Clinical Policy: Lapatinib (Tykerb)

Reference Number: PA.CP.PHAR.79
Effective Date: 01/18
Last Review Date: 11/16 Revision Log

Description
The intent of the criteria is to ensure that patients follow selection elements established by Pennsylvania Health and Wellness ® clinical policy for lapatinib (Tykerb®) tablets for oral use.

Policy/Criteria
It is the policy of Pennsylvania Health and Wellness that Tykerb is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Breast Cancer (must meet all):

1. Tykerb will be used in one of the following ways (a or b):
   a. FDA approved use (i or ii):
      i. Diagnosis of advanced (stage III) or metastatic (stage IV) breast cancer and (a-d):
         a) Tykerb is prescribed in combination with capecitabine;
         b) Disease is human epidermal receptor type 2 (HER2)-positive;
         c) Member previously received trastuzumab, an anthracycline and a taxane (Appendix B) AND disease progressed on trastuzumab;
         d) Prescribed daily dose of Tykerb does not exceed 1,250 mg, or if Tykerb is administered with a strong CYP3A4 inducer (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's wort), prescribed daily dose of Tykerb does not exceed 4,500 mg;
      ii. Diagnosis of metastatic (stage IV) breast cancer and (a-d):
         a) Tykerb is prescribed in combination with letrozole;
         b) Disease is HER2-positive AND hormone receptor-positive*;
         c) Member is postmenopausal;
         d) Prescribed daily dose of Tykerb does not exceed 1,500 mg, or if Tykerb is administered with a strong CYP3A4 inducer (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's wort), prescribed daily dose of Tykerb does not exceed 5,500 mg;
   b. Off-label NCCN recommended use (i or ii):
      i. Diagnosis of recurrent or metastatic (stage IV) breast cancer and (a-d);
         a) Tykerb is prescribed in combination with trastuzumab or capecitabine;
         b) Disease is characterized by any of the following:
            1) Presence of symptomatic visceral disease or visceral crisis;
            2) Hormone receptor-negative*;
            3) Hormone receptor-positive* AND refractory to endocrine therapy (Appendix B);
         c) Disease progressed on trastuzumab;
         d) Prescribed daily dose of Tykerb does not exceed the following:
            1) 1,250 mg if prescribed in combination with capecitabine;

2) 1,000 mg if prescribed in combination with trastuzumab;

ii. Diagnosis of recurrent or metastatic (stage IV) breast cancer and (a-d);
   a) Tykerb is prescribed in combination with an aromatase inhibitor (Appendix B);
   b) Disease is estrogen receptor-positive AND HER2-positive;
   c) Member is postmenopausal or male;
   d) If male, an agent that suppresses testicular steroidogenesis is also prescribed;

2. Baseline left ventricular ejection fraction (LVEF) is within the institution's normal limits;
3. Member has no known history of severe hypersensitivity (e.g., anaphylaxis) to Tykerb or any of its components.

**Hormone receptor-positive can indicate either estrogen receptor-positive (ER-positive) or progesterone receptor-positive (PR-positive)*

Approval duration: 3 months

B. Other diagnoses/indications: Refer to PA.CP.PHAR.57 - Global Biopharm Policy.
1. The following NCCN recommended uses for Tykerb, meeting NCCN categories 1, 2a or 2b, are approved per the PA.CP.PHAR.57 Global Biopharm Policy:
   a. Bone cancer - chordoma; Single-agent therapy for the treatment of epidermal growth factor receptor (EGFR)-positive recurrent disease;
   b. Central nervous system cancers: In combination with capecitabine for brain metastases if active against the primary tumor (breast) for recurrent disease;

II. Continued Approval

A. HER2-Positive Metastatic Breast Cancer (must meet all)**:**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Member has none of the following reasons to discontinue:
   a. Disease progression or unacceptable toxicity;
   b. Known severe hypersensitivity (e.g., anaphylaxis) to Tykerb or any of its components;
   c. Unresolved decrease in LVEF that is ≥ Grade 2 per NCI CTCAE or that drops below the institution's lower limit of normal;
   d. Severe changes in liver function (i.e., alanine aminotransferase/aspartate aminotransferase > 3 time the upper limit of normal [ULN] and total bilirubin > 2 ULN);
   e. Pulmonary symptoms indicative of interstitial lung disease/pneumonitis which are ≥ Grade 3 per NCI CTCAE (i.e., severe/disabling symptoms; may need oxygen);
   f. Life-threatening cutaneous reactions such as erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis (e.g., progressive skin rash often with blisters or mucosal lesions);

g. Diarrhea which is NCI CTCAE Grade 4 (life-threatening).

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies; or
2. Refer to PA.CP.PHAR.57 - Global Biopharm Policy.

Background
Description/Mechanism of Action:
Lapatinib is an inhibitor of the intracellular tyrosine kinase domains of both EGFR (ErbB1) and HER (ErbB2). Lapatinib inhibits ErbB-driven tumor cell growth in vitro and in various animal models.
- An *in vitro* additive effect was demonstrated when lapatinib and 5-FU (the active metabolite of capecitabine) were used in combination.
- Lapatinib also retained significant *in vitro* growth inhibitory activity against breast cancer cell lines selected for long-term growth in trastuzumab-containing medium.

Hormone receptor-positive (estrogen receptor-positive or progesterone receptor-positive) that coexpress HER2 tend to be resistant to established endocrine therapies. Similarly, hormone receptor-positive breast cancer cells that initially lack EGFR or HER2 upregulate these receptor proteins as the tumor becomes resistant to endocrine therapy.

Formulations:
Tykerb is available in 250 mg tablets for oral administration.

FDA Approved Indications:
Tykerb is a kinase inhibitor/oral tablet formulation indicated in combination with:
- Capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.
  - Limitation of use: Patients should have disease progression on trastuzumab prior to initiation of treatment with Tykerb in combination with capecitabine.
- Letrozole for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer that overexpresses the HER2 receptor for whom hormonal therapy is indicated.

Appendices
Appendix A: Abbreviation Key
5-FU: fluorouracil
EGFR: epidermal growth factor receptor
ER: estrogen receptor
HER2: human epidermal receptor type 2
LVEF: Left ventricular ejection fraction

NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events
PR: progesterone receptor

Appendix B: Examples of Breast Cancer Antineoplastic Agents by Drug Class

Drug Class	Drug Class Subcategory	Drug: Generic (Brand)
Anthracyclines	Topoisomerase II inhibitors	Doxorubicin (Adriamycin) Epirubicin (Ellence)
Antimetabolites	Pyrimidine analogs	Capecitabine (Xeloda)
Antimicrotubulars	Taxane derivatives	Paclitaxel Docetaxel (Docefrez, Taxotere)
Endocrine agents	Nonsteroidal AIs	Anastrozole (Arimidex) Letrozole (Femara)
	Steroidal AIs	Exemestane (Aromasin)
	Serum ER modulators	Tamoxifen (Soltamox) Toremifene (Fareston)
	ER down-regulators	Fulvestrant (Fodex)
	Progestins	Megestrol acetate (Megace)
	Androgens	Fluoxymesterone (Androxy)
	High-dose estrogens	Ethinyl estradiol
Monoclonal antibodies	Anti-HER2s	Trastuzumab (Herceptin)
Tyrosine kinase inhibitors	Anti-HER2s; EGFR inhibitors	Lapatinib (Tykerb)

Abbreviations: aromatase inhibitor (AI); epidermal growth factor receptor (EGFR); estrogen receptor (ER); human epidermal receptor type 2 (HER2)

Reviews, Revisions, and Approvals	Date	Approval Date

References

1. Tykerb Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; June 2015. Available at https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/tykerb.pdf. Accessed November 11, 2016.
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3. Breast cancer (Version 2.2016). In: National Comprehensive Cancer Network Guidelines. Available at www.NCCN.org. Accessed November 14, 2016.
4. National Institutes of Health/National Cancer Institute, U.S. Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE). Version 4.0. May 28, 2009. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed November 14, 2016.