Tucatinib (Tukysa™)
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Tucatinib is a tyrosine kinase inhibitor that is highly selective for the human epidermal growth factor receptor 2 (HER2) kinase domain, with minimal inhibition of the epidermal growth factor receptor
- Tucatinib inhibits HER2 and HER3 phosphorylation, resulting in downstream inhibition of MAPK and AKT signaling and cell proliferation

Indication(s) Under Review in This Document

- In combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting

Dosage Form(s) Under Review

- Recommended dosage: 300 mg taken orally twice daily with or without food
- For patients with severe hepatic impairment, the recommended dosage is 200 mg orally twice daily

Clinical Evidence Summary

Efficacy Considerations

- The efficacy of tucatinib in combination with trastuzumab and capecitabine was established in the HER2CLIMB phase II trial. Adding tucatinib to trastuzumab and capecitabine resulted in improved progression-free survival and overall survival outcomes compared with placebo
- Efficacy data are summarized in Table 1

Table 1: Efficacy results from HER2CLIMB

Design	Results
Phase II randomized, double-blinded controlled study **Inclusion**: Age ≥18 years; HER2-positive (FISH and/or 3+ staining by IHC) advanced breast carcinoma; previous treatment with trastuzumab, pertuzumab, and trastuzumab emtansine; ECOG PS 0-1; active brain metastases permitted if urgent local intervention not needed, in which case they could receive local therapy and be enrolled subsequently **Exclusion:** Previous treatment for metastatic disease with capecitabine or a HER2-targeted tyrosine kinase inhibitor; leptomeningeal disease; untreated brain metastases larger than 2 cm in diameter unless approved by the medical monitor Randomized 2:1 Tucatinib 300 mg PO twice daily + trastuzumab 6 mg/kg IV or subQ every 21 days (with an initial LD of 8 mg/kg) + capecitabine 1000 mg/m^2 PO twice daily on days 1-14 of each 21-day cycle vs. Placebo + trastuzumab + capecitabine Stratified by (1) presence of brain metastases, (2) ECOG performance status, and (3) geography **Primary (primary end-point analysis population):** Progression-free survival (PFS) in the first 480 patients **Secondary (total population):** Overall survival (OS); progression-free survival among all patients and those who had brain metastases at baseline; confirmed objective response rate (ORR)	**Demographics:** Median age ~55 years; ~99% female; ~60% of patients HR+; 47.5% had brain metastases at baseline; ~49%, 35%, and 55% had lung, liver, and bone metastases at baseline, respectively; median of 3 previous lines of therapy for metastatic disease **Results at median follow-up of 14 months**, Tucatinib/trastuzumab/capecitabine vs. PBO/trastuzumab/capecitabine **Primary end-point analysis population (*n* = 480):** **1 year estimated PFS:** 33.1% vs 12.3% **mPFS:** 7.8 mo vs. 5.6 mo **Risk of disease progression/death:** HR 0.54; 95% CI 0.42-0.71; p<0.001 **Stratification results:** Subgroup / # events / total # / HR (95% CI) Brain mets Yes 138/219 0.46 (0.31-0.67) No 136/260 0.62 (0.44-0.89) ECOG 0 134/235 0.56 (0.39-0.80) 1 141/245 0.55 (0.38-0.79) Region U.S./Canada 179/307 0.57 (0.41-0.78) Other 96/173 0.51 (0.33-0.79) **Total population (*n* = 612):** **2 year estimated OS:** 44.9% vs. 26.6% **mOS:** 21.9 mo vs. 17.4 mo **Risk of death:** HR 0.66; 95% CI 0.50-0.88; p=0.005 **mPFS:** 8.1 mo vs. 5.5 mo **Risk of disease progression/death:** HR 0.54, 95% CI 0.42-0.68 **ORR:** 40.6% vs. 22.8% (95% CI 17.7-29.8) **mPFS among patients with brain metastases:** 7.6 mo vs. 5.4 mo **Risk of disease progression/death:** HR 0.48; 95% CI 0.34-0.69; p<0.001

- The HER2CLIMB trial evaluated tucatinib combined with trastuzumab and capecitabine in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine
- The population represented in the study was heavily pre-treated and approximately half of the patients had brain metastases at baseline
- Adding tucatinib to trastuzumab and capecitabine resulted in better PFS and OS outcomes than adding placebo

- The improvement in terms of PFS in the primary end-point analysis population was seen across all prespecified subgroups when stratified by presence of brain metastases, ECOG performance status, and geography
- The improvement in terms of OS in the total population was not statistically significant in patients without brain metastases at baseline, ECOG PS 1, or the rest of the world (outside of the U.S. and Canada)
- For patients with active brain metastases at baseline, the improvement in terms of PFS was not statistically significant for patients with an ECOG PS 1 or those residing in the rest of the world

Safety Considerations

Safety Results from Clinical Trials:

- The safety of tucatinib in combination with trastuzumab and capecitabine was evaluated in HER2CLIMB
- Among the 404 patients who received at least one dose of tucatinib, the median duration of exposure was 5.8 months (range, <0.1 to 24)
- Common adverse events in the tucatinib group included diarrhea, palmar-plantar erythrodysesthesia (PPE) syndrome, nausea, fatigue, and vomiting
- Diarrhea and elevated aminotransferase levels of grade 3 or higher were more common in the tucatinib-combination group than in the placebo-combination group

Table 2: Safety results from HER2CLIMB

Adverse Event	Tucatinib-Combination % (n = 404)	Placebo-Combination % (n = 197)
Any Grade ≥3	55.2	48.7
Grade ≥3 (≥5%)		
Diarrhea	12.9	8.6
PPE syndrome	13.1	9.1
Increased ALT	5.4	0.5
Common (≥20%)		
Diarrhea	80.9	53.3
PPE syndrome	63.4	52.8
Nausea	58.4	43.7
Fatigue	45.0	43.1
Vomiting	35.9	25.4
Stomatitis	25.5	14.2
Decreased appetite	24.8	19.8
Headache	21.5	20.3
Increased AST	21.3	11.2
Increased ALT	20.0	6.6

- **Boxed warnings:**
  - None
- **Contraindications:**
  - None
- **Other warnings / precautions**:
  - **Diarrhea:** Severe diarrhea, including dehydration, acute kidney injury, and death, has been reported. Administer antidiarrheal treatment as clinically indicated. Interrupt dose, then dose reduce, or permanently discontinue tucatinib based on severity
    - Median time to onset of diarrhea is 12 days, with median time to resolution in 8 days
    - ~81% of patients experienced diarrhea in clinical trials (grade 3: 12%; grade 4: 0.5%)

    - **Hepatotoxicity:** Severe hepatotoxicity has been reported on tucatinib. Monitor ALT, AST, and bilirubin prior to starting tucatinib, every 3 weeks during treatment and as clinically indicated. Interrupt dose, then dose reduce, or permanently discontinue tucatinib based on severity
        - 8% of patients who received tucatinib in clinical trials had an ALT increase >5 times the upper limit of normal (ULN), 6% had an AST increase >5 times the ULN, and 1.5% had a bilirubin increase >3 times the ULN (grade 3)
    - **Embryo-Fetal Toxicity:** Tucatinib can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception
- **Adverse reactions**
    - **Common (≥20%):** Diarrhea, PPE syndrome, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, rash
    - **Serious Adverse events / Deaths / Discontinuation:** In HER2CLIMB, adverse events were the cause of death in 6 of 404 patients (1.5%) in the tucatinib-combination group (cardiac arrest, cardiac failure, dehydration, multiple-organ dysfunction syndrome, sepsis, and septic shock in 1 patient each)

Other Considerations

- **Dosage Adjustment for Concomitant Therapy:** Significant drug interactions exist, requiring dose/frequency adjustment or avoidance
    - Strong CYP3A Inducers or Moderate CYP2C8 Inducers: Avoid concomitant use
    - Strong CYP2C8 Inhibitors: Avoid concomitant use; reduce tucatinib dose if concomitant use cannot be avoided
    - CYP3A Substrates: Avoid concomitant use with CYP3A substrates, where minimal concentration changes may lead to serious or life-threatening toxicities
    - P-gp Substrates: Consider reducing the dose of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities
- **Serum Creatinine Increases:** Tucatinib increases serum creatinine by inhibiting renal tubular secretion, but without affecting glomerular filtration.
    - The mean increase in serum creatinine was 32% within the first 21 days o treatment; serum creatinine increases persisted throughout treatment and were reversible upon treatment completion
    - Consider alternative markers of renal function if persistent elevations in serum creatinine are observed
- **Use in Specific Populations:**
    - **Pregnancy:** Based on the mechanism of action and data from animal reproduction studies, in utero exposure to tucatinib may cause fetal harm. Females of reproductive potential should use effective contraception during tucatinib therapy and for ≥1 week after the last tucatinib dose. Males with female partners of reproductive potential should use effective contraception during tucatinib therapy and for ≥1 week after the last tucatinib dose
    - **Lactation:** It is not known if tucatinib is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer during tucatinib treatment or for ≥1 week after the last tucatinib dose
    - **Older Adult**: The incidence of serious adverse reactions was higher in patients ≥65 years of age compared to younger patients
- **Emetogenic Risk:** The emetic risk of tucatinib is low to minimal. As needed antiemetic therapy should be provided.

Risk-Benefit Assessment (for Oncology NMEs only)

- **Outcome in clinically significant area:** mPFS 7.8 mo vs. 5.6 mo; mOS 21.9 mo vs. 17.4 mo
- **Effect Size:** mPFS HR 0.54 (95% CI 0.42 to 0.71); mOS HR 0.66 (95% CI 0.50 to 0.88)
- **Potential Harms:** Moderate
- **Net Clinical Benefit:** Moderate

Other Therapeutic Options

Supporting efficacy and safety data for regimens in the second-line and third-line and beyond settings are summarized in table 3.

Table 3: Supporting data for regimens in the second-line and third-line and beyond settings

Regimen	Supporting Data
Tucatinib + trastuzumab + capecitabine Murthy RK, et al. (2020)	• N = 612 (480 in primary end-point analysis population) randomized to tucatinib or placebo plus trastuzumab + capecitabine • Heavily pretreated patients (prior trastuzumab, pertuzumab, and trastuzumab emtansine); brain metastases permitted as long as urgent local intervention not needed • mPFS in primary endpoint population: 7.8 mo vs. 5.6 mo (HR 0.54; 95% CI 0.42-0.71); mOS 21.9 mo vs. 17.4 mo (HR 0.66; 95% CI 0.50-0.88); mPFS among patients with brain metastases: 7.6 mo vs. 5.4 mo (HR 0.48; 95% CI 0.34-0.69) • Grade ≥3 AEs: Diarrhea and elevated LFTs
Second-Line	
Trastuzumab deruxtecan Modi S, et al. (2020)	• N = 184 • Heavily pretreated patients (median of 6 previous treatments); patients with treated and asymptomatic brain metastases eligible (~13%) • mPFS 16.4 mo (95% CI 12.7 to NR) among all patients and 18.1 mo (95% CI 6.7 to 18.1) among patients with brain metastases • ILD occurred in 13.6% of patients
Bartsch R, et al. (2022)	• N = 15 • Pretreated patients (trastuzumab and pertuzumab) with newly diagnosed, active brain metastases not requiring immediate local therapy • Best overall intracranial response rate: 73.3% (95% CI 48.1% to 89.1%) • 2 patients (13.3%) had complete intracranial response, 9 (60%) had partial intracranial response, and 3 (20%) had stable disease
Trastuzumab emtansine **Verma S, et al. (2012)**	• N = 991 randomized to TDM1 vs. lapatinib vs. capecitabine • Previously treated patients (trastuzumab and a taxane); patients with symptomatic brain metastases excluded • mPFS 9.6 mo vs. 6.4 mo (HR 0.65, 95% CI 0.55 to 0.77); mOS 30.9 mo vs. 25.1 mo (HR 0.68, 95% CI 0.55 to 0.85) • Grade ≥3 AEs: 41% vs. 57%; thrombocytopenia and increased LFTs higher with TDM1, whereas diarrhea, N/V, and PPE syndrome higher with lapatinib + capecitabine
Third-Line and Beyond	
Trastuzumab + docetaxel or vinorelbine Andersson M, et al. (2011)	• N = 143 assigned to docetaxel or vinorelbine plus trastuzumab • No prior treatment for metastatic disease permitted; patients with brain metastases excluded • Similar mTTP (12.4 mo vs. 15.3 mo) and mOS (35.7 mo vs. 38.8 mo) • Vinorelbine more well tolerated than docetaxel

Trastuzumab + paclitaxel ± carboplatin Robert N, et al. (2006)	• N = 196 randomized to 6 cycles of trastuzumab with paclitaxel (TP) ± carboplatin (TPC), followed by trastuzumab monotherapy • No prior treatment for metastatic disease permitted; active brain metastases not responding to treatment excluded • Improved ORR (52% vs. 36%) and PFS (10.7 mo vs. 7.1 mo) with TPC vs. TP • Grade 4 neutropenia: 36% vs. 12%
Capecitabine + trastuzumab Bartsch R, et al. (2007)	• N = 40 • Heavily pretreated patients (prior anthracycline, taxane or vinorelbine, and trastuzumab-containing therapy required); patients with controlled brain metastases eligible • mTTP of 8 mo and mOS of 24 mo, with no difference for second-line and beyond second-line treatment • Grade ≥3 AEs: hand-foot syndrome (15%), diarrhea (5%)
Capecitabine + lapatinib Geyer CE, et al. (2006)	• N = 324 randomized to lapatinib + capecitabine vs. capecitabine monotherapy • Heavily pretreated patients (prior anthracycline, taxane, and trastuzumab); patients with controlled brain metastases eligible • mTTP of 8.4 mo vs. 4.4 mo • No increase in serious toxic effects or cardiac events • Option when oral regimen preferred
Trastuzumab + lapatinib Blackwell KL, et al. (2010)	• N = 296 randomized to lapatinib and trastuzumab vs. lapatinib monotherapy • Heavily pretreated patients (prior anthracycline, taxane, and trastuzumab); patients with brain metastases eligible • mPFS 12.0 weeks vs. 8.1 weeks (HR 0.75; 95% CI 0.57 to 0.93) ○ PFS not different in the brain metastasis subgroup, but limited by small sample size • Diarrhea more common in combination group
Neratinib + capecitabine Saura C, et al. (2020)	• N = 621 randomized to neratinib plus capecitabine vs. lapatinib plus capecitabine • Heavily pretreated patients (≥2 HER2-directed therapies); patients with controlled brain metastases eligible • mPFS 8.8 mo vs. 6.6 mo (HR 0.76; 95% CI 0.63 to 0.93); mOS not significantly different • Fewer interventions for CNS disease occurred in the neratinib group
Margetuximab + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) Rugo HS, et al. (2021)	• N = 536 randomized to margetuximab or trastuzumab plus chemotherapy • Heavily pretreated patients (≥2 HER2-directed therapies); prior brain metastases allowed if treated and stable • mPFS 5.8 mo vs. 4.9 mo (HR 0.76; 95% CI 0.59 to 0.98); mOS not significantly different • Safety was comparable

Formulary agents include capecitabine, docetaxel, gemcitabine, trastuzumab, and vinorelbine; nonformulary agents include eribulin and lapatinib; formulary status is to be determined for margetuximab, neratinib, and tucatinib.

Projected Place in Therapy

- Breast cancer is the second most common cancer among women in the United States. Approximately 15% of breast cancers are HER2-positive
- First-line treatment of HER2-positive breast cancer in the metastatic setting is well-established and consists of pertuzumab, trastuzumab, and a taxane
- Historically, trials have either excluded patients with brain metastases or required them to be controlled or previously treated. Recently, however, TUXEDO-1 (trastuzumab deruxtecan) and HER2CLIMB (tucatinib/trastuzumab/capecitabine) enrolled patients with active brain metastases not requiring immediate local intervention
- Standard of care second-line therapy was previously trastuzumab emtansine until the approval of trastuzumab deruxtecan, which is now generally preferred
- Choice of therapy for third-line and beyond depends largely on which regimen the individual patient received as second-line therapy, in addition to consideration of patient-specific comorbidities, functional status, and drug-specific toxicities
    - For patients who received trastuzumab emtansine as second-line therapy, trastuzumab deruxtecan is generally the preferred third-line therapy
    - For patients who received trastuzumab deruxtecan as second-line therapy, tucatinib in combination with trastuzumab and capecitabine may be preferred as the third-line option, especially in patients with active brain metastases based on the HER2CLIMB trial
- The HER2CLIMB trial evaluated tucatinib or placebo with trastuzumab and capecitabine in patients who had previously received pertuzumab, trastuzumab, and trastuzumab emtansine. Progression free survival and overall survival were significantly improved with the addition of tucatinib
- In the VA, the combination of tucatinib with trastuzumab and capecitabine should be reserved for patients who have received two or more previous lines of therapy for HER2-positive metastatic breast cancer

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