swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Tukysa

International non-proprietary name:	tucatinib
Pharmaceutical form:	Film-coated tablets
Dosage strength(s):	50 mg and 150 mg
Route(s) of administration:	Oral
Marketing authorisation holder:	Pfizer AG
Marketing authorisation no.:	67798
Decision and decision date:	extension of therapeutic indication approved on 11 March 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
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)

2 Background information on the procedure

2.1 Applicant's request(s)

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested 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 two or more anti-HER2 regimens in any setting, including trastuzumab, pertuzumab and either trastuzumab-emtansine (T–DM1) or trastuzumab-deruxtecan (T-DXd), (see "Clinical Efficacy").

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 at least two anti-HER2 treatment regimens (see «Clinical Efficacy»).

2.2.3 Requested dosage

Summary of the requested standard dosage:

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	1 October 2024
Formal control completed	9 October 2024
Preliminary decision	20 January 2025
Response to preliminary decision	20 February 2025
Final decision	11 March 2025
Decision	approval

3 Medical context

The HER2-targeted antibody drug conjugate (ADC) Tukysa was approved in Switzerland in 2020 for use in third-line after prior exposure to trastuzumab, pertuzumab, and trastuzumab emtansine (T-DM1), based on the results of the randomised, double-blind HER2CLIMB study comparing tucatinib + trastuzumab + capecitabine vs. placebo + trastuzumab + capecitabine (PFS HR=0.54; 95% CI: 0.42, 0.71; P<0.001; OS HR=0.66; 95% CI: 0.50, 0.88; P=0.005) (please refer to the SwissPAR Tukysa dated 02 June 2020 for further information) (reference: Murthy RK et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N Engl J Med. 2020 Feb 13;382(7):597-609. doi: 10.1056/NEJMoa1914609. Epub 2019 Dec 11. Erratum in: N Engl J Med. 2020 Feb 6;382(6):586.). Tukysa was a new standard of care third-line treatment after prior trastuzumab + pertuzumab + taxane followed by T-DM1.

With the second-line approval of the HER2-targeted ADC trastuzumab deruxtecan (T-DXd) in 2022, based on the results of the randomised, open-label study DESTINYBreast-03 (reference: Cortés J et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. N Engl J Med. 2022 Mar 24;386(12):1143-1154), the standard of care recommended by national and international treatment guidelines issued by Arbeitsgemeinschaft Gynäkologische Onkologie (AGO), European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN) changed to trastuzumab + pertuzumab + taxane → T-DXd → tucatinib + trastuzumab + capecitabine.

While the clinical scenario of the first and second treatment lines is clearly defined, there is currently no consensus on subsequent treatment lines, as currently there are no available clinical data for therapies beyond T-DXd progression. Among various available treatment options, decision making must be supported by patient- and disease-related factors, including overall tolerability, clinical benefit to prior therapies, disease burden, and eventual central nervous system (CNS) involvement (reference: Antonarelli G et al. Management of patients with HER2-positive metastatic breast cancer after trastuzumab deruxtecan failure. ESMO Open. 2023 Aug;8(4):101608).

Conducting randomised controlled trials on treatment sequences evaluating tucatinib after prior T-DM1 or T-DXd is challenging due to ethical reasons and in light of the rapidly evolving treatment landscape.

4 Clinical aspects

4.1 Clinical pharmacology

No new data from clinical pharmacology studies were submitted.

4.2 Dose finding and dose recommendation

No new data regarding dose finding were submitted.

4.3 Efficacy

The Applicant provided updated results of the pivotal study HER2CLIMB with data cut-off (DCO) 08 Feb 2021 (please refer to SwissPAR Tukysa for detailed information on the study design and prior results).

With a median follow-up of 29.6 months (original DCO: 10.4 months), the analysis of PFS per investigator assessment demonstrated continued benefit of treatment with the tucatinib triplet arm (tucatinib arm) compared with the control arm, with a 43% reduction in the risk of disease progression or death (HR = 0.57 [95% CI: 0.47, 0.70], p < 0.00001). The median PFS was 7.6 months (95%CI 6.9, 8.3) in the tucatinib arm and 4.9 months (95%CI 4.1, 5.6) in the control arm.
The analysis of OS likewise demonstrated a 27% reduction in the risk of death (HR = 0.73 [95% CI: 0.59, 0.90]; p = 0.004), with median OS rates of 24.7 months (95%CI 21.6, 28.9) and 19.2 months (95%CI 16.4, 21.4) for the tucatinib arm and placebo arm, respectively.
PFS in subjects with brain metastases per Blinded Independent Central Review (BICR) was an alpha-controlled secondary endpoint in study HER2CLIMB. Among patients with known brain metastases (48%), the PFS was increased in the tucatinib arm (HR=0,48 [95%-KI: 0,34, 0,69], P<0,00001) with a median PFS of 7.6 months compared to 5.4 months in the control arm.

In addition, the Applicant submitted real world evidence (RWE) regarding the use of tucatinib after prior exposure to T-DXd. Overall, four different cohort studies based on datasets provided by different healthcare databases (Flatiron, Komodo, Merative, Unicancer) using a variety of data sources were submitted.
The interpretability of the RWE was highly limited due to reasons including the limited sample sizes, the retrospective nature of the studies, the risk of potential (unknown) confounders, missing data, potential misclassification of lines of therapies, and changes in treatment guidelines during the study period. Therefore, submitted RWE data were accepted as supportive evidence only.

4.4 Safety

The safety assessment was based mainly on the pivotal study HER2CLIMB. Based on post marketing data, no safety signals have been reported regarding the use of tucatinib after prior T-DXd – a sequence that is applicable in the European Union and the United States based on the approved indications.

4.5 Final clinical benefit risk assessment

The totality of evidence, including clinical evidence from the study HER2CLIMB, the recommendation of prior T-DXd therapy by internationally accepted clinical guidelines NCCN and ESMO, and supportive data from real world studies, can be accepted for the requested indication extension,

particularly in light of the rapidly evolving treatment landscape in this disease setting and in the absence of relevant safety concerns.

5 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken 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. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. 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 that occur in populations or indications not included in the Swiss authorisations.

6 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for 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 valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

TUKYSA®

Composition

Active substances

Tucatinib.

Excipients

Film-coated tablets of 50 mg:

Tablet core: Copovidone (E 1208); Crospovidone (E 1202); Sodium chloride; Potassium chloride (E 508); Sodium hydrogen carbonate (E 500ii); Colloidal silicon dioxide (E 551); Magnesium stearate (E 470b); Microcrystalline cellulose (E 460i).

Tablet coating:

Polyvinyl alcohol (E 1203); Titanium dioxide (E 171); Macrogol 4000 (E 1521); Talc (E 553b); Yellow iron oxide (E 172iii).

1 film-coated tablet contains 10.10 mg of potassium and 9.21 mg of sodium.

Film-coated tablets of 150 mg:

Tablet core:

Copovidone (E 1208); Crospovidone (E 1202); Sodium chloride; Potassium chloride (E 508); Sodium hydrogen carbonate (E 500ii); Colloidal silicon dioxide (E 551); Magnesium stearate (E 470b); Microcrystalline cellulose (E 460i).

Tablet coating:

Polyvinyl alcohol (E 1203); Titanium dioxide (E 171); Macrogol 4000 (E 1521); Talc (E 553b); Yellow iron oxide (E 172iii)

1 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.

Film-coated tablets of 50 mg: 1 film-coated tablet contains 50 mg tucatinib.

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

Film-coated tablets of 150 mg: 1 film-coated tablet contains 150 mg tucatinib.

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 at least two anti-HER2 treatment regimens (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 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

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)	Interrupt 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. Interrupt 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. Interrupt 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	Interrupt 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 total 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»). Prompt medical management should also be instituted in the event of persistence of concomitant Grade 2 diarrhoea with concomitant Grade ≥2 nausea and/or vomiting. 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 (≥1/1000 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

L01EH03

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. All patients (100%) had prior exposure to T-DM1.

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

TUKYSA film-coated tablets 50 mg: 88. [A]

TUKYSA film-coated tablets 150 mg: 84. [A]

Marketing authorisation holder

Pfizer AG, Zürich.

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