Date: 2 June 2020
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Tukysa

International non-proprietary name: tucatinibum

Pharmaceutical form: tablet

Dosage strength: 150 mg, 50 mg

Route(s) of administration: oral

Marketing Authorisation Holder: SFL Regulatory Affairs & Scientific Communication GmbH

Marketing Authorisation No.: 67798

Decision and Decision date: approved on 07 May 2020

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 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 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 antibodies
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BC	Breast cancer
BID	Twice a day
Cmax	Maximum observed plasma/serum concentration of drug
CNS	Central nervous system
CYP	Cytochrome P450
DLT	Dose-limiting toxicities
ECOG	Eastern Cooperative Oncology Group
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
HER2	Human epidermal growth receptor factor 2
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
Max	Maximum
MAH	Marketing Authorisation Holder
MBC	Metastatic breast cancer
Min	Minimum
MTD	Maximum-tolerated dose
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
OS	Overall survival
PBPK	Physiologically based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PPE	Palmar-plantar erythrodysaesthesia
PSP	Pediatric Study Plan (US-FDA)
PIC	Powder-in-capsule
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
RECIST	Response evaluation criteria in solid tumours
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TDM1	Trastuzumab emtansine
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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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 (INN) of the medicinal product mentioned above.

2.2 Indications and Dosage

2.2.1 Requested Indication

Tukysa is indicated in combination with trastuzumab and capecitabine for the treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received at least 2 prior anti-HER2 treatment regimens.

2.2.2 Approved Indication

TUKYSA in combination with trastuzumab and capecitabine is indicated for the treatment of patients with metastatic HER2-positive breast cancer, who have previously received 2 or more anti-HER2 regimens in any setting, including trastuzumab, pertuzumab and trastuzumab-emtansine (T–DM1) (see "Clinical Efficacy").

2.2.3 Requested Dosage

Usual dosage:
The recommended dose of Tukysa is 300 mg (two 150 mg tablets) taken orally twice daily continuously in combination with trastuzumab and capecitabine, at doses described in Table 1. Refer to the information for healthcare professionals for co-administered trastuzumab and capecitabine for additional information. The treatment components can be administered in any order.

Table 1: Recommended dosing

Treatment	Dose	Treatment Days	Timing Relative to Food Intake
Tukysa	300 mg orally twice daily	Continuously	With or without a meal
Capecitabine	1000 mg/m2 orally twice daily	Days 1 to 14 every 21 days	Within 30 minutes after a meal
Trastuzumab Intravenous dosing Initial dose Subsequent doses OR Subcutaneous dosing	 8 mg/kg intravenously 6 mg/kg intravenously 600 mg subcutaneously	 Day 1 Every 21 days Every 21 days	Not applicable

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	06 January 2020
Formal control completed	7 January 2020
Predecision	14 April 2020
Answers to Predecision	30 April 2020
Final Decision	07 May 2020
Decision	approval

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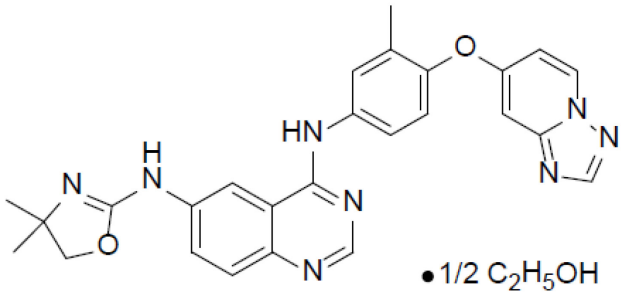
2.4 Medical Context

Breast cancer (BC) is the most frequent cancer in women and the leading cause of death from cancer in women. In Switzerland, nearly 6,000 new cases of breast cancer are diagnosed per year, with approximately 1,400 deaths from the disease (www.nicer.org). While localised breast cancer is often curable, once the disease has metastasised beyond locoregional lymph nodes it remains incurable, with a median overall survival (OS) of approximately 3 years and a 5-year survival of only about 25% (Cardoso et al., Breast; 2018). A lot of progress has been made in the treatment of metastatic breast cancer that overexpresses the human epidermal growth factor 2 (HER2) over the past decade, with therapies specifically targeting this membrane protein. Established first-line treatment of HER2-positive metastatic breast cancer is the combination of the anti-HER2 antibodies trastuzumab and pertuzumab with a taxane, resulting in a median progression-free survival (PFS) of 18.5 months (Swain et al., NEJM; 2015). The currently established second-line treatment for these patients is trastuzumab emtansine (TDM1), an antibody-drug conjugate adding another median PFS of 9.6 months in the second line (Dieras et al., Lancet Oncol; 2017). Nevertheless, there is no established third-line treatment combination, and overall survival is estimated at less than 2 years. In addition, approximately 50% of patients will have developed brain metastases at this stage of the disease. Therefore, there is a clear unmet medical need for HER2-positive, metastatic breast cancer patients.

3 Quality Aspects

3.1 Drug Substance

INN: Tucatinib
Chemical name: Ethanol, compound with N6-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)-N4-[3-methyl-4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)phenyl]-4,6-quinazolinediamine (1:2)
Molecular formula: $C_{26}H_{24}N_8O_2$ – ½ C_2H_5OH
Molecular mass: 503.57 g/mol
Molecular structure:



Physico-chemical properties: off-white to yellow crystalline powder with polymorphic form B (hemi-ethanolate). It is practically insoluble in aqueous solutions above pH 4.6.

Synthesis: The drug substance is manufactured by a multiple-step chemical synthesis with final crystallisation and followed by polymorphic transformation resulting in the hemi-ethanolate form. The synthesis of the drug substance and the necessary in-process controls are described in detail.

Specification: In order to ensure a consistent quality of tucatinib, the specifications include all relevant test parameters as recommended by the relevant ICH Guidelines.

Stability: Appropriate stability data have been presented for three production batches. Based on these results, a satisfactory re-test period has been established when stored in tight packaging (LDPE-bags).

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3.2 Drug Product

Description and composition: The 50 mg strength tablet is a round, yellow film-coated tablet, debossed “TUC” on one side and “50” on the other. The 150 mg strength tablet is an oval-shaped yellow film-coated tablet, debossed “TUC” on one side and “150” on the other.

Pharmaceutical development: An amorphous spray-dried dispersion (SDD) of the drug substance has been developed to improve the solubility of the active pharmaceutical ingredient in the pH 4-6 range.

Manufacture: The tucatinib tablet manufacturing process consists of dry granulation by roller compaction, followed by compression and pan coating.

Specification: 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 (visual examination), identity (FTIR, HPLC), assay (HPLC), uniformity of dosage units (HPLC), degradation products (HPLC), water content, dissolution and microbial tests. Analytical methods have been described and validated according to ICH requirements.

Container-Closure System: The tucatinib drug product is packaged in an aluminium-aluminium (Alu/Alu) blister pack.

Stability: Appropriate stability data have been generated for 50 mg and 150 mg primary batches in the packaging material intended for commercial use and according to the relevant international guidelines.

3.3 Quality Conclusions

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

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4 Nonclinical Aspects

4.1 Introduction

The applicant developed Tukysa (drug substance tucatinib) in accordance with ICH S9. Relevant safety pharmacology and toxicity studies were GLP-compliant.

4.2 Pharmacodynamics

The applicant provided numerous *in vitro* and *in vivo* investigations to characterise the pharmacodynamic properties of tucatinib and its metabolite ONT-993. Tucatinib blocked HER2 phosphorylation and, consequently, the signal transduction cascade of the MAP and PI3K kinases. Tucatinib bound to the target structure HER2 with an inhibitory constant (K_i) between 0.8 and 2.6 nM. The K_i for the metabolite ONT-993 was 0.7 nM. Tucatinib had a clear selectivity for HER2 over epidermal growth factor receptor (EGFR) (K_i 70 nM) and ErB4 (K_i 250 nM); similar applies to the metabolite (K_i for EGFR: 36 nM).
The *in vitro* cytotoxicity assays demonstrated that a high HER2 expression (> 300,000 HER2 receptors/cells) was relevant for the cytotoxic activity on tumour cells and reconfirmed the preference for HER2 over EGFR (factor > 100 to 1,000). The ONT-993 enantiomers (*S*- and *R*-ONT-993) also had a more potent inhibitory activity on the phosphorylation of HER2 (IC_{50}: 53 and 55 nM) compared to the effect on EGFR (IC_{50} > 10,000 nM).
In combination with trastuzumab, tucatinib showed synergistic effects regarding inhibition of phosphorylation as well as induction of apoptosis. No nonclinical data were available for the combination with capecitabine.
In murine subcutaneous or intracranial allo- or xenograft tumour models, including breast carcinoma, tucatinib was tolerated up to 150 mg/kg without significant body weight loss. The tumour growth inhibition (TGI) was generally above 80% in cell suspension-based xenografts. Biochemical investigations indicated reduced levels of phosphorylated HER2. Partial regression (PR) occurred at doses greater than 100 mg/kg in some animals. The treatment in combination with trastuzumab increased the TGI and number of PR or complete regressions compared to the treatment with the individual agents, with the exception of the patient-derived human adenocarcinoma xenografts. In the intracranial model, 75 mg/kg tucatinib twice a day (BID) prolonged the survival of the treated animals compared to the control (69% versus 23% on Day 56).
Regarding secondary pharmacodynamics, the applicant provided a bibliographic review on the potential toxicity of the inhibition of HER2 activity in patients treated with tucatinib due to HER2 expression in normal tissues or cells. Tucatinib is not a first-in-class molecule, and side effects due to the inhibition of HER2 are clinically well known.
Safety pharmacology studies with tucatinib did not identify any relevant risks regarding the cardiovascular, respiratory or central nervous system (CNS). However, the compound could have irritating potential in the stomach, which was confirmed in the repeat-dose toxicity studies recording mortality or dose-limiting toxicity at 90 or 200 mg/kg in cynomolgus monkeys and rats.

4.3 Pharmacokinetics

The applicant provided GLP-compliant validations for the detection of tucatinib and ONT-993 in rats, cynomolgus monkeys and rabbit plasma using LC-MS/MS methods.
The pharmacokinetics of tucatinib was characterised in rats and cynomolgus monkeys. In both species, absorption after oral administration was fast (T_{max} 1.67-3.33 h), similar to that in humans. Plasma elimination was shorter ($T_{1/2}$ 1.95-2.51 h) than in humans (8.7 h). After multiple dosing, the AUC_{inf} was increased 3- to 5-fold, indicating accumulation, although this was not observed in humans. Plasma protein binding of tucatinib in relevant species overall was > 93%. The compound did not preferentially distribute to blood cells *in vitro*.
Studies with oral administration of [^{14}C]-labelled tucatinib to pigmented rats showed rapid and wide tissue distribution. [^{14}C]Tucatinib-derived radioactivity was completely eliminated by 72 h (females) or 168 h (males) post-dose. The compound bound specifically to melanin-containing tissues.

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[^{14}C]Tucatinib-derived radioactivity did not distribute across the blood-brain barrier (BBB) into the non-circumventricular CNS tissues in this study, although murine PD models with intracranial xenografts indicated crossing of the BBB. It is unclear whether this is due to the species (rat versus mouse) or the different dosing regimen (single versus multiple). The applicant also referred to other factors that may have an impact on brain penetration, such as the relatively acidic tumour microenvironment. Overall, the penetration to the brain for the treatment of brain metastases, as requested in the indication, remains contradictory in terms of nonclinical data.
Metabolism of tucatinib *in vitro* in hepatocytes and liver microsomes was comparable across species (rat, cynomolgus monkey, and human). The main metabolite was the hydroxylation product M1 (ONT-993). In a cross-species study using plasma samples from rats, monkeys, and humans, the applicant did not identify a unique human metabolite. Tucatinib was the major component (87-91% of total drug related exposure) in plasma. In the human samples, all other metabolites were below 10% and are hence considered minor metabolites. Most of the drug-related radioactivity was excreted via bile/faeces (90% in rats and 80% in cynomolgus monkeys), as in humans. Based on the recovery in bile and urine in rats, at least 13% of the dose was absorbed.

4.4 Toxicology

The toxicological profile of tucatinib was characterised in rats, cynomolgus monkeys, and rabbits. Based on the pharmacokinetic data and the conservation of the target structure across species, the species selection is considered acceptable. Animals were treated once or twice a day via the oral route, which is consistent with the proposed clinical setting.

Tucatinib induced mortalities and dose-limiting toxicities in rats and cynomolgus monkeys in the repeat-dose studies with duration up to 4 weeks at doses of 200 mg/kg/day in rats and 90 mg/kg/day in cynomolgus monkeys. Both species showed typical signs of discomfort, such as hunched posture, decreased activity, and reduced food consumption. In rats, the cause of death was determined as gastrointestinal (GI) erosion/ ulceration. Monkeys were also euthanised prematurely due to dose-limiting adverse clinical signs likewise involving the GI tract.

Liver was a target organ in both species. Effects observed included increased weight (absolute and relative) from 60 mg/kg/day in rats and 90 mg/kg/day in monkeys. In the 13-week study in rats, tucatinib-related clinical chemistry findings suggested hepatocellular and/or hepatobiliary alterations, but microscopic correlates were limited to centrilobular hepatocyte hypertrophy. According to the Nonclinical Safety Specifications in the RMP, hepatotoxicity is considered an identified risk and will be monitored.
At doses ≥ 60 mg/kg/day, the female reproductive organs in rats were affected. The organ weights of uterus and cervix were reduced, which correlates with the observed atrophy in the uterus. Furthermore, the number of corpora lutea was decreased, and vaginal epithelial atrophy and mucification in the vagina were recorded. The female mammary glands showed atrophy. In the males, the prostate weight was reduced. However, there was no microscopic correlate. In monkeys at 90 mg/kg/day, the kidney was identified as a potential target organ, with increased organ weight and degeneration of the tubular epithelium. The tucatinib treatment did not have an impact on ECG findings or troponin T levels (monkeys only), ophthalmology, urinalysis, or coagulation. Except for hair loss, which could be related to the mode of action, and the decreased number of corpora lutea, both in rats, all observations were reversible after a 4-week treatment-free period.
The safety margins are non-existent. Considering the indication, the lack of safety margins is acceptable.

Tucatinib tested negative for genotoxicity in the bacterial reverse mutation assay and in mammalian test systems *in vitro* and *in vivo*. Carcinogenicity studies were not conducted and are not warranted (ICH S9).

As outlined in ICH S9, no dedicated fertility studies were carried out. Based on microscopic changes in the female reproductive organs in the repeat-dose studies, an impact of tucatinib treatment on fertility cannot be excluded. The embryo-foetal toxicity assessment is based on preliminary data in rats and rabbits (only six pregnant females in the main study). In rats treated with up to 150

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mg/kg/day tucatinib from gestation day (GD) 7 to GD 17, maternal toxicity was limited to fur loss or thin fur at doses ≥ 120 mg/kg/day and reduced body weight and food consumption in the high dose group. An increase in pre- and post-implantation loss at doses ≥ 90 mg/kg/day was recorded. The skeletal examination of the foetuses revealed incomplete ossification (variations) ≥ 90 mg/kg/day and tucatinib-related effects on foetal ossification sites from 120 mg/kg/day. Rabbits showed similar clinical signs at the same dose levels. The tucatinib-related effects on ovarian and uterine parameters at doses ≥ 90 mg/kg/day included a reduction in the total number of foetuses and an increased number of early resorptions. The foetal examinations revealed head malformations from 90 mg/kg/day (domed head, severe lateral brain dilation and skeletal skull variations). The safety margins were below 10. In addition, the applicant discussed the role of HER2 in embryo-foetal development. In mice, the catalytic activity of HER2 kinase is essential for embryonic development. This provides sufficient information to allow recommendations for healthcare professionals. As outlined in ICH S9, no dedicated pre- and postnatal development studies were carried out.

Juvenile toxicity was not assessed. The EMA PDCO granted a waiver regarding the paediatric development on the grounds that the disease does not occur in the paediatric population.

Based on the results of an *in vitro* 3T3 assay and *in vivo* study in pigmented rats, tucatinib is not considered phototoxic.

The applicant provided data regarding the qualification of impurities above the ICH 3A/B qualification threshold. The final report of the 28-day study in rats with SGD-8864 should be submitted.

Based on the ERA, the environmental risk posed by the introduction of Tukysa to the market is considered to be low, but the ongoing studies should be adequately reflected in an updated assessment.

The description and evaluation of the findings in the nonclinical studies in the Nonclinical Safety Specifications of the RMP are considered sufficient.

4.5 Nonclinical Conclusions

Overall, the submitted nonclinical documentation is considered sufficient to support the approval of Tukysa with the new active substance tucatinib in the proposed indication. The pharmacological properties as well as the pharmacokinetic and toxicity profiles of tucatinib were adequately characterised. All nonclinical data that are relevant for safety are included in the information for healthcare professionals.

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5 Clinical and Clinical Pharmacology Aspects

5.1 Clinical Pharmacology

Biopharmaceutical Development
Three different oral formulations were used in early clinical studies, i.e. a powder-in-capsule (PIC) formulation, an aqueous suspension, and a solution. Since high intra- and inter-subject variabilities were observed with these formulations, a tablet formulation was developed in order to reduce the variability and the sensitivity to gastric pH, and this was eventually used in the later clinical studies, including the pivotal Phase 2 study, and is intended for commercialisation. The final to-be-marketed drug product is supplied as immediate-release, film-coated tablets in 50 mg and 150 mg strengths. Since the solubility of tucatinib was shown to be pH-dependant, the impact of food and agents that modify the gastric pH, such as proton pump inhibitors (PPIs), is of concern. In healthy subjects, a high-fat meal resulted in increased tucatinib plasma exposures (AUC_{last} +47%; C_{max} +8%) and delayed absorption. Tucatinib was administered irrespective of food in the pivotal phase 2 study, which is also the proposed dosing recommendation in the information for healthcare professionals. Co-administration with omeprazole under fasted conditions led to slightly decreased tucatinib exposures (AUC_{last} -12%; C_{max} -13%), which can be considered negligible.

ADME
The pharmacokinetic profiles of tucatinib following single and multiple doses (25 mg to 800 mg) were evaluated in a set of Phase 1/2 studies in healthy subjects and cancer patients.

Following a single dose of 300 mg tucatinib, the maximal plasma concentrations in healthy subjects and cancer patients were reached within 1 h to 6 h. The steady state pharmacokinetics were characterised based on a population PK analysis using data from five studies. Following the administration of 300 mg tucatinib BID, AUC_{ss}, C_{max}, and C_{trough} were estimated at 5,234 ng*h/mL, 630 ng/mL, and 257 ng/mL respectively, in metastatic breast cancer (MBC) subjects. The estimated accumulation ratio ranged from 1.52 to 2.01 suggesting weak accumulation, and the steady state was reached after approximately four days.
Across the investigated dose range up to 800 mg, tucatinib exposures increased approximately proportionally with the dose. However, dose-proportionality was not formally demonstrated, and there was a trend towards a greater than dose-proportional increase. In general, the PK of tucatinib is characterised by a high degree of variability, which makes the demonstration of dose-proportionality difficult.
The absolute bioavailability of tucatinib was not determined.

Protein binding of tucatinib and its main metabolite ONT-993 was high (>97%) as shown in *in vitro* experiments. Tucatinib was shown to be equally distributed to the blood and plasma compartments. Protein binding was not altered in subjects with hepatic impairment.
Based on the population PK analysis, the volume of distribution in cancer patients was estimated at 730 L.

In vitro experiments using human liver microsomes revealed that tucatinib was primarily metabolised by CYP2C8 and, to a lesser extent, by CYP3A4, CYP3A5, and aldehyde oxidase. ONT-993 was the most abundant metabolite *in vitro* and was also shown to be a selective HER2 kinase inhibitor. Based on a physiologically based pharmacokinetic (PBPK) analysis, the contributions of CYP2C8, CYP3A, and aldehyde oxidase were estimated at 70%, 15%, and 15%, respectively, of total tucatinib metabolism.
Tucatinib was predominantly excreted via faeces, accounting for 85.8% of the administered dose, of which 36.8% and 15.9% were ONT-993 and unchanged tucatinib, respectively. Only 4.09% of the administered dose was excreted via urine, and unchanged tucatinib was present only in trace amounts. Unchanged tucatinib was the predominant entity in plasma, accounting for 75% of plasma radioactivity, whereas 9.16% of the plasma radioactivity was identified as ONT-993.

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Based on the population PK analysis, the clearance and the terminal elimination half-life of tucatinib were estimated at 57.3 L/h and 14.9 h, respectively.

Special Populations
The impact of liver function on the tucatinib exposures following a single 300 mg dose was investigated in a dedicated study in subjects with normal hepatic function and mild to severe hepatic impairment. Hepatic impairment was associated with increased exposures in subjects with moderate and severe hepatic impairment ($AUC_{0-\infty}$ +14% and +61%). Overall, a very high inter-individual variability was observed. Considering the observed variability and the trend towards non-linearity of the PK of tucatinib, it is questionable whether a single dose study is sufficient. Dose adjustment of the starting dose to 200 mg BID may be an option for those patients; however, the use of capecitabine is contraindicated anyway in patients with severe hepatic impairment.
The effect of renal impairment on the PK of tucatinib was not investigated. Considering that only 4.09% of the administered dose was excreted in urine, this is acceptable. Creatinine clearance and renal function categories were not identified as significant in the context of the population PK analyses. However, no data from subjects with severe renal impairment were available. Furthermore, the use of capecitabine is contraindicated in patients with severe renal impairment.
Following multiple 300 mg doses, the values for C_{max} and AUC_{0-12h} for tucatinib were slightly increased, by 33% and 0.4% respectively, in healthy Japanese subjects. The differences were more pronounced at lower doses. In the context of the population PK analyses, the covariate race was not identified as relevant.
An exploratory covariate analysis based on linear regression using the data from the pivotal Phase 2 study HER2CLIMB was conducted in order to investigate the relationship between the observed tucatinib trough levels and the covariates age, race, body size, hepatic function (mild and moderate), renal function (mild and moderate), albumin, and Cooperative Oncology Group (ECOG) status. Subjects with mild/moderate hepatic impairment had higher trough levels, whereas lower trough levels were associated with increasing body weight and age. Overall, the impact of these covariates on C_{trough} was low; however, the analysis also confirmed that the PK of tucatinib is characterised by a high variability.
Based on the data from five Phase 1/1b studies, the PK of tucatinib was described by a 2-compartment model with linear elimination and a first-order absorption preceded by a lag time. The impact of the covariates body weight, body surface area (BSA), race, population, cancer type, formulation, prandial state, creatinine clearance, age, hepatic function tests, albumin, ECOG performance status, and combination chemotherapy on the PK of tucatinib was investigated. Only population, body weight, albumin, prandial state, and body weight were identified as statistically significant covariates and were included in the final model. Gender was not evaluated.

Interactions
The drug-drug-interaction (DDI) potential of tucatinib and its major metabolite ONT-993 was investigated in a battery of *in vitro* studies. Tucatinib and ONT-993 were found to be substrates for BCRP and P-gp, ONT-993 was an OATP1B3 substrate as well. Tucatinib was found to be an inhibitor of the transporters P-gp, OCT2, BCRP, BSEP, OATP1B1, OATP1B3, MATE1 and MATE2-K, whereas ONT-993 exhibited inhibitory activity on MATE1, MATE2-K, OAT2, and OCT2. Tucatinib weakly induced CYP3A4, CYP1A2, and CYP2B6. Both tucatinib and ONT-993 were shown to be metabolism-dependent inhibitors of CYP3A. Furthermore, tucatinib was a direct inhibitor of CYP2C8, CYP2C9, CYP3A, and UGT1A1, whereas ONT-993 was found to be a direct inhibitor of CYP2D6 only.
Based on the *in vitro* findings, two dedicated DDI studies were conducted. The potential of tucatinib being the victim was investigated with regard to CYP2C8 and CYP3A4. Whereas CYP2C8 inhibition with gemfibrozil resulted in increased tucatinib exposures (AUC +204%), CYP2C8/CYP3A4 induction with rifampin led to lower exposures (AUC -48%). The increase in tucatinib exposures following CYP3A4 inhibition with itraconazole was less pronounced (+34%). The DDI risk of tucatinib as perpetrator was studied with regard to CYP2C8, CYP2C9, CYP3A4, MATE1/MATE2-K, and P-gp. Tucatinib was a weak inhibitor of CYP2C8 and a strong inhibitor of CYP3A4, leading to increased

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repaglinide and midazolam exposures (AUC +72% and +430% respectively). Tucatinib did not inhibit CYP2C9, as shown by unchanged tolbutamide exposures (AUC +3%). Lastly, minor increases in digoxin (AUC +53%) and metformin (AUC +36%) suggest that tucatinib was a weak inhibitor of P-gp and MATE1/MATE2-K, respectively.
Lastly, a PBPK analysis suggests that tucatinib had a rather low DDI risk with substrates of UGT1A1 or OATP1B1/3.
Overall, the submitted *in vitro*, *in vivo*, and modelling DDI package is substantial. In accordance with current guidelines, the relevant transporters and enzymes were evaluated at adequate tucatinib and ONT-993 concentrations *in vitro*. Generally, the two dedicated DDI studies covered the interaction potential that was identified *in vitro*. However, the findings based on the submitted PBPK analysis can be considered as supportive at most and should not be included in the information for healthcare professionals.
Dose adjustments and recommendations with regard to concomitant medications are addressed in the attached information for healthcare professionals; see Chapter 7.1 of this report.

Pharmacodynamics
Tucatinib is a reversible human epidermal growth factor receptor type 2 (HER2)-targeted small molecule tyrosine kinase inhibitor (TKI). Binding to HER2 inhibits MAP and PI3 kinase signalling pathways, which in turn leads to inhibition of tumour cell proliferation, survival, and metastasis. Biochemical assays have shown that tucatinib is a potent and selective HER2 kinase inhibitor.

The absence of a clinically relevant prolongation in cardiac repolarisation compared to placebo was demonstrated in a tQT study. However, 300 mg of tucatinib was administered instead of a supratherapeutic dose.

5.2 Dose Finding and Dose Recommendation

There are 3 dose-finding and safety phase 1 studies, two conducted in HER2-positive MBC patients and one in patients with advanced solid malignancies.

The ARRAY-380-101 study determined the maximum tolerated dose of tucatinib as monotherapy in a powder-in-capsule (PIC) formulation to be 600 mg (BID). Determination of the maximum tolerated dose (MTD) was based on 2/4 patients presenting dose-limiting toxicities (DLTs) in the 800 mg BID cohort (liver enzyme elevations). Consequently, the 650 mg BID cohort should have been expanded. However, according to the applicant the inventory of 25 mg capsules was limited, therefore 7 patients were enrolled in a 600 mg BID dose-escalation cohort.

ONT-380-005 was a phase 1b dose-escalation study evaluating the safety of combinations of tucatinib with capecitabine, tucatinib with trastuzumab and tucatinib with both capecitabine and trastuzumab. Tucatinib was formulated as tablet, and the maximum tolerated dose showing a similar exposure to the 600 mg PIC formulation was 300 mg. Therefore, tucatinib was administered at 300°mg BID and was escalated to 350 mg BID in combination with capecitabine and in combination with trastuzumab.

The recommended phase 2 dose was tucatinib 300 mg BID in combination with capecitabine and trastuzumab. Although there were no DLTs within the DLT period, patients on 350 mg tucatinib developed grade 3 diarrhoea, nausea and vomiting after the DLT period. In addition, serum blood levels of the 300 mg tablet form were similar to the 600 mg powder-in-capsule formulation that was determined to be the MTD of the monotherapy.

5.3 Efficacy

One pivotal clinical study was submitted for the indication. HER2CLIMB is a randomised phase 2 study investigating the effect of tucatinib/placebo in combination with trastuzumab and capecitabine on progression-free survival (PFS) in patients with metastatic HER2-positive breast cancer (BC). The

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study included patients who had previously received trastuzumab, pertuzumab and TDM1. The study enrolled nearly 50% of patients with brain metastases (previously treated and stable, previously treated and progressing or newly diagnosed but not in need of immediate treatment). The inclusion of these patients is relevant because it reflects the clinical reality of approximately half of HER2-positive metastatic breast cancer patients presenting with brain metastases after two prior lines of treatment. These patients are often excluded from clinical trials and have a large unmet medical need. Patients were stratified according to presence, or history of, versus absence of brain metastases, according to ECOG performance status 1 versus 0 and to region of the world (North America [US and Canada] versus rest of the World). Randomisation was 2:1 to either tucatinib or placebo in combination with trastuzumab and capecitabine at standard doses. Biosimilars for trastuzumab were allowed. Tucatinib/placebo was administered at 300 mg twice daily. Patients with brain metastases who progressed in the brain only, were allowed to receive local treatment while continuing on study drugs until further progression in the CNS or systemically. The first progression in the brain was counted as a PFS event.

The essential inclusion criteria were HER2-positive breast cancer and previous treatment with trastuzumab, pertuzumab and TDM1, with progression on the last line of systemic treatment. Prior treatment with an anti-HER2 tyrosine kinase inhibitor (such as lapatinib, neratinib, afatinib, etc.) was not allowed except for lapatinib if the treatment was stopped more than 12 months prior to initiating study treatment. Prior exposure to capecitabine in the metastatic setting was not allowed.

Primary endpoint of the study was PFS in the first 480 patients enrolled based on RECIST1.1 and assessed by blinded independent central review (BICR). The analysis was event driven. Key secondary endpoints were overall survival (OS) in all enrolled patients (N=612), PFS in patients with brain metastases and objective response rate (ORR) assessed by BICR.

At time of data cutoff, the median follow-up for PFS was 10.4 months. The PFS improved from 5.6 months in the placebo arm to 7.8 months in the tucatinib arm in the first 480 randomised patients (ITT-PFS population). The stratified hazard ratio was HR=0.54 (95% CI: 0.42, 0.71), p<0.00001. In these heavily pre-treated patients (median of 4 prior treatment lines), and with nearly 50% of patients with brain metastases, this is a clinically meaningful improvement. All sensitivity analyses were consistent with the primary analysis. The observed PFS benefit was consistent in all analysed subgroups (age, race, hormone receptor status, baseline brain metastasis, ECOG performance status, region). The PFS benefit was also observed in the overall study population (ITT-OS population, 612 patients) with a hazard ratio of 0.54 (95% CI: 0.42, 0.68) and a median PFS of 8.1 months (95% CI: 7.6, 9.6) in the tucatinib arm versus 5.5 months (95% CI: 4.3, 6.9) in the placebo arm.

Key secondary endpoints were OS, PFS in patients with brain metastases and ORR. All key secondary endpoints were reached. With a median follow-up time of 14 months, OS was significantly prolonged in the tucatinib arm versus the control arm, with a 34% reduction in the risk of death (HR=0.66 [95% CI: 0.50, 0.88]; p=0.0048). The median OS was 21.9 months (95% CI: 18.3, 31.0) and 17.4 months (95% CI: 13.6, 19.9) respectively for the tucatinib and control arms. The endpoint of PFS in patients with brain metastases was also met, with a stratified hazard ratio of HR=0.48 (95% CI: 0.34, 0.69) and a median PFS of 7.6 months (95% CI: 6.2, 9.5) in the tucatinib arm and 5.4 months (95% CI: 4.1, 5.7) in the placebo arm. The third key secondary alpha controlled endpoint was ORR and was also reached. The ORR in the tucatinib arm was 40.6% versus 22.8% in the placebo arm.

The supportive ONT-380-005 phase 1b dose-escalation study enrolled 27 patients in the triple combination arm of tucatinib, capecitabine and trastuzumab. These patients had a median PFS of 7.8 months (95% CI: 4.1, 12.5; range, 1.3 to 28.9). Of the 27 patients, 11 had baseline brain metastases and these patients had a PFS of 6.7 months.

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5.4 Safety

Tucatinib exposure for all patients receiving the MTD or higher was 5.8 months. Exposure was longer when tucatinib was given in combination than when given as monotherapy (median exposure as monotherapy: 2.7 months).

Nearly all patients (99.4%) in both the tucatinib safety pool and the HER2CLIMB placebo arm (henceforth referred to as “control”) experienced at least one adverse event (AE). Roughly 54% of the patients receiving tucatinib in combination with capecitabine and trastuzumab developed TEAEs of grade 3 or more compared to 48% in the control arm. There does not seem to be excess mortality in the tucatinib-treated patients compared to the control arm. Serious AEs (SAEs) were observed in 27% of patients receiving the tucatinib combination treatments as well as in the placebo arm of the HER2CLIMB study. However, in the monotherapy study the incidence of SAEs was higher, at 35%. This is possibly due to a more heavily pre-treated patient population and the fact that disease progression was considered as an AE, which was not the case for the other studies. Treatment was discontinued due to TEAE in approximately 10% of patients, and there was no difference compared to the placebo control.

Diarrhoea was the most frequently observed AE overall (79%). While it was also observed in the control arm of the HER2CLIMB study (53%), it was more frequent in the combination arms. Diarrhoea also occurred in 61% of patients with tucatinib monotherapy. Palmar-plantar erythrodysaesthesia (PPE) was also more frequent in the tucatinib combination arms (61%) than in the control arm (53%), although PPE is a known AE of capecitabine and no PPE was observed with tucatinib monotherapy. Nevertheless, the addition of tucatinib increases the incidence of PPE in combination with capecitabine. Nausea (58%) and vomiting (36%) were more frequent with tucatinib than with placebo (44% and 25% respectively) and were frequent in the tucatinib monotherapy study (55% and 39% respectively) as well. Stomatitis and anaemia were more frequent in the tucatinib combination arms compared to monotherapy or the HER2CLIMB control arm. Transaminases were more frequently elevated in the tucatinib combination and monotherapy arms than in the control arm. Elevation of transaminases was also the dose-limiting toxicity (DLT) in the ARRAY-380-101 study of tucatinib monotherapy. Arthralgia was more frequent in the tucatinib-containing regimens than in the control arm. Blood creatinine was more frequently increased in the tucatinib-containing arms, although this seems to be due to the inhibition of creatinine excretion in the kidneys without impairment of renal function.

As mentioned above, Grade 3 and higher AEs were more common in tucatinib-treated patients and the observed AEs correspond to the overall incidence of AEs. The most frequent grade ≥ 3 AEs are diarrhoea (12%, compared to 9% in control arm), PPE (12% compared to 9% in control arm), and elevated transaminases (5.4% for ALT and 4.5% for AST compared to 0.5% for each in the control arm).

Deaths
In the HER2CLIMB study, there were 8 deaths in the tucatinib arm and 6 in the placebo arm on treatment or during the 30-day safety period. Only 2/8 deaths in the tucatinib arm were considered treatment related by the investigator and only 1/6 in the placebo arm. However, the narratives reveal that 5/8 deaths in the tucatinib arm were linked to sepsis and 4/8 associated with ≥ grade 3 diarrhoea. Two sudden deaths of unknown cause were observed early on during study treatment in the tucatinib arm (day 5 and day 38). In the placebo arm, one patient died of sepsis (considered treatment related by the investigator) and one patient developed Clostridium difficile colitis. Three out of the six patients died after having discontinued study treatment due to progressive disease, and one patient suffered a fatal myocardial infarction after discontinuing study treatment due to subject decision.

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Serious AEs
The overall incidence of SAEs was similar across the tucatinib-integrated safety population. Although the highest incidence observed was in the tucatinib monotherapy study (35.5%), these subjects were more heavily pre-treated and included a higher percentage of patients having an ECOG performance status of 1 or higher. The most frequently reported SAEs in the tucatinib arm were diarrhoea (3.4%), vomiting (2.4%), and nausea (1.9%).

5.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Breast cancer is the most frequent cancer in women worldwide and the most frequent cause of cancer death in women. Metastatic breast cancer remains a fatal disease. There is no established third-line treatment combination for HER2-positive metastatic breast cancer, and overall survival is estimated at less than 2 years. In addition, approximately 50% of patients will have developed brain metastases at this stage of the disease. Therefore, there is a clear unmet medical need for these patients.

Overall, the clinical pharmacology package was comprehensive and covered all the relevant aspects. Population pharmacokinetic analysis revealed that no dose adjustment is necessary based on any of the evaluated covariates including, amongst others, body weight, age, and race.

The addition of tucatinib to the combination of capecitabine and trastuzumab, one option of third-line combination therapy in HER2-positive metastatic breast cancer, shows an improvement of 2.2 months in median PFS (HR=0.54) but, more importantly, an overall survival benefit of 4.5 months with a hazard ratio of HR=0.66. The study included patients who had received standard treatment with trastuzumab, pertuzumab and TDM1, and nearly half of the patients had brain metastases at study inclusion. Both subgroups of patients, with and without brain metastases, benefitted from the addition of tucatinib.

The addition of tucatinib to capecitabine and trastuzumab increases the toxicity of the regimen particularly regarding diarrhoea, nausea and vomiting, as well as PPE. However, the toxicity is manageable and there is no excess in SAEs or fatalities.

Given the OS benefit of 4.5 months in this heavily pre-treated patient population, with a manageable safety profile, the benefit-risk is favourable for patients who have received at least two prior lines of anti-HER2 treatment, including trastuzumab, pertuzumab and trastuzumab emtansine. This benefit also extends to patients with brain metastases.

5.6 Approved Indication and Dosage

See Information for healthcare professionals in the Appendix.

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6 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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7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Tukysa 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 will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

NAME OF THE MEDICINAL PRODUCT

TUKYSA™, film-coated tablets

Composition

Active substances

Tucatinib

Excipients

TUKYSA 50 mg film-coated tablet
Tablet core:
Copovidone (E1208); Crospovidone (E1202); Sodium chloride; Potassium chloride (E508); Sodium hydrogen carbonate (E500ii); Colloidal silicon dioxide (E551); Magnesium stearate (E470b); Microcrystalline cellulose (E460i)

Tablet coating:
Polyvinyl alcohol (E1203) 2.8 mg; Titanium dioxide (E171) 1.715 mg;
Macrogol 4000 (E1521) 1.414 mg; Talc (E553b) 1.036 mg; Yellow iron oxide (E172iii) 0.035 mg

Each TUKYSA 50 mg film-coated tablet contains 10.10 mg of potassium and 9.21 mg of sodium.

TUKYSA 150 mg film-coated tablet
Tablet core:
Copovidone (E1208); Crospovidone (E1202); Sodium chloride; Potassium chloride (E508); Sodium hydrogen carbonate (E500ii); Colloidal silicon dioxide (E551); Magnesium stearate (E470b); Microcrystalline cellulose (E460i)

Tablet coating:
Polyvinyl alcohol (E1203) 7.2 mg; Titanium dioxide (E171) 4.41 mg; Macrogol 4000 (E1521) 3.636 mg; Talc (E553b) 2.664 mg; Yellow iron oxide (E172iii) 0.09 mg

Each TUKYSA 150 mg film-coated tablet contains 30.29 mg of potassium and 27.65 mg of sodium.

Pharmaceutical form and active substance quantity per unit

Film-coated tablet with 50 mg or 150 mg tucatinib.

TUKYSA 50 mg film-coated tablet

Round, yellow, film-coated, debossed with “TUC” on one side and “50” on the other side.

TUKYSA 150 mg film-coated tablet

Oval shaped, yellow, film-coated, debossed with “TUC” on one side and “150” on the other side.

Indications/Uses

TUKYSA in combination with trastuzumab and capecitabine is indicated for the treatment of patients with metastatic HER2-positive breast cancer, who have previously received 2 or more anti-HER2 regimens in any setting, including trastuzumab, pertuzumab and trastuzumab-emtansine (T–DM1) (see “Clinical Efficacy”).

Dosage/Administration

TUKYSA treatment should be initiated and supervised by a physician experienced in the administration of anti–cancer medicinal products.

Usual dosage

The recommended dose of TUKYSA is 300 mg (two 150 mg tablets) taken orally twice daily in combination with trastuzumab and capecitabine, at doses described in table 1. Refer to the Information for Professionals for co-administered trastuzumab and capecitabine for additional information. The treatment components can be administered in any order.

Table 1: Recommended dosing

Treatment	Dose	Treatment Days (21-day cycles)	Timing Relative to Food Intake
TUKYSA	300 mg orally twice daily	Days 1 to 21	With or without a meal
Capecitabine	1000 mg/m^2 orally twice daily	Days 1 to 14 every 21 days	Within 30 minutes after a meal
Trastuzumab			
Intravenous dosing			
Initial dose	8 mg/kg intravenously	Day 1	
Subsequent doses	6 mg/kg intravenously	Every 21 days	Not applicable
OR			
Subcutaneous dosing	600 mg subcutaneously	Every 21 days	

Duration of treatment

Treatment with TUKYSA should be continued until disease progression or unacceptable toxicity.

Dose adjustment following undesirable effects/interactions

The recommended TUKYSA dose modifications for patients with adverse reactions are provided in Tables 2 to 5. Refer to the Information for Professionals for dose modifications due to adverse events suspected to be trastuzumab or capecitabin-related.

Table 2: TUKYSA Dose Reduction Schedule for Adverse Reactions

Dose Level	**TUKYSA Dose**
Recommended starting dose	300 mg twice daily
First dose reduction	250 mg twice daily
Second dose reduction	200 mg twice daily
Third dose reduction	150 mg twice daily*

* A dose reduction below 150 mg twice daily is not recommended.

Table 3: TUKYSA Dose Modifications – Hepatotoxicity

Liver Function Abnormalities[$]	**TUKYSA Dose Modification**
Grade 3 elevation of ALT or AST (> 5 – ≤ 20 x ULN) OR Grade 3 elevation of bilirubin (> 3 – ≤ 10 x ULN)	Hold TUKYSA until severity ≤ Grade 1. Then resume TUKYSA at the next lower dose level.
Grade 4 elevation of ALT or AST (> 20 x ULN) OR Grade 4 elevation of bilirubin (> 10 x ULN)	Permanently discontinue TUKYSA.
ALT or AST > 3 x ULN AND Bilirubin > 2 x ULN	Permanently discontinue TUKYSA.

ULN: upper limit of normal; ALT: alanine aminotransferase; AST: aspartate aminotransferase
[$] Grading per CTCAE v4.03

Table 4: TUKYSA Dose Modifications – Diarrhoea

Diarrhoea	**TUKYSA Dosage Modification**
Grade 3 without anti-diarrhoeal treatment	Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.
Grade 3 with anti-diarrhoeal treatment	Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.
Grade 4	Permanently discontinue TUKYSA.

Table 5: TUKYSA Dose Modifications for Other Adverse Reactions

General Adverse Reactions[#]	**TUKYSADose Modification**
Grade 3	Hold TUKYSA until severity ≤ Grade 1. Then resume TUKYSA at the next lower dose level.
Grade 4	Permanently discontinue TUKYSA.

[#] Grading per CTCAE v4.03

Coadministration with strong CYP2C8 inhibitors

Avoid coadministration with strong CYP2C8 inhibitors during treatment with TUKYSA. If coadministration with a strong CYP2C8 inhibitor cannot be avoided, reduce the TUKYSA starting dose to 100 mg orally twice daily (see section “Interactions”).

Patients with impaired hepatic function

No dose adjustment is required in patients with mild or moderate hepatic impairment. For patients with severe hepatic impairment (Child-Pugh C), the use of TUKYSA in combination with capecitabine and trastuzumab is not recommended, since capecitabine is contraindicated in these patients.

Patients with impaired renal function

No dose adjustment is required in patients with mild or moderate renal impairment. The effect of severe renal impairment (creatinine clearance < 30 mL/min) on the pharmacokinetics of tucatinib is unknown (see section “Pharmacokinetics”). However, the use of TUKYSA in combination with capecitabine and trastuzumab in these patients is not recommended, since capecitabine is contraindicated in patients with severely impaired renal function.

Elderly patients

No dose adjustment is required in patients ≥ 65 years of age (see section “Pharmacokinetics”). In HER2CLIMB, 82 patients who received TUKYSA were ≥ 65 years, of whom 8 patients were

≥ 75 years. The incidence of serious adverse reactions in those receiving TUKYSA was 34% in patients ≥ 65 years compared to 24% in patients < 65 years. There were no observed overall differences in the effectiveness of TUKYSA in patients ≥ 65 years compared to younger patients. There were too few patients ≥ 75 years to assess differences in effectiveness or safety.

Children and adolescents

The safety and efficacy of TUKYSA in paediatric patients have not been established.

Delayed administration

In the case of a missed dose or the patient vomits, the patient should take their next dose at the regularly scheduled time.

Mode of administration

For oral use.
The tablets should be swallowed whole and should not be chewed, crushed, or split prior to swallowing.
TUKYSA should be taken approximately 12 hours apart, at the same time every day with or without a meal. TUKYSA may be taken at the same time with capecitabine.

Contraindications

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

Warnings and precautions

Hepatotoxicity

Hepatotoxicity has been reported during treatment with TUKYSA (see section “Undesirable effects”). TUKYSA can cause severe liver toxicity. In HER2CLIMB, 8% of patients treated with TUKYSA had an increase of ALT > 5 × ULN, 6% had an increase of AST > 5 × ULN, and 1.5% had an increase of bilirubin > 3 × ULN (grade ≥ 3). Liver toxicity led to dose reductions in 8% of patients treated with TUKYSA and treatment was discontinued in 1.5% due to liver toxicity.
Monitor ALT, AST, and bilirubin every three weeks or as clinically indicated. Based on the severity of the adverse reaction, interrupt dose, then reduce the dose or permanently discontinue TUKYSA (see section “Dosage/Administration”).

Diarrhoea

Diarrhoea, including severe events, has been reported during treatment with TUKYSA (see section “Undesirable effects”). TUKYSA can cause severe diarrhoea and associated dehydration, low blood pressure, acute kidney failure with fatal outcome. In HER2CLIMB, 81% of the patients had diarrhoea

with TUKYSA, thereof 12% were grade 3 diarrhoea and 0.5% grade 4 diarrhoea. Both patients who developed grade 4 diarrhoea died and the diarrhoea contributed to the death of these patients. Diarrhoea led to dose reduction in 6% of the treated patients and treatment discontinuation in 1% of the patients.
If diarrhoea occurs, administer anti-diarrhoeals as clinically indicated. Based on the severity of the diarrhoea, interrupt dose, then reduce the dose or permanently discontinue TUKYSA (see section “Dosage/Administration”). Perform diagnostic tests as clinically indicated to exclude infectious causes of grade 3 or 4 diarrhoea or diarrhoea of any grade with complicating features (dehydration, fever, neutropenia).

Embryo-foetal toxicity

Based on findings from animal studies and its mechanism of action, TUKYSA may cause foetal harm when administered to a pregnant woman. In animal reproduction studies, administration of tucatinib to pregnant rabbits during organogenesis caused foetal abnormalities in rabbits at maternal exposures similar to the clinical exposures at the recommended dose.
Advise pregnant women of the potential risk to a foetus. Advise females of reproductive potential and female partners of male patients to use reliable contraception during treatment and for at least 1 week after the last dose (see section “Pregnancy/Lactation”).

Excipients

This medicinal product contains 55.3 mg sodium per 300 mg dose. This is equivalent to 2.75% of the recommended maximum daily dietary intake of sodium for an adult.
This medicinal product contains 60.6 mg potassium per 300 mg dose. This should be taken into consideration for patients who have impaired kidney function or are on a controlled potassium diet (diet with low potassium content).

Interactions

Other interactions

Drugs without Clinically Significant Interactions with TUKYSA
Based on drug interaction studies conducted with TUKYSA, no clinically significant drug interactions have been observed when TUKYSA is combined with omeprazole (a proton pump inhibitor) or tolbutamide (a sensitive CYP2C9 substrate).

Effect of TUKYSA on other medicinal products

Table 6 and Table 7 summarise the effect of TUKYSA on other drugs.

Table 6: TUKYSA drug interactions that affect other drugs

CYP3A Substrates	
Clinical Impact	Concomitant use with CYP3A substrates may increase the plasma concentrations of CYP3A substrates (see Table 7). Increased plasma concentrations of CYP3A substrates may lead to increased toxicity of the CYP3A substrates.
Prevention or Management	Avoid concomitant use with sensitive CYP3A substrates. If the use of sensitive CYP3A substrates is unavoidable, consider dose modification of CYP3A substrates with narrow therapeutic indices and/or increased monitoring for potential adverse reactions as described in the medication's prescribing information.
P-glycoprotein (P-gp) Substrates	
Clinical Impact	Concomitant use with P-gp substrates may increase the plasma concentrations of P-gp substrates. Concomitant use with digoxin, a P-gp substrate, increased digoxin concentrations (see Table 7). Increased concentrations of digoxin may lead to increased risk of adverse reactions, including cardiac toxicity.
Prevention or Management	P-gp substrates with narrow therapeutic indices, such as digoxin, should be used with caution when coadministered with TUKYSA. Refer to the prescribing information of sensitive P-gp substrates for dose adjustment recommendations due to drug interactions.

Table 7: Effect of TUKYSA on Other Drugs

Concomitant Drug (Dose)	**TUKYSA Dose**	**Ratio (90% CI) of Exposure Measures of Tucatinib Combination/No combination**	
		C_{max}	**AUC**
Repaglinide (CYP2C8) (0.5 mg single dose)	300 mg twice daily	1.69 (1.37, 2.10)	1.69 (1.51, 1.90)
Midazolam (CYP3A) (2 mg single dose)		3.01 (2.63, 3.45)	5.74 (5.05, 6.53)
Digoxin (P-gp) (0.5 mg single dose)		2.35 (1.90, 2.90)	1.46 (1.29, 1.66)
Metformin (MATE1/2-K)[a] (850 mg single dose)		1.08 (0.95, 1.23)	1.39 (1.25, 1.54)

a. TUKYSA reduced the renal clearance of metformin without any effect on GFR as measured by iohexol clearance and serum cystatin C.

Effect of other medicinal products on TUKYSA

Table 8 and Table 9 summarise drug interactions that affect the pharmacokinetics of TUKYSA.

Table 8: Drug interactions that affect TUKYSA

Strong CYP3A or Moderate CYP2C8 Inducers	
Clinical Impact	Concomitant use with a strong CYP3A or moderate CYP2C8 inducer decreases tucatinib AUC (see Table 9) which may reduce tucatinib efficacy.
Prevention or Management	Avoid concomitant use with a strong CYP3A or a moderate CYP2C8 inducer.
Strong or Moderate CYP2C8 Inhibitors	
Clinical Impact	Concomitant use with a strong CYP2C8 inhibitor increases tucatinib AUC (see Table 9) which may increase the risk of tucatinib toxicity.
Prevention or Management	Avoid concomitant use with strong CYP2C8 inhibitors. If coadministration with a strong CYP2C8 inhibitor cannot be avoided, reduce the starting TUKYSA dose to 100 mg orally twice daily (see section “Dosage/Administration”). Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.

Table 9: Effect of Other Drugs on TUKYSA

Concomitant Drug (Dose)	**TUKYSA Dose**	**Ratio (90% CI) of Exposure Measures of Tucatinib Combination/No combination**	
		C_{max}	**AUC**
CYP3A Inhibition Itraconazole (200 mg twice daily)	300 mg single dose	1.32 (1.23, 1.42)	1.34 (1.26, 1.43)
CYP3A/2C8 Induction Rifampin (600 mg once daily)		0.632 (0.531, 0.753)	0.520 (0.452, 0.597)
CYP2C8 Inhibition Gemfibrozil (600 mg twice daily)		1.62 (1.47, 1.79)	3.04 (2.66, 3.46)

In vitro studies

Tucatinib is a substrate of CYP2C8 and CYP3A.

Tucatinib is a reversible inhibitor of CYP2C8 and CYP3A and a time-dependent inhibitor of CYP3A, at clinically relevant concentrations.

Tucatinib has low potential to inhibit CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and UGT1A1 at clinically relevant concentrations.

Tucatinib is a substrate of P-gp and BCRP. Tucatinib is not a substrate of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, and BSEP.
Tucatinib inhibits MATE1/MATE2-K-mediated transport of metformin and OCT2/MATE1-mediated transport of creatinine. The observed serum creatinine increase in clinical studies with tucatinib is due to inhibition of tubular secretion of creatinine via OCT2 and MATE1.

Pregnancy, lactation

Women of childbearing age

Women of childbearing potential and female partners of male patients should be advised to use a reliable method of contraception during treatment with TUKYSA and for up to 1 week after taking the last dose.
The pregnancy status of women of childbearing potential should be verified prior to initiating treatment with TUKYSA.

Pregnancy

There are no sufficient data from the use of TUKYSA in pregnant women. Animal studies showed reproductive toxicity (see section "Preclinical data"). The potential risk for humans is unknown. TUKYSA must not be administered during pregnancy unless absolutely necessary. If the patient becomes pregnant while receiving TUKYSA, the potential hazard to the foetus must be explained to the patient.

Lactation

It is unknown whether TUKYSA or its metabolites are excreted in human milk. A risk to the breast-fed infant cannot be excluded. Women should not breast feed during treatment with TUKYSA and for at least 1 week after the last dose.

Fertility

No fertility studies in men or women have been conducted. Based on findings from animal studies, TUKYSA may impair fertility in females of reproductive potential (see section “Preclinical data”).

Effects on ability to drive and use machines

No studies on the effects of TUKYSA on the ability to drive or use machines have been performed. Caution when driving or using machines is advised for patients who experience nausea during treatment with TUKYSA (see section “Undesirable effects”).
The clinical status of the patient should be considered when assessing the patient’s ability to perform tasks that require judgment, motor, or cognitive skills.

Undesirable effects

Summary of the safety profile

The data summarised in this section reflect exposure to TUKYSA in 431 patients with locally advanced unresectable or metastatic HER2-positive breast cancer who received TUKYSA in combination with trastuzumab and capecitabine across two studies, HER2CLIMB and ONT-380-005. The median duration of exposure to TUKYSA across these studies was 5.8 months (range, < 0.1, 35.1).

The most common grade 3 and 4 adverse reactions (≥ 5%) in patients treated with TUKYSA were diarrhoea (13%), palmar-plantar erythrodysesthesia (13%), ALT increased (6%) and AST increased (5%).

Serious adverse reactions occurred in 27% of patients treated with TUKYSA. The most common serious adverse reactions (≥ 2%) were diarrhoea (4%), vomiting (2%), and nausea (2%).

Adverse events leading to discontinuation of TUKYSA occurred in 6% of patients; the most common adverse reactions leading to discontinuation were diarrhoea (1%) and ALT increased (1%). Adverse events leading to dose reduction of TUKYSA occurred in 21% of patients; the most common adverse reactions leading to dose reduction were diarrhoea (5%), ALT increased (5%), and AST increased (4%).

The most common adverse reactions in patients that were treated with TUKYSA, were (≥ 20%) diarrhoea, palmar-plantar erythrodysesthesia, nausea, hepatotoxicity, vomiting, stomatitis, decreased appetite, anaemia and rash.

The undesirable effects are listed by MedDRA System Organ Class (SOC) at the preferred term level. Frequencies of occurrence of undesirable effects are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000).

Blood and lymphatic system disorders

Very common: Anaemia (20%)

Gastrointestinal disorders

Very common: Diarrhoea (81%), Nausea (60%), Vomiting (37%), Stomatitis[1] (32%)

[1]Stomatitis includes stomatitis, oropharyngeal pain, mouth ulceration, oral pain, lip ulceration, glossodynia, tongue blistering, lip blister, oral dysaesthesia, tongue ulceration, aphthous ulcer

Hepatobiliary disorders

Very common: AST increased (22%), ALT increased (20%), Blood bilirubin increased[2] (18%)

Common: increased alkaline phosphatase

[2]Blood bilirubin increased also includes hyperbilirubinemia

Metabolism and nutrition disorder

Very common: Decreased appetite (25%), Hypokalaemia (16%), Weight decreased (14%)

Common: Hypomagnesemia, Hypophosphataemia, Hyponatremia

Musculoskeletal and connective tissue disorders

Very common: Arthralgia (15%)

Respiratory, thoracic, and mediastinal disorders

Very common: Epistaxis (11%)

Nervous system disorders

Very common: peripheral sensory neuropathy (11%)

Skin and subcutaneous tissue disorders

Very common: Palmar-plantar erythrodysesthesia (64%), Rash[3] (21%)

[3]Rash includes rash maculo-papular, rash, dermatitis acneiform, erythema, rash macular, rash papular, rash pustular, rash pruritic, rash erythematous, skin exfoliation, urticaria, dermatitis allergic, palmar erythema, plantar erythema and skin toxicity

Description of selected undesirable effects

Increased ALT, AST, or bilirubin

In HER2CLIMB, the median time to onset of any grade increased ALT, AST, or bilirubin was 36 days; 84% of events resolved, with a median time to resolution of 22 days.

Diarrhoea

In HER2CLIMB, the median time to onset of any grade diarrhoea was 12 days; 80% of diarrhoea events resolved, with a median time to resolution of 8 days. Prophylactic use of anti-diarrhoeals was not required. Anti-diarrhoeal medications were used in less than half of the treatment cycles where diarrhoea events were reported. The median duration of anti-diarrhoeal use was 3 days per cycle.

Creatinine Increased

Although not an adverse reaction, increase in serum creatinine has been observed in patients treated with TUKYSA due to inhibition of renal tubular transport of creatinine without affecting glomerular function. In clinical studies, increases in serum creatinine (30% mean increase) occurred within the first cycle of TUKYSA, remained elevated but stable throughout treatment and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated GFR, which are not based on creatinine, may be considered to determine whether renal function is impaired.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

One patient took TUKYSA 600 mg twice daily for 14 days of each 21-day cycle for 14 cycles.

Signs and symptoms

Reported events considered to be related to TUKYSA treatment included grade 1 nausea and stomatitis. No significant lab abnormalities were reported.

Treatment

There is no specific antidote, and the benefit of haemodialysis in the treatment of TUKYSA overdose is unknown. In the event of an overdose, withhold TUKYSA and apply general supportive measures.

Properties/Effects

ATC code

L01{XXXX}

Mechanism of action

HER2 gene amplification in tumour cells results in over-expression of the HER2 protein and drives formation of HER2 homodimers and HER2/HER3 heterodimers, which leads to constitutive activation of downstream signalling cascades, increased cell proliferation, and metastasis.
Tucatinib is a reversible, potent and selective tyrosine kinase inhibitor of HER2. In cellular signalling assays, tucatinib is 1000-fold more selective for HER2 compared to epidermal growth factor receptor. *In vitro*, tucatinib inhibits phosphorylation of HER2 and HER3, resulting in inhibition of downstream cell signalling and cell proliferation, and induces death in HER2 driven tumour cells. *In vivo*, tucatinib inhibits the growth of HER2 driven tumours and the combination of tucatinib and trastuzumab showed enhanced anti-tumour activity *in vitro* and *in vivo* compared to either drug alone.

Pharmacodynamics

Cardiac Electrophysiology
Multiple doses of TUKYSA 300 mg twice daily did not have an effect on the QTc interval in a TQT study in healthy subjects.

Clinical efficacy

The efficacy of TUKYSA in combination with trastuzumab and capecitabine was evaluated in a randomised, double-blind, placebo-controlled, active comparator, global Phase 2 trial (HER2CLIMB).

Patients enrolled had locally advanced unresectable or metastatic HER2 -positive breast cancer, with or without brain metastases, and had prior treatment with trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1) separately or in combination, in the neoadjuvant, adjuvant or metastatic setting. Capecitabine in the metastatic setting was not allowed before enrolment in the study. HER2 overexpression or amplification was confirmed by central laboratory analysis.
Patients with brain metastases were eligible to enroll provided they were neurologically stable and did not require immediate radiation or surgery. Patients who required immediate local intervention could receive local therapy and be subsequently enrolled. The study included patients with untreated brain metastases and patients with treated brain metastases that were either stable or progressing since last treatment. The trial excluded patients with leptomeningeal disease.

A total of 612 patients were randomised 2:1 to receive TUKYSA in combination with trastuzumab and capecitabine (N=410) or placebo in combination with trastuzumab and capecitabine (N=202). Randomisation was stratified by the presence or history of brain metastases (yes vs. no), general condition according to the ECOG-PS (Eastern Cooperative Oncology Group performance status) (0 vs. 1), and region (U.S., Canada, or rest of world).

Patient demographics were balanced between treatment arms. The median age was 54 years (range, 25 to 82); 116 (19%) patients were age 65 or older. The majority were white (73%) and female (99%), and 51% had an ECOG-PS of 1. Sixty percent had estrogen and/or progesterone receptor-positive disease. Forty-eight percent of patients had a presence or history of brain metastases; of these, 23% had untreated brain metastases, 40% had treated but stable brain metastases, and 37% had treated but radiographically progressing brain metastases. Additionally, 49% of patients had lung metastases, 35% had liver metastases, and 14% had skin metastases. Patients had a median of 4 (range, 2 to 17) prior lines of systemic therapy and a median of 3 (range, 1 to 14) prior lines of systemic therapy in the metastatic setting.

TUKYSA or placebo, 300 mg orally twice per day, was administered until disease progression or unacceptable toxicity. Trastuzumab was administered intravenously as a loading dose of 8 mg/kg on Day 1 of Cycle 1, followed by a maintenance dose of 6 mg/kg on Day 1 of each subsequent 21-day cycle. An alternate dosing option for trastuzumab was a fixed dose of 600 mg administered subcutaneously on Day 1 of each 21-day cycle. Capecitabine, 1000 mg/m^2 orally twice per day, was administered on Days 1 through 14 of each 21-day cycle.

The primary endpoint was progression-free survival (PFS) by blinded independent central review (BICR) in the first 480 randomised patients. The median duration of exposure to TUKYSA was 7.3 months (range < 0.1, 35.1) for patients on the TUKYSA + trastuzumab and capecitabine arm compared to 4.4 months (range < 0.1, 24.0) of placebo for patients on the placebo + trastuzumab and capecitabine arm. Similar differences in exposure to trastuzumab and capecitabine were observed.

Secondary endpoints were evaluated in all randomised patients (N=612) and included overall survival (OS), PFS among patients with a history or presence of brain metastases ($PFS_{BrainMets}$), and confirmed objective response rate (ORR).

The results of the primary analysis are summarised in Table 10. There was a 46% reduction in the risk of progression or death on the TUKYSA + trastuzumab and capecitabine arm (HR=0.54 [95% CI: 0.42, 0.71]; P<0.00001). The median PFS was 7.8 months on the TUKYSA + trastuzumab and capecitabine arm (TUKYSA arm) and 5.6 months on the placebo + trastuzumab and capecitabine arm (placebo arm).

Table 10: PFS per BICR

PFS[1,2]	TUKYSA + Trastuzumab + Capecitabine	Placebo + Trastuzumab + Capecitabine
	N=320	N=160
Number of events (%)	178 (56)	97 (61)
Hazard ratio (95% CI)[2]	0.54 (0.42, 0.71)	
P-value[3]	<0.00001	
Median (months) (95% CI[4])	7.8 (7.5, 9.6)	5.6 (4.2, 7.1)

BICR=blinded independent central review; CI=confidence interval; PFS=progression-free survival.

1. Primary PFS analysis conducted in first 480 randomised patients. PFS based on Kaplan-Meier analyses.
2. Hazard ratio and 95% confidence intervals are based on stratified Cox proportional hazards regression model controlling for stratification factors (presence or history of brain metastases, ECOG status, and region of world)
3. Two-sided p-value based on re-randomisation procedure controlling for stratification factors
4. Calculated using the complementary log-log transformation method

All multiplicity adjusted secondary endpoints were also met. The risk of death was reduced by 34% on the TUKYSA arm (HR=0.66 [95% CI: 0.50, 0.87], P=0.0048). The median OS was 21.9 months on the TUKYSA arm and 17.4 months on the placebo arm. Among patients with brain metastases, there was a 52% reduction in the risk of progression or death on the TUKYSA arm (HR=0.48 [95% CI: 0.34, 0.69], P<0.00001). The median PFS in patients with brain metastases was 7.6 months on the TUKYSA arm and 5.4 months on the placebo arm. The confirmed ORR in patients with measurable disease (N=511) was significantly higher on the TUKYSA arm compared to the placebo arm (40.6% [95% CI: 35.3, 46.0] vs 22.8% [95% CI: 16.7, 29.8] respectively; P=0.00008). Efficacy results were consistent across all patient subgroups including hormone receptor status, presence or history of brain metastases, ECOG status, and region.

Safety and efficacy in paediatric patients

The European Medicines Agency has waived the obligation to submit the results of studies with TUKYSA in all subsets of the paediatric population in malignant breast neoplasms, for the granted indication.

Pharmacokinetics

Plasma tucatinib exposure (AUC_{inf} and C_{max}) demonstrated approximately dose proportional increases at oral doses from 50 to 300 mg (0.17 to 1 time the recommended dose). Tucatinib exhibited 1.7-fold accumulation for AUC and 1.5-fold accumulation for C_{max} following administration of 300 mg tucatinib twice daily for 14 days. Time to steady state was approximately 4 days.

Absorption

Following a single oral dose of 300 mg tucatinib, the median time to peak plasma concentration was approximately 2.0 hours (range: 1.0 to 4.0 hours) in healthy subjects.

Effects of Food

Following administration of a single dose of tucatinib in 11 subjects after a high-fat meal (approximately 58% fat, 26% carbohydrate, and 16% protein), the mean AUC_{inf} increased by 1.5-fold, the T_{max} shifted from 1.5 hours to 4.0 hours, and C_{max} was unaltered. The effect of food on the pharmacokinetic of tucatinib was not clinically meaningful, thus tucatinib may be administered without regard to food.

Distribution

The apparent volume of distribution of tucatinib was approximately 1670 liter in healthy subjects. The plasma protein binding was 97.1% at clinically relevant concentrations.

Metabolism

Tucatinib is metabolised primarily by CYP2C8 and to a lesser extent via CYP3A.

Elimination

Following a single oral dose of 300 mg, tucatinib is cleared from plasma with a mean half-life of approximately 8.7 hours and apparent clearance of 148 L/h in healthy subjects.

Tucatinib is predominantly eliminated by the hepatobiliary route and is not appreciably renally eliminated. Following a single oral dose of 300 mg [14C]-tucatinib, approximately 85.8% of the total radiolabelled dose was recovered in faeces (15.9% of the administered dose as unchanged tucatinib) and 4.1% in urine with an overall total recovery of 89.9% within 13 days post-dose. In plasma,

approximately 75.6% of the plasma radioactivity was unchanged, 19% was attributed to identified metabolites, and approximately 5% was unassigned.

Kinetics in specific patient groups

Based on population pharmacokinetic analysis according to demographic characteristics, age (< 65 years (N=211); ≥ 65 years (N=27)), albumin (25.0 to 52.0 g/L), creatinine clearance (CLcr 60 to 89 mL/min (N=89); CLcr 30 to 59 mL/min (N=5)), body weight (40.7 to 138.0 kg), and race (White (N=168), Black (N=53), or Asian (N=10)) did not have a clinically meaningful effect on tucatinib exposure.

Hepatic impairment

Mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment had no clinically relevant effect on tucatinib exposure. Tucatinib AUC_{inf} was increased 1.6 fold in subjects with severe (Child-Pugh C) hepatic impairment compared to subjects with normal hepatic function.

Renal impairment

The pharmacokinetics of tucatinib have not been evaluated in a dedicated renal impairment study. Data from subjects with mild (creatinine clearance: 60 to 89 mL/min) and moderate (creatinine clearance: 30 to 59 mL/min) renal impairment were included in the population pharmacokinetic analysis. No data from subjects with severe renal impairment (creatinine clearance: < 30 mL/min) are available.

Preclinical data

Long-term toxicity (or repeat dose toxicity)

High systemic exposures to tucatinib were associated with mortality in rats and cynomolgus monkeys. Deaths were observed at exposure levels that were 22 times (in rat) and 7 times (in monkey) above the human exposure at the maximum recommended clinical dose. In both rats and cynomolgus monkeys, non specific and/or gastrointestinal toxicity was the primary cause of moribundity and/or mortality. The rat and cynomolgus monkey deaths were preceded by monitorable signs of toxicity.

Mutagenicity

Tucatinib was not mutagenic in an *in vitro* bacterial reverse-mutation study (Ames test) or clastogenic in a mouse bone marrow chromosomal aberration assay.

Carcinogenicity

Carcinogenicity studies have not been conducted with tucatinib.

Reproductive toxicity

No histological effects were observed on male or female reproductive tracts in cynomolgus monkeys or on male reproductive tracts in rats at doses resulting in exposures up to 3 times (in monkey) or 13 times (in rat) the human exposure at the recommended dose, based on AUC_{0-12}.
In repeat-dose toxicity studies in female rats, decreased corpora lutea/corpus luteum cyst, increased interstitial cells of the ovary, atrophy of the uterus, and mucification of the vagina were observed at doses of ≥ 6 mg/kg/day administered twice daily, which resulted in exposures of approximately 15% of the human exposure at the recommended dose, based on AUC_{0-12}.
Embryo-fetal development studies were conducted in rabbits and rats (6 dams/group). In pregnant rabbits, increased resorptions, decreased percentages of live foetuses (males more affected than females), and skeletal, visceral, and external malformations were observed in fetuses at ≥ 90 mg/kg/day; at this dose, maternal exposure is approximately equivalent to the human exposure at the recommended dose based on AUC. In pregnant rats, decreased maternal body weight and body weight gain were observed at doses of ≥ 90 mg/kg/day. Fetal effects of decreased body weight and delayed ossification were observed at ≥ 120 mg/kg/day; at this dose, maternal exposure is approximately 9-fold higher than human exposure at the recommended dose based on AUC.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

Store at room temperature (15-25°C).
Store in the original packaging.
Keep out of the reach of children.

Instructions for handling

Not applicable.

Authorisation number

67798 (Swissmedic)

Packs

150 mg blister presentation of 84 film-coated tablets: 4 film-coated tablets per blister and 21 blisters per carton. [A]
50 mg blister presentation of 88 film-coated tablets: 8 film-coated tablets per blister and 11 blisters per carton. [A]

Marketing authorisation holder

SFL Regulatory Affairs & Scientific Communication GmbH

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