HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TARCEVA® safely and effectively. See full prescribing information for TARCEVA.

TARCEVA (erlotinib) tablets, for oral use
Initial U.S. Approval: 2004

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.1)	06/2016
Dosage and Administration, Dose Modifications (2.4)	05/2016

----------INDICATIONS AND USAGE----------

TARCEVA is a kinase inhibitor indicated for:

- First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. (1.1)
- Maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. (1.1)
- Treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. (1.1)
- First-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine. (1.2)

Limitations of Use:

- TARCEVA is not recommended for use in combination with platinum-based chemotherapy.
- Safety and efficacy of TARCEVA have not been evaluated as first-line treatment in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution.

----------DOSAGE AND ADMINISTRATION----------

- NSCLC: 150 mg orally, on an empty stomach, once daily. (2.2)
- Pancreatic cancer: 100 mg orally, on an empty stomach, once daily. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 25 mg, 100 mg, and 150 mg. (3)

----------CONTRAINDICATIONS----------

- None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Interstitial Lung Disease (ILD): Occurs in 1.1% of patients. Withhold TARCEVA for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever. Discontinue TARCEVA if ILD is diagnosed. (5.1)
- Renal Failure: Monitor renal function and electrolytes, particularly in patients at risk of dehydration. Withhold TARCEVA for severe renal toxicity. (5.2)
- Hepatotoxicity with or without hepatic impairment including hepatic failure and hepatorenal syndrome: Monitor periodic liver testing. Withhold or discontinue TARCEVA for severe or worsening liver tests. (5.3)
- Gastrointestinal perforations: Discontinue TARCEVA. (5.4)
- Bullous and exfoliative skin disorders: Discontinue TARCEVA. (5.5)
- Myocardial infarction (MI)/ischemia: The risk of MI is increased in patients with pancreatic cancer. (5.6)
- Cerebrovascular accident (CVA): The risk of CVA is increased in patients with pancreatic cancer. (5.7)
- Microangiopathic hemolytic anemia (MAHA): The risk of MAHA is increased in patients with pancreatic cancer. (5.8)
- Ocular disorders: Discontinue TARCEVA for corneal perforation, ulceration or persistent severe keratitis. (5.9)
- Hemorrhage in patients taking warfarin: Regularly monitor INR in patients taking warfarin or other coumarin-derivative anticoagulants. (5.10)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to the fetus and to use highly effective contraception. (5.11, 8.6)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (≥ 20%) with TARCEVA from a pooled analysis of Studies 1-4 were rash, diarrhea, anorexia, fatigue, dyspnea, cough, nausea, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact OSI Pharmaceuticals, LLC, at 1-800-572-1932 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- CYP3A4 inhibitors or a combined CYP3A4 and CYP1A2 inhibitor increase erlotinib plasma concentrations. Avoid concomitant use. If not possible, reduce TARCEVA dose (2.4, 7)
- CYP3A4 inducers decrease erlotinib plasma concentrations. Avoid concomitant use. If not possible, increase TARCEVA dose (2.4, 7)
- Cigarette smoking and CYP1A2 inducers decrease erlotinib plasma concentrations. Avoid concomitant use. If not possible, increase TARCEVA dose (2.4, 7).
- Drugs that increase gastric pH decrease erlotinib plasma concentrations. For proton pump inhibitors avoid concomitant use if possible. For H-2 receptor antagonists, take TARCEVA 10 hours after H-2 receptor antagonist dosing. For use with antacids, separate dosing by several hours (2.4, 7)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing Mothers: Discontinue drug or nursing. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 09/2016

FULL PRESCRIBING INFORMATION: CONTENTS *

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Non-Small Cell Lung Cancer (NSCLC)

TARCEVA® is indicated for:

- The first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test *[see Clinical Studies (14.1)]*.
- The maintenance treatment of patients with locally advanced or metastatic non-small cell lung cancer whose disease has not progressed after four cycles of platinum-based first-line chemotherapy *[see Clinical Studies (14.2)]*.
- The treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen *[see Clinical Studies (14.3)]*.

Limitations of use:

- TARCEVA is not recommended for use in combination with platinum-based chemotherapy *[see Clinical Studies (14.4)]*.
- Safety and efficacy of TARCEVA have not been evaluated as first-line treatment in patients with metastatic NSCLC whose tumors have EGFR mutations other than exon 19 deletions or exon 21 (L858R) substitution *[see Clinical Studies (14.1)]*.

1.2 Pancreatic Cancer

TARCEVA in combination with gemcitabine is indicated for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer *[see Clinical Studies (14.5)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the first-line treatment of metastatic NSCLC with TARCEVA based on the presence of EGFR exon 19 deletions or exon 21 (L858R) substitution mutations in tumor or plasma specimens *[See Clinical Studies (14.1)]*. If these mutations are not detected in a plasma specimen, test tumor tissue if available. Information on FDA-approved tests for the detection of EGFR mutations in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dose – NSCLC

The recommended daily dose of TARCEVA for NSCLC is 150 mg taken on an empty stomach, i.e., at least one hour before or two hours after the ingestion of food. Treatment should continue until disease progression or unacceptable toxicity occurs.

2.3 Recommended Dose – Pancreatic Cancer

The recommended daily dose of TARCEVA for pancreatic cancer is 100 mg taken once daily in combination with gemcitabine. Take TARCEVA on an empty stomach, i.e., at least one hour before or two hours after the ingestion of food. Treatment should continue until disease progression or unacceptable toxicity occurs *[see Clinical Studies (14.5)]*.

2.4 Dose Modifications

Discontinue TARCEVA for:

- Interstitial Lung Disease (ILD) *[see Warnings and Precautions (5.1)]*.
- Severe hepatic toxicity that does not improve significantly or resolve within three weeks *[see Warnings and Precautions (5.3)]*.
- Gastrointestinal perforation *[see Warnings and Precautions (5.4)]*.
- Severe bullous, blistering or exfoliating skin conditions *[see Warnings and Precautions (5.5)]*.
- Corneal perforation or severe ulceration *[see Warnings and Precautions (5.9)]*.

Withhold TARCEVA:

- During diagnostic evaluation for possible ILD.
- For severe (CTCAE grade 3 to 4) renal toxicity, and consider discontinuation of TARCEVA *[see Warnings and Precautions (5.2)]*.
- In patients without pre-existing hepatic impairment for total bilirubin levels greater than 3 times the upper limit of normal or transaminases greater than 5 times the upper limit of normal, and consider discontinuation of TARCEVA *[see Warnings and Precautions (5.3)]*.
- In patients with pre-existing hepatic impairment or biliary obstruction for doubling of bilirubin or tripling of transaminases values over baseline and consider discontinuation of TARCEVA *[see Warnings and Precautions (5.3)]*.
- For persistent severe diarrhea not responsive to medical management (e.g., loperamide).
- For severe rash not responsive to medical management.
- For keratitis of (NCI-CTC version 4.0) grade 3-4 or for grade 2 lasting more than 2 weeks *[see Warnings and Precautions (5.9)]*.
- For acute/worsening ocular disorders such as eye pain, and consider discontinuation of TARCEVA *[see Warnings and Precautions (5.9)]*.

Reduce TARCEVA by 50 mg decrements:

- If severe reactions occur with concomitant use of strong CYP3A4 inhibitors or with a combined CYP3A4 and CYP1A2 inhibitor. Avoid concomitant use if possible *[see Drug Interactions (7)]*.
- When restarting therapy following withholding treatment for a dose-limiting toxicity that has resolved to baseline or grade ≤ 1.

Increase TARCEVA by 50 mg increments as tolerated for:

- Concomitant use with CYP3A4 inducers. Increase doses by 50 mg increments at 2-week intervals to a maximum of 450 mg. Avoid concomitant use, if possible *[see Drug Interactions (7)]*.
- Concurrent cigarette smoking or concomitant use of moderate CYP1A2 inducers. Increase by 50 mg increments at 2-week intervals to a maximum of 300 mg. Immediately reduce the dose of TARCEVA to the recommended dose (150 mg or 100 mg daily) upon cessation of smoking *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

Drugs that Increase Gastric pH

- Avoid concomitant use of TARCEVA with proton pump inhibitors if possible. Separation of doses may not eliminate the interaction since proton pump inhibitors affect the pH of the upper GI tract for an extended period.
- If treatment with an H-2 receptor antagonist such as ranitidine is required, TARCEVA must be taken 10 hours after the H-2 receptor antagonist dosing and at least 2 hours before the next dose of the H-2 receptor antagonist.
- Although the effect of antacids on erlotinib pharmacokinetics has not been evaluated, the antacid dose and the TARCEVA dose should be separated by several hours, if an antacid is necessary.

3 DOSAGE FORMS AND STRENGTHS

25 mg tablets
White film-coated tablets for daily oral administration. Round, biconvex face and straight sides, white film-coated, printed in orange with a "T" and "25" on one side and plain on the other side.

100 mg tablets
White film-coated tablets for daily oral administration. Round, biconvex face and straight sides, white film-coated, printed in gray with "T" and "100" on one side and plain on the other side.

150 mg tablets
White film-coated tablets for daily oral administration. Round, biconvex face and straight sides, white film-coated, printed in maroon with "T" and "150" on one side and plain on the other side.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease (ILD)

Cases of serious ILD, including fatal cases, can occur with TARCEVA treatment. The overall incidence of ILD in approximately 32,000 TARCEVA-treated patients in uncontrolled studies and studies with concurrent chemotherapy was approximately 1.1%. In patients with ILD, the onset of symptoms was between 5 days to more than 9 months (median 39 days) after initiating TARCEVA therapy.

Withhold TARCEVA for acute onset of new or progressive unexplained pulmonary symptoms such as dyspnea, cough, and fever pending diagnostic evaluation. If ILD is confirmed, permanently discontinue TARCEVA *[see Dosage and Administration (2.4)]*.

5.2 Renal Failure

Hepatorenal syndrome, severe acute renal failure including fatal cases, and renal insufficiency can occur with TARCEVA treatment. Renal failure may arise from exacerbation of underlying baseline hepatic impairment or severe dehydration. The pooled incidence of severe renal impairment in the 3 monotherapy lung cancer studies was 0.5% in the TARCEVA arms and 0.8% in the control arms. The incidence of renal impairment in the pancreatic cancer study was 1.4% in the TARCEVA plus gemcitabine arm and 0.4% in the control arm. Withhold TARCEVA in patients developing severe renal impairment until renal toxicity is resolved. Perform periodic monitoring of renal function and serum electrolytes during TARCEVA treatment *[see Adverse Reactions (6.1) and Dosage and Administration (2.4)]*.

5.3 Hepatotoxicity with or without Hepatic Impairment

Hepatic failure and hepatorenal syndrome, including fatal cases, can occur with TARCEVA treatment in patients with normal hepatic function; the risk of hepatic toxicity is increased in patients with baseline hepatic impairment. In clinical studies where patients with moderate to severe hepatic impairment were excluded, the pooled incidence of hepatic failure in the 3 monotherapy lung cancer studies was 0.4% in the TARCEVA arms and 0% in the control arms. The incidence of hepatic failure in the pancreatic cancer study was 0.4% in the TARCEVA plus gemcitabine arm and 0.4% in the control arm. In a pharmacokinetic study in 15 patients with moderate hepatic impairment (Child-Pugh B) associated with significant liver tumor burden, 10 of these 15 patients died within 30 days of the last TARCEVA dose. One patient died from hepatorenal syndrome, 1 patient died from rapidly progressing liver failure and the remaining 8 patients died from progressive disease. Six out of the 10 patients who died had baseline total bilirubin > 3 x ULN.

Perform periodic liver testing (transaminases, bilirubin, and alkaline phosphatase) during treatment with TARCEVA. Increased frequency of monitoring of liver function is required for patients with pre-existing hepatic impairment or biliary obstruction. Withhold TARCEVA in patients without pre-existing hepatic impairment for total bilirubin levels greater than 3 times the upper limit of normal or transaminases greater than 5 times the upper limit of normal. Withhold TARCEVA in patients with pre-existing hepatic impairment or biliary obstruction for doubling of bilirubin or tripling of transaminases values over baseline. Discontinue TARCEVA in patients whose abnormal liver tests meeting the above criteria do not improve significantly or resolve within three weeks *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

5.4 Gastrointestinal Perforation

Gastrointestinal perforation, including fatal cases, can occur with TARCEVA treatment. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, or taxane-based chemotherapy, or who have prior history of peptic ulceration or diverticular disease may be at increased risk of perforation *[see Adverse Reactions (6.1, 6.2)]*. The pooled incidence of gastrointestinal perforation in the 3 monotherapy lung cancer studies was 0.2% in the TARCEVA arms and 0.1% in the control arms. The incidence of gastrointestinal perforation in the pancreatic cancer study was 0.4% in the TARCEVA plus gemcitabine arm and 0% in the control arm. Permanently discontinue TARCEVA in patients who develop gastrointestinal perforation *[see Dosage and Administration (2.4)]*.

5.5 Bullous and Exfoliative Skin Disorders

Bullous, blistering and exfoliative skin conditions, including cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis, which in some cases were fatal, can occur with TARCEVA treatment *[see Adverse Reactions (6.1, 6.2)]*. The pooled incidence of bullous and exfoliative skin disorders in the 3 monotherapy lung cancer studies was 1.2% in the TARCEVA arms and 0% in the control arms. The incidence of bullous and exfoliative skin disorders in the pancreatic cancer study was 0.4% in the TARCEVA plus gemcitabine arm and 0% in the control arm. Discontinue TARCEVA treatment if the patient develops severe bullous, blistering or exfoliating conditions *[see Dosage and Administration (2.4)]*.

5.6 Myocardial Infarction/Ischemia

In the pancreatic carcinoma trial, six patients (incidence of 2.1%) in the TARCEVA/gemcitabine group developed myocardial infarction/ischemia. One of these patients died due to myocardial infarction. In comparison, 3 patients in the placebo/gemcitabine group developed myocardial infarction (incidence 1.1%), and one died due to myocardial infarction. The pooled incidence of myocardial infarction/ischemia in the 3 monotherapy lung cancer studies was 0.2% in the TARCEVA arms and 0.4% in the control arms.

5.7 Cerebrovascular Accident

In the pancreatic carcinoma trial, seven patients in the TARCEVA/gemcitabine group developed cerebrovascular accidents (incidence: 2.5%). One of these was hemorrhagic and was the only fatal event. In comparison, in the placebo/gemcitabine group there were no cerebrovascular accidents. The pooled incidence of cerebrovascular accident in the 3 monotherapy lung cancer studies was 0.6% in the TARCEVA arms and 0.9% in the control arms.

5.8 Microangiopathic Hemolytic Anemia with Thrombocytopenia

The pooled incidence of microangiopathic hemolytic anemia with thrombocytopenia in the 3 monotherapy lung cancer studies was 0% in the TARCEVA arms and 0.1% in the control arms. The incidence of microangiopathic hemolytic anemia with thrombocytopenia in the pancreatic cancer study was 1.4% in the TARCEVA plus gemcitabine arm and 0% in the control arm.

5.9 Ocular Disorders

Decreased tear production, abnormal eyelash growth, keratoconjunctivitis sicca or keratitis can occur with TARCEVA treatment and can lead to corneal perforation or ulceration *[see Adverse Reactions (6.1) and (6.2)]*. The pooled incidence of ocular disorders in the 3 monotherapy lung cancer studies was 17.8% in the TARCEVA arms and 4% in the control arms. The incidence of ocular disorders in the pancreatic cancer study was 12.8% in the TARCEVA plus gemcitabine arm and 11.4% in the control arm. Interrupt or discontinue TARCEVA therapy if patients present with acute or worsening ocular disorders such as eye pain *[see Dosage and Administration (2.4)]*.

5.10 Hemorrhage in Patients Taking Warfarin

Severe and fatal hemorrhage associated with International Normalized Ratio (INR) elevations can occur when TARCEVA and warfarin are administered concurrently. Regularly monitor prothrombin time and INR during TARCEVA treatment in patients taking warfarin or other coumarin-derivative anticoagulants *[see Adverse Reactions (6.1) and Drug Interactions (7)]*.

5.11 Embryo-Fetal Toxicity

Based on its mechanism of action, TARCEVA can cause fetal harm when administered to a pregnant woman. When given during organogenesis, erlotinib administration resulted in embryo-fetal lethality and abortion in rabbits at doses approximately 3 times the recommended human daily dose of 150 mg. If TARCEVA is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use highly effective contraception during therapy, and for at least 2 weeks after the last dose of TARCEVA. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking TARCEVA *[see Use in Specific Populations (8.1) and (8.6)]*.

6 ADVERSE REACTIONS

DOCKET ALARM

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Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

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Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

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Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.