PDL DRUG REVIEW

Proprietary Name: Tukysa®
Common Name: tucatinib
PDL Category: Antineoplastics

Comparable Products	Preferred Drug List Status
Nerlynx	Non-Recommended with Conditions
Tykerb	Non-Recommended with Conditions

Summary

Pharmacology/Usage: Tucatinib, the active ingredient of Tukysa®, is a tyrosine kinase inhibitor of HER2. In vitro, tucatinib inhibits phosphorylation of HER2 and HER3, resulting in inhibition of downstream MAPK and AKT signaling and cell proliferation, and demonstrated anti-tumor activity in HER2 expressing tumor cells. The combination of tucatinib and trastuzumab demonstrated increased anti-tumor activity in vitro and in vivo as compared to either drug alone.

Indication: In combination with trastuzumab and capecitabine for the 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.

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings in animals and its mechanism of action, Tukysa® can cause fetal harm when administered to a pregnant woman. There are no available human data on use in pregnant women to inform a drug-associated risk. Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Furthermore, verify the pregnancy status of females of reproductive potential prior to starting treatment with Tukysa®, and advise this population (as well as male patients with female partners of reproductive potential) to use effective contraception during treatment with Tukysa® and for at least 1 week after the last dose. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets: 50mg, 150mg. Swallow whole and do not chew, crush or split prior to swallowing.

Recommended Dosage: Take 300mg PO BID in combination with trastuzumab and capecitabine until disease progression or unacceptable toxicity. When given in combination with Tukysa®, the recommended dosage of capecitabine is 1000mg/m^2 PO BID within 30 minutes after a meal. Treatments can be taken at the same time.

Dose modifications may be required for adverse reactions, such as diarrhea, hepatotoxicity, or other adverse reactions. Refer to the prescribing information for additional information.

Dose adjustments are not required with mild or moderate hepatic impairment. Reduce the dosage to 200mg PO BID with severe hepatic impairment. Dose adjustments are not required with mild or moderate renal impairment. The use of Tukysa® in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment.

Drug Interactions: Avoid the concomitant use of Tukysa® with a strong CYP3A inducer or a moderate CYP2C8 inducer. Avoid the concomitant use of Tukysa® with a strong CYP2C8 inhibitor. If concomitant use with a strong CYP2C8 inhibitor cannot be avoided, reduce the recommended dosage to 100mg PO BID. After discontinuation of the strong CYP2C8 inhibitor for 3 elimination half-lives, resume the Tukysa® dose that was taken prior to starting the inhibitor. Increase monitoring for Tukysa® toxicity with moderate CYP2C8 inhibitors.

Avoid concomitant use of Tukysa® with CYP3A substrates, where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage in accordance with approved product labeling.

Consider reducing the dosage of P-gp substrates, where minimal concentration changes may lead to serious or life-threatening toxicities.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Tukysa® plus trastuzumab plus capecitabine) minus reported % incidence for trastuzumab plus capecitabine plus placebo for all grades. Please note that an incidence of 0% means the incidence was the same as or less than comparator.* The most frequently reported adverse events included diarrhea (28%), nausea (14%), vomiting (11%), stomatitis (11%), palmar-plantar erythrodysesthesia syndrome (10%), rash (5%), hepatotoxicity (18%), decreased appetite (5%), anemia (8%), arthralgia (10.4%), creatinine increased (12.5%), weight decreased (7%), peripheral neuropathy (6%), and epistaxis (7%).

Laboratory abnormalities included decreased hemoglobin (8%), decreased phosphate (12%), increased bilirubin (17%), increased ALT (19%), increased AST (18%), decreased magnesium (15%), decreased potassium (5%), increased creatinine (27%), decreased sodium (5%), and increased alkaline phosphatase (9%).

Tukysa® can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. The median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to dose reductions of Tukysa® in 6% of patients and discontinuation of Tukysa® in 1% of patients. If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of diarrhea, interrupt dose, then dose reduce or permanently discontinue Tukysa®.

Tukysa® can cause severe hepatotoxicity, and it led to dose reduction of Tukysa® in 8% of patients and discontinuation of Tukysa® in 1.5% of patients. Monitor ALT, AST, and bilirubin prior to starting Tukysa®, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue Tukysa®.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Seattle Genetics, Inc

Analysis: The efficacy of Tukysa® in combination with trastuzumab and capecitabine was assessed in a randomized, double-blind, placebo-controlled trial that included patients required to have HER2-positive, unresectable locally advanced or metastatic breast cancer, with or without brain metastases (N=612). In addition, patients were required to have prior treatment with trastuzumab, pertuzumab, and adotrastuzumab emtansine separately or in combination, in the neoadjuvant, adjuvant, or metastatic setting. Patients were randomized to receive Tukysa® 300mg or placebo until disease progression or unacceptable toxicity. Tumor assessments, including brain-MRI in patients with presence or history of brain metastases at baseline, occurred every 6 weeks for the first 24 weeks and every 9 weeks thereafter. The median age of included patients was 54 years, while 19% were age 65 or older. In addition, most were white (73%), female (99%), had an ECOG performance status of 1 (51%), had estrogen and/or progesterone receptor-positive disease (60%), and 48% had a presence or history of brain metastases. Patients had received a median of 4 prior lines of systemic therapy and a median of 3 prior lines of systemic therapy in the metastatic setting.

The main efficacy outcome measure was progression-free survival (PFS) in the first 480 randomized patients assessed by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Additional efficacy outcome measures were assessed in all randomized patients and included overall survival (OS), PFS among patients with a history or presence of brain metastases (PFS BrainMets) and confirmed objective response rate (ORR). Results can be seen in the table below, which was adapted from the prescribing information.

	Tukysa® + trastuzumab + capecitabine	Placebo + trastuzumab + capecitabine
Progression-Free Survival (PFS)	N=320	N=160
Number of events (%)	178 (56%)	97 (61%)
Median, months	7.8	5.6
Hazard Ratio (HR); p-value	0.54, p<0.00001	
Overall Survival	N=410	N=202
Number of deaths (%)	130 (32%)	85 (42%)
Median, months	21.9	17.4
HR; p-value	0.66; p=0.00480	
PFS BrainMets	N=198	N=93
Number of events (%)	106 (53.5%)	51 (54.8%)
Median, months	7.6	5.4
HR; p-value	0.48; p<0.00001	
Confirmed ORR for patients with measurable disease	N=340	N=171
ORR	40.6	22.8
Complete Response (%)	3 (0.9%)	2 (1.2%)
Partial Response (%)	135 (39.7%)	37 (21.6%)
p-value	p=0.00008	
Duration of Response (DOR)		
Median, months	8.3	6.3

Place in Therapy: Tukysa® is indicated in combination with trastuzumab and capecitabine for the 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. In a placebo-controlled trial, Tukysa® significantly prolonged progression free survival and overall survival as compared with placebo.

It is recommended that Tukysa® should be non-recommended with conditions in order to confirm the appropriate diagnosis and clinical parameters for use, as well as prior trials.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Tukysa [package insert]. Bothell, WA: Seattle Genetics, Inc; 2020.