PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Erlotinib Prior Authorization Policy
- Tarceva® (erlotinib tablets – Genentech, generic)

REVIEW DATE: 01/25/2023

INSTRUCTIONS FOR USE

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CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Erlotinib, a tyrosine kinase inhibitor, is indicated for the following uses:[1]

- **Non-Small Cell Lung Cancer (NSCLC)**, treatment of patients whose tumors have epidermal growth factor receptor **(*EGFR*) exon 19 deletions** or **exon 21 (L858R) substitution mutations** as detected by an FDA-approved test, receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen. Limitations of use: The safety and efficacy of erlotinib have not been established in patients with NSCLC whose tumors have other *EGFR* mutations. Erlotinib is not recommended for use in combination with platinum-based chemotherapy.
- **Pancreatic Cancer**, in combination with gemcitabine as first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer.

Guidelines

Erlotinib has been addressed in National Comprehensive Cancer Network (NCCN) guidelines.[2-7]

- **Bone Cancer:** Guidelines (version 2.2023 – September 28, 2022) note erlotinib as a treatment option for patients with chordoma (useful in certain

circumstances).[3] The efficacy of erlotinib was demonstrated in patients with advanced chordoma resistant to imatinib.

- **Non-Small Cell Lung Cancer:** Guidelines (version 1.2023 – December 22, 2022) recommend erlotinib and other *EGFR* tyrosine kinase inhibitors as first-line treatment for patients with advanced or metastatic NSCLC with *EGFR* exon 19 deletions, exon 21 (L858R) substitution mutations, L861Q, G719X, and S768I.
- **Pancreatic Adenocarcinoma:** Guidelines (version 2.2022 – December 6, 2022) recommend the combination of gemcitabine and erlotinib as first-line treatment option for patients with locally advanced or metastatic disease (other recommended regimens).[5] In addition, the combination is recommended as a subsequent therapy option for locally advanced, metastatic, or recurrent disease (other recommended regimens).
- **Kidney Cancer:** Guidelines (version 4.2023 – January 18, 2023) note erlotinib as a treatment option for patients with recurrent or advanced renal cell carcinoma of non-clear cell histology (useful in certain circumstances).[6] The combination of bevacizumab with erlotinib is a treatment option for select patients with non-clear cell and papillary cell histology, including hereditary leiomyomatosis and renal cell carcinoma (useful in certain circumstances).
- **Vulvar Cancer:** Guidelines (version 1.2023 – December 22, 2022) recommend erlotinib as a treatment option for patients with advanced, recurrent, or metastatic vulvar cancer (other recommended regimens).[7]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of erlotinib. All approvals are provided for the duration noted below.

- **Tarceva® (erlotinib tablets (Genentech, generic)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indications

1. **Non-Small Cell Lung Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has advanced or metastatic disease; AND
   - **C)** Patient has sensitizing *EGFR* mutation-positive non-small cell lung cancer as detected by an approved test.
     Note: Examples of sensitizing *EGFR* mutation-positive non-small cell lung cancer include the following: exon 19 deletions, exon 21 (L858R) substitution mutations, L861Q, G719X, and S768I.

2. **Pancreatic Cancer.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND

B) Patient has locally advanced, metastatic, or recurrent disease; AND
C) The medication is used in combination with gemcitabine.

Other Uses with Supportive Evidence

3. Bone Cancer. Approve for 1 year if the patient meets the following criteria (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patient has chordoma; AND
C) Patient has tried at least one previous therapy.

4. Renal Cell Carcinoma. Approve for 1 year if the patient meets the following criteria (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient meets one of the following criteria (i or ii):
i. Patient has recurrent or advanced renal cell carcinoma of non-clear cell histology; OR
ii. Patient meets both of the following criteria (a and b):
a) Patient has hereditary leiomyomatosis and renal cell carcinoma; AND
b) The medication is used in combination with bevacizumab.

5. Vulvar Cancer. Approve for 1 year if the patient meets the following criteria (A and B):
A) Patient is ≥ 18 years of age; AND
B) Patient has advanced, recurrent, or metastatic disease.

CONDITIONS NOT COVERED

- **Tarceva® (erlotinib tablets (Genentech, generic)**

is(are) considered experimental, investigational or unproven for ANY other use(s) including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. Breast Cancer. One Phase II, non-randomized, open-label, bi-institutional trial did not demonstrate a beneficial effect of erlotinib plus bevacizumab in patients with metastatic breast cancer with stage IV disease that was stable or had progressed after treatment with one or two chemotherapy regimens. If the patient's tumor was human epidermal growth factor receptor-2 (HER-2) positive, prior therapy with trastuzumab was required (n = 38).[8] As single-agent therapy, erlotinib had minimal activity in unselected, previously treated women with locally advanced or metastatic breast cancer in one multicenter, Phase II study (n = 69).[9] Metronomic (frequent low-dose) capecitabine tablets and cyclophosphamide plus bevacizumab and erlotinib was effective in patients with untreated advanced metastatic HER-2 negative, estrogen receptor-negative, and progesterone receptor-poor advanced breast cancer (n = 26).[10] Among 24 patients assessable for response, 4% of patients had a complete response (CR) [n = 1], 58% of patients had partial response (PR) [n = 14], 21% of patients had stable disease

(SD) > 9 weeks duration (n = 5) and 4% of patients (n = 1) had early progression of disease. The overall clinical benefit (CR + PR + SD > 24 weeks) was 75% (95% confidence interval [CI]: 53, 90). Median time to progression was 43 weeks (95% CI: 21, 69). Overall survival was 108 months (95% CI: 70, 110). NCCN Breast Cancer guidelines (version 4.2022 – June 21, 2022) do not mention erlotinib.[11]

2. **Colon Cancer, Advanced**. NCCN Colon Cancer guidelines (version 2.2022 – October 27, 2022) note several drug combinations, including bevacizumab plus erlotinib, produced negative results in phase III trials involving patients with advanced colorectal cancer and these regimens are not recommended.[12] In addition, the panel recommends against the use of several medications, including erlotinib, for the treatment of patients who progressed after treatment with standard therapies.

3. **Glioblastoma Multiforme (GBM).** In one Phase II study, concurrent radiation therapy (RT) and temozolomide in combination with erlotinib in patients newly diagnosed with glioblastoma (n = 27) was not efficacious.[13] In two Phase II studies, erlotinib plus temozolomide given during and after RT produced favorable median survival, and progression free survival (PFS), as well as 12- or 14-month survival rates in patients with newly diagnosed GBM or gliosarcoma.[14,15] In patients with newly diagnosed (untreated; could have had resection) GBM or gliosarcoma who received erlotinib plus temozolomide during and after radiation, median survival was longer with erlotinib plus temozolomide vs. historical controls (19.3 months vs. 14.1 months, respectively; hazard ratio for survival 0.64; 95% confidence interval [CI]: 0.45, 0.91; P = 0.01) in one open-label, single-center, Phase II trial (n = 65).[14] The historical controls were comparable in patients from two prospective, Phase II trials (n = 128); the first trial included the use of Thalomid® (thalidomide capsules) in combination with temozolomide during and after radiotherapy; the second included the use of *cis*-retinoic acid with temozolomide during and after radiotherapy. In one open-label, Phase I/II trial, treatment with erlotinib plus temozolomide during and after RT resulted in favorable survival rate (61% of patients were alive at 1 year) and median PFS (7.2 months) in patients with newly diagnosed GBM (following resection); however, there was no significant difference in overall survival with the addition of erlotinib compared with the temozolomide/RT arm of a historical control trial (15.3 months vs. 15 months, respectively).[24] Erlotinib has failed to demonstrate benefit in recurrent glioblastomas.[16-19] In a recent study involving patients with recurrent gliobastoma, the combination regimen of sorafenib and erlotinib failed to meet the predetermined efficacy endpoint and the study was terminated.[20] NCCN Central Nervous System guidelines (version 2.2022 – September 29, 2022) do not mention erlotinib as a treatment option for patients with glioblastoma.[21]

4. **Head and Neck Cancer, Squamous Cell, Recurrent and/or Metastatic.** Two Phase II studies assessed the use of erlotinib and bevacizumab in different settings and showed promising results.[22,23] One multicenter, Phase II trial assessed the addition of bevacizumab and erlotinib to chemoradiation as first-line treatment for previously untreated patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) [n = 60].[22] After a median follow-up of

32 months the estimated 3-year progression free survival (PFS) and overall survival rates were 71% and 82%, respectively. After induction therapy, 65% of patients had major responses; after completion of therapy, 95% of patients had either partial or complete radiographic responses. One multi-institutional Phase I/II study enrolled patients with recurrent or metastatic SCCHN (previously treated with ≤ 1 prior regimen for recurrent disease) to receive erlotinib and bevacizumab (n = 56).[23] The median overall survival and PFS durations were 7.1 months (95% confidence interval [CI]: 5.7, 9.0) and 4.1 months (95% CI: 2.8, 4.4), respectively. Treatment with erlotinib monotherapy produced few partial responses in unselected (*EGFR* status not known at baseline) patients with locally recurrent and/or metastatic SCCHN in one open-label, Phase II clinical trial (n = 115); 38.3% of patients achieved stable disease for a median of 16.1 weeks.[24] In one Phase II study, 204 patients with locally advanced SCCHN were randomized to receive cisplatin in combination with radiation therapy (RT) with or without erlotinib.[25] Complete response rates evaluated by central review were reported in 40% of patients (n = 42/105) on cisplatin/RT vs. 52% of patients (n = 51/99) on cisplatin/RT/erlotinib (P = 0.08). At a median follow-up of 26 months and 54 progression events, there was no difference in PFS between the two treatment arms (hazard ratio 0.0; P = 0.71). In a Phase II study, patients with recurrent SCCHN were treated with erlotinib for 12 months (n = 31). The overall survival was 61% at 1 year and 56% at 2 years.[26] Disease-free survival was 54% at 1 year and 45% at 2 years. The mean time to recurrence (n = 16) was 8.7 months. Only 8 patients completed the full 12-month course of erlotinib; the median duration of erlotinib therapy was 5 months. NCCN Head and Neck Cancer guidelines (version 1.2023 – December 20, 2022) do not mention erlotinb.[27]

5. **Hepatocellular Carcinoma, Advanced**. NCCN Hepatobiliary Cancers guidelines (version 5.2022 – January 13, 2023) note the combination regimen of sorafenib and erlotinib did not significantly improve survival compared with sorafenib monotherapy in the treatment of patients with advanced hepatocellular carcinoma (sorafenib is one of several agents recommended for first-line treatment).[28] In addition, the disease control rate was significantly lower for patients who received the combination vs. those who received sorafenib monotherapy; treatment duration was also shorter for those received sorafenib and erlotinib. .

6. **Renal Cell Carcinoma, Advanced – Clear Cell Histology.** NCCN Kidney Cancer guidelines (version 4.2023 – January 18, 2023) do not note erlotinib as a treatment option for advanced clear-cell renal cell carcinoma.[6]

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HISTORY

Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Non-Small Cell Lung Cancer:** A requirement was added that patient is ≥ 18 years of age. The criterion "metastatic disease" was revised to include "advanced or metastatic disease". Regarding the *EGFR* mutations, the criterion was revised to "Patient has sensitizing *EGFR* mutation-positive non-small cell lung disease" and examples of the *EGFR* mutations are listed in a Note. Previously, only exon 19 deletions and exon 21 (L858R) substitution mutations were listed. **Pancreatic Cancer:** Requirements were added that patient is ≥ 18 years of age and that the patient has locally advanced, metastatic, or recurrent disease. **Bone Cancer:** A requirement was added that patient is ≥ 18 years of age. **Renal Cell Carcinoma:** A requirement was added that patient is ≥ 18 years of age. The criterion that patient has relapsed or Stage IV non-clear cell histology renal cell carcinoma was revised to read: "Patient has recurrent or advanced renal cell carcinoma of non-clear cell histology". A new criterion was added for patients with hereditary leiomyomatosis and renal cell carcinoma – erlotinib must be used with bevacizumab for this condition. **Vulvar Cancer:** This was added as a new condition of approval. **Conditions Not Covered :** **Biliary Cancer:** Removed from this section but was not added to the approvable section due to insufficient evidence of efficacy. A new systematic review and network meta-analysis noted that compared with best supportive care, gemcitabine + oxaliplatin + erlotinib can improve progression-free survival in patients with advanced biliary tract carcinoma. NCCN guidelines do not address use of erlotinib in biliary cancer. **Occult primary/Cancer of Unknown Primary Site:** Removed from this section but was not added to the approvable section due to insufficient evidence of efficacy. The combination of bevacizumab and erlotinib resulted in longer median survival compared with historically-reported survival time with second-line chemotherapy in patients with carcinoma of unknown primary site.	01/19/2022
Selected Revision	For all approval conditions, the approval duration was changed from 3 years to 1 year.	06/22/2022
Annual Revision	No criteria changes.	01/25/2023