tucatinib (Tukysa™)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO194

Description

Tucatinib (Tukysa) is an orally administered tyrosine kinase inhibitor that targets the growth of HER2-expressing tumors.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
tucatinib (Tukysa)	HER2- positive metastatic breast cancer	50 mg tablets	60 tablets/30 days
	HER2-positive RAS wild-type unresectable or metastatic colorectal cancer	150 mg tablets	120 tablets/30 days

Initial Evaluation

I. **Tucatinib (Tukysa)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. The member has **not** previously progressed on or after treatment with another tyrosine kinase inhibitor (e.g., lapatinib [Tykerb], neratinib [Nerlynx]); **AND**
   D. A diagnosis of **advanced or metastatic breast cancer** when the following are met:
      1. Documentation is provided showing the disease is HER2-positive; **AND**
      2. Will be used in combination with trastuzumab and capecitabine; **AND**
      3. Will not be used with any other oncology therapy outside of trastuzumab and capecitabine; **AND**
      4. Member does **not** have brain metastases; **AND**
         i. Member has progressed on, has a contraindicated to, or did not tolerate treatment with trastuzumab, pertuzumab, and trastuzumab emtansine (TDM-1); **OR**
      5. Member has brain metastases; **AND**
         i. Member has received ≥1 prior anti-HER2-based regimens in the metastatic setting

I. Tucatinib (Tukysa) is considered investigational when used for all other conditions, including but not limited to:
   A. Metastatic colorectal cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has experienced response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
IV. Tucatinib (Tukysa) will be used in combination with trastuzumab and capecitabine; **AND**
V. Tucatinib (Tukysa) will not be used with any other oncology therapy outside of trastuzumab and capecitabine

Supporting Evidence

I. Tucatinib (Tukysa) was studied in a phase 2, double blind, placebo controlled, randomized trial (HER2CLIMB) in 612 patients with HER2-positive metastatic breast cancer with, or without, brain metastases who had been previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine (TDM-1). The trial evaluated treatment with tucatinib (Tukysa) in combination with trastuzumab and capecitabine versus placebo, trastuzumab, and capecitabine. Patients in the trial had a median of 4 previous lines of therapy and 48% of patients had brain metastases. Overall survival at 2 years was 44.9% with the tucatinib (Tukysa) combination and 26.6% with trastuzumab, capecitabine, and placebo combination (hazard ratio for death, 0.66; 95% CI, 0.50-0.88; P = 0.005). Median overall survival was 21.9 months (tucatinib (Tukysa) combination) and 17.4 months (placebo, trastuzumab, and capecitabine). Secondary outcome of progression free survival at 1 year in patients with brain metastases was 24.9% with the tucatinib (Tukysa) combination and 0% with trastuzumab, capecitabine, and placebo combination (hazard ratio, 0.48; 95% CI, 0.34-0.69; P < 0.001).
II. Patients in the HER2CLIMB trial were excluded if they were previously treated with neratinib, afatinib, or any HER2 tyrosine kinase inhibitor at any time previously. Those who were treated with lapatinib more than 12 months from the start of the study were allowed to enroll in the trial; however, this accounted for only 6% of patients in the HER2CLIMB trial. At this time, there is lack of scientific evaluation for safety and efficacy of tucatinib (Tukysa) following progression on or after another tyrosine kinase inhibitor.

III. Although patients in the trial were heavily pretreated having failed trastuzumab, pertuzumab, and trastuzumab emtansine (TDM-1), FDA approval was granted in adults with or without brain metastases who have received ≥1 prior anti-HER2-based regimens in the metastatic setting. Agents such as TDM-1 and other oral tyrosine kinase inhibitors (i.e., neratinib, lapatinib) also have FDA approval and overall survival data in the previously treated metastatic setting. No head to head trials are available comparing tucatinib (Tukysa) to other tyrosine kinase inhibitors in this space.

IV. Given the population included in the HER2CLIMB trial consisted of heavily pretreated patients, criteria for coverage is set to reflect this patient population. Patients with CNS metastases, however, require only ≥1 prior anti-HER2-based regimen given limited treatment options and lack of strong data with other therapies in this population.

Investigational or Not Medically Necessary Uses

I. Tucatinib (Tukysa) has not been sufficiently studied for safety or efficacy for the following indication(s):
   A. Metastatic colorectal cancer, RAS wild-type, HER2+
      i. HER2 is overexpressed in 3-5% of patients with mCRC and in 10% of patients with RAS wild type mCRC. Tucatinib (Tukysa) with trastuzumab is the first FDA-approved treatment, under accelerated approval, for HER2-positive RAS wild-type unresectable or metastatic colorectal cancer (mCRC) with progression following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.
      ii. Tucatinib was studied in a phase II, open-label, cross over multicenter trial. The trial was initially designed as a single arm study with 45 participants enrolled to receive tucatinib 300mg orally twice daily with trastuzumab (loading dose of trastuzumab 8mg/kg IV on day 1 of cycle 1, maintenance dose of trastuzumab 6mg/kg on day 1 of each subsequent 21 day cycle). The trial was then expanded globally to include patients who were randomly assigned to receive tucatinib plus trastuzumab (cohort B, N=41) or tucatinib monotherapy (cohort C, N=31). Cohort C was allowed to cross over from tucatinib monotherapy to tucatinib + trastuzumab combination therapy was allowed after 12 weeks if there was disease progression at any time. All participants had to have HER2-positive, RAS wildtype, unresectable or metastatic CRC and received prior treatment with fluoropyrimidines, oxaliplatin, irinotecan, and anti-vascular endothelial growth factor (VEGF) monoclonal antibody, and anti-PD-1 therapy. Participants were not allowed to have received prior anti-HER2 targeting therapy. Participants were treated until disease progression or unacceptable toxicity. The median age was 55

years, 14% of participants were >65 years, 67% white, 61% male, 70.2% of participants had lung metastases, 64.3% had lung metastases. Ninety-nine percent of participants received prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan, 83% and 52% received anti-VEGF antibodies and anti-EGFR antibodies.

iii. The primary outcome was overall response rate (ORR) with secondary endpoints of duration of response, progression-free survival, overall survival and adverse events. After a median follow-up of 20.7 months, efficacy was evaluated in 84 patients. Cohort A and B had a confirmed ORR per blinded independent central review (BICR) of 38.1%, median duration of response 12.4 months, median PFS of 8.2 months (95% CI, 4.2-10.3), and a median OS of 24.1 months (95% CI, 20.3-36.7). Results for the secondary end points showed a median PFS of 8.2 months (95% CI, 4.2-10.3), and a median OS of 24.1 months (95% CI, 20.3-36.7), in the combination cohorts.

iv. The most common grade ≥ 3 toxicity was hypertension (7%), ALT elevation (3%), AST elevation (2%), hypertransaminasemia (1%). There were no deaths related to toxicity.

v. As of March 2023, current subsequent therapy recommendations for HER2-amplified RAS wild-type mCRC after progression following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy are based on limited evidence. NCCN guidelines currently recommend trastuzumab with tucatinib (or pertuzumab (Perjeta) or lapatinib (Tykerb)) if the patient has not had prior HER2 treatment (category 2A recommendation). NCCN guideline directed therapies, trastuzumab with pertuzumab (Perjeta) or lapatinib (Tykerb), for HER2-positive RAS wild-type mCRC are not FDA approved and considered off-label use. After progression following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, NCCN guidelines recommend trifluridine and tipiracil (Lonsurf) and regorafenib (Stivarga) for mCRC irrespective of HER2 and KRAS mutations and encorafenib (Braftovi) for mCRC in combination with cetuximab (Erbitux) for mCRC with BRAF V600E mutation. Trifluridine and tipiracil (Lonsurf), regorafenib (Stivarga), and encorafenib (Braftovi) are FDA approved for treatment of mCRC.

vi. There is unknown clinical impact on the overall survival rate, health quality of life, or symptom improvement in participants treated with tucatinib and trastuzumab. Results from this phase II trial may be subjected to confounders and biases due to lack of a comparator and an open-label design. ORR is a surrogate marker and does not directly measure clinical outcomes. Change in ORR does not predict morbidity or mortality outcomes. Confirmatory trials are needed to establish safety and efficacy of tucatinib in mCRC, and therefore coverage for tucatinib (Tukysa) for mCRC is considered experimental and investigational.

vii. Despite the accelerated FDA-approval, continued approval of tucatinib (Tykusa) as a subsequent-line treatment of MCL, remains contingent upon verification of clinical benefit in confirmatory trials. There is an ongoing trial to evaluate tucatinib (Tukysa) in HER2-positive mCRC in the ongoing global, randomized Phase 3 clinical trial (MOUNTAINEER-03), comparing tucatinib (Tukysa) in combination with trastuzumab and mFOLFOX6 with standard of care. This trial is intended to serve as the confirmatory trial that is required as part of the accelerated approval pathway.

References

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
lapatinib (Tykerb)	Breast cancer
neratinib (Nerlynx)	Breast cancer, early stage, HER2-positive, following trastuzumab
	Breast cancer, advanced or metastatic HER2-positive
gonadotropin-releasing hormone (GnRH)	Advanced breast cancer in premenopausal women
regorafenib (Stivarga)	Colorectal cancer, metastatic, previously treated

encorafenib (Braftovi), binimetinib (Mektovi)	Colorectal cancer, metastatic, BRAF V600E mutation, combination therapy
trifluridine/tipiracil (Lonsurf)	Colorectal cancer, metastatic, previously treated

Policy Implementation/Update

Action and Summary of Changes	Date
Policy updated to include MOUNTAINEER trial results in E/I section for metastatic colorectal cancer. Updated policy formatting. Added related policies. Updated supporting evidence, references.	03/2023
Policy created	08/2020