmatinib is an oral, 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 1,000 times or greater when compared to more than 400 other kinases or mutant kinase variants. At tolerated doses capmatinib treatment results in regression of tumour 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 signalling proteins as well as proliferation and survival of MET-dependent cancer cells.

Pharmacodynamics

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 tumour 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 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 ms. A concentration-QT analysis showed that the estimated mean QTcF increase from baseline was 1.33 ms with an upper-bound 90% confidence interval (CI) of 2.58 ms at the mean steady-state C_{max} following 400 mg twice daily.

Clinical efficacy

Locally advanced or metastatic NSCLC with a MET exon 14 skipping mutation (treatment-naïve and previously treated)

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 central, global, prospective, non-randomised, 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 patients were required to have epidermal growth factor receptor (EGFR) wild-type status (for exon 19 deletions and exon 21 L858R substitution mutations), anaplastic lymphoma kinase (ALK)-negative rearrangement and MET-mutated NSCLC with at least one measurable lesion as per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, along with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1. Patients with symptomatic central nervous system (CNS) metastases who were neurologically unstable or required increased doses of steroids within the prior 2 weeks to manage CNS symptoms, patients with clinically significant uncontrolled cardiac disease and patients pretreated 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 (2 previously treated subjects) or metastatic (95 subjects) NSCLC with a MET exon 14 skipping mutation as determined using an RNA-based clinical study assay at a central lab were enrolled and treated with Tabrecta. The treatment-naïve cohort enrolled 28 patients. The previously treated cohort enrolled 69 patients who had been treated with 1 or 2 prior lines of systemic therapy for advanced disease.

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 was analysed independently.

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 carcinoma study population were 60% female, median age 71 years (age range: 49 to 90 years), 82% aged 65 years or older, 75% white, 24% Asian, 0% black, 60% never smoked, 80% had adenocarcinoma, 99% had ECOG performance status of 0 or 1, 12% had CNS metastases. In the previously treated cohort (n = 69), 94% had prior chemotherapy, 28% had prior immunotherapy and 23% had received 2 prior systemic therapies.

Efficacy results from study A2201 (GEOMETRY-mono 1) for both treatment-naïve and previously treated MET-mutated NSCLC patients are summarised in Tables 4 and 5. 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.

Table 4 Treatment-naïve, MET-mutated, locally advanced or metastatic NSCLC patients – efficacy results in patients treated with Tabrecta in study A2201 (GEOMETRY-mono 1)

Efficacy parameter	**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)
Duration of response[a]		
Number of responders, n	19	17
Median, months (95% CI)[c]	11.14 (5.55, NE)	13.96 (4.27, NE)
% responders with DOR ≥ 6 months	68.4	76.5
% responders with DOR ≥ 12 months	36.8	47.1
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)
Death, (%)	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)	

List of 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% confidence interval
[c]Based on Kaplan-Meier estimate.

Table 5 Previously treated, MET-mutated, locally advanced or metastatic NSCLC patients – efficacy results in patients treated with Tabrecta in study A2201 (GEOMETRY-mono 1)

Efficacy parameter	**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)

Efficacy parameter	Tabrecta by BIRC n=69	Tabrecta by investigator n=69
Partial response (PR), n (%)	28 (40.6)	28 (40.6)
Duration of response[a]		
Number of responders, n	28	29
Median, months (95% CI)[c]	9.72 (5.55, 12.98)	8.31 (4.34, 12.06)
% responders with DOR ≥ 6 months	64.3	58.6
% responders with DOR ≥ 12 months	21.4	27.6
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)
Death, (%)	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)	
Median, months (95% CI)[c]	13.57 (8.61, 21.19)	

List of 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% confidence interval
[c]Based on Kaplan-Meier estimate.

Temporary marketing authorisation

As the clinical data were incomplete at the time of the review of the marketing authorisation application, Tabrecta is subject to a temporary marketing authorisation (Art. 9a of the Therapeutic Products Act).
The temporary marketing authorisation is mandatorily associated with the prompt fulfilment of relevant conditions. Upon their fulfilment the temporary authorisation can be converted to a standard marketing authorisation.

Pharmacokinetics

Absorption

In humans absorption is rapid after oral administration of capmatinib. Peak plasma levels of capmatinib are reached approximately 1 to 2 hours (T_{max}) after an oral 400 mg dose of capmatinib tablets in cancer patients. Oral absorption of capmatinib tablets is estimated to be greater than 70%.

Capmatinib exhibited dose-proportional increases in systemic exposure (AUC_{inf} and C_{max}) over the dose range from 200 to 400 mg twice daily.

Food effect:
Food does not alter capmatinib bioavailability to a clinically meaningful extent. Tabrecta can be administered with or without food (see “Dosage/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_{inf} by 46% and C_{max} by 15% compared to when capmatinib was administered under fasted conditions. A low-fat meal increased AUC_{inf} by 20% and C_{max} by 11%.
When capmatinib was administered at 400 mg twice daily in cancer patients, exposure (AUC_{0-12h}) was similar after administration of capmatinib with food or 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_{ss}/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.

Metabolism

Biotransformation
In vitro and *in vivo* studies indicated that capmatinib is cleared mainly through metabolism involving 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 oxidised metabolites. The most abundant radioactive component in plasma is unchanged capmatinib (42.9% of radioactivity AUC_{0-12h}). The major circulating metabolite, M16 (CMN288), is pharmacologically inactive and accounts for 21.5% of the radioactivity in plasma AUC_{0-12h}.

Elimination

The geometric mean apparent plasma terminal half-life ($T_{1/2}$) of capmatinib ranged from 3.5 to 6.3 hours in cancer patients. Steady state is expected to be achieved approximately 3 days after oral dosing of 400 mg capmatinib twice daily, with a geometric mean accumulation ratio of 1.39 (coefficient of variation (CV): 42.9%). The effective half-life (calculated based on geometric mean accumulation ratio) of capmatinib is 6.54 hours. The geometric mean steady-state apparent oral clearance (CL_{ss}/F) of capmatinib was 19.8 l/hr.

Capmatinib is eliminated mainly through metabolism and subsequent faecal excretion. Following a single oral administration of [^{14}C]-capmatinib to healthy subjects 78% of the total radioactivity was recovered in the faeces, 42% of which as unchanged capmatinib, and 22% in the urine. Excretion of unchanged capmatinib in urine is negligible.

Pharmacokinetics in special patient populations

Hepatic impairment

A study was conducted in non-cancer subjects with various degrees of hepatic impairment based on Child-Pugh classification who each received a 200 mg single dose of capmatinib. The geometric mean systemic exposure (AUC_{inf}) of capmatinib was decreased by approximately 23% and 9% in subjects with mild (n = 6) and moderate (n = 8) hepatic impairment, respectively, and increased by approximately 24% in subjects with severe (n = 6) hepatic impairment compared to subjects with normal (n = 9) hepatic function. C_{max} was decreased by approximately 28% and 17% in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal hepatic function, while C_{max} was similar (increased by 2%) in subjects with severe hepatic impairment compared to subjects with normal hepatic function (see “Dosage/Administration”).

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 (see “Dosage/Administration”).

Age/gender/ethnicity/body weight

In study A2201 (GEOMETRY-mono 1) 57% of the 334 patients were aged 65 years or older and 16% were aged 75 years or older. Population pharmacokinetic analysis showed that there is no clinically relevant effect of age/gender/ethnicity/body weight on the systemic exposure of capmatinib.

Preclinical data

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.

Repeated-dose toxicity

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

Reversible findings in the pancreas were observed in rats and monkeys in 28-day and 13-week studies, including pancreatic acinar cell vacuolation and/or apoptosis without inflammation, occasionally accompanied by increased amylase or lipase. In rats the doses of 60 mg/kg/day (1.5 times human exposure) or higher in males and 30 mg/kg/day (1.5 times human exposure) 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 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. 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. These results were observed at doses ≥2.2 times the human exposure (AUC) at the clinical dose of 400 mg twice daily. Brain lesions were in some cases associated with early death and/or convulsions or tremor. No signs of CNS toxicity or brain abnormalities were observed in cynomolgus monkey studies. Capmatinib concentrations in the brain tissue of rats were approximately 9% of corresponding plasma concentrations.
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 relationship. 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 (2.2 times human exposure) 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, 2.9 times human exposure). 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.
In the general toxicology studies in rats and monkeys no effects were determined on male and female reproductive organs at doses equivalent to exposures of up to approximately 3.6 times human exposure at the clinical dose of 400 mg twice daily, based on AUC.

Mutagenicity

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.

Carcinogenicity

Carcinogenicity studies with capmatinib have not been conducted.

Reproductive toxicity

In embryo-fetal development studies in rats and rabbits pregnant animals received oral doses of capmatinib up to 30 mg/kg/day and 60 mg/kg/day, respectively, during organogenesis. At a dose of 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 maximum recommended human dose (MRHD) of 400 mg twice daily.
Reduced fetal weight and an increased incidence 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).
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 weight, irregular/incomplete ossification and an increased incidence of fetal malformations (e.g. abnormal flexure/inward malrotation of hindpaws/forepaws, thinness of forelimbs, lack of/reduced flexion at the humerus/ulna joints) 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 (1.5 times human exposure). Fetal effects included small lung lobes 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 weight, irregular/incomplete ossification and an increased incidence 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 and/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).

Photosensitivity

In vitro and *in vivo* photosensitisation assays with capmatinib suggest that capmatinib has the potential for photosensitisation. The NOAEL for *in vivo* photosensitisation is 30 mg/kg/day (C_{max} of 14000 ng/mL), about 2.9 times the human C_{max} at a dose of 400 mg twice daily.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use after the expiry date (= EXP) printed on the container.

Special precautions for storage

Do not store above 25°C.
Store in the original pack. Protect from moisture.
Keep out of the reach of children.

Instructions for use and handling

Any unused medicinal product or waste material must be properly disposed of.

Swissmedic number

67648

Pack sizes

Tabrecta 150 mg: Pack with 120 film-coated tablets. [A]
Tabrecta 200 mg: Pack with 120 film-coated tablets. [A]

Marketing authorisation holder

Novartis Pharma Schweiz AG, Risch, Switzerland; domicile: 6343 Rotkreuz, Switzerland

Information last revised

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