

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

Indications and Usage, Non-Small Cell Lung Cancer (NSCLC) (1.1)	10/2016
Dosage and Administration (2.1)	06/2016
Dosage and Administration, Dose Modifications (2.4)	05/2016
Warnings and Precautions, Cerebrovascular Accident (5.6)	10/2016
Warnings and Precautions, Embryo-fetal Toxicity (5.10)	10/2016

INDICATIONS AND USAGE

TARCEVA is a kinase inhibitor indicated for:

- The 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 receiving first-line, maintenance, or second or greater line treatment after progression following 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:

- Safety and efficacy of TARCEVA have not been established in patients with NSCLC whose tumors have other EGFR mutations. (1.1)
- TARCEVA is not recommended for use in combination with platinum-based chemotherapy. (1.1)

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:** Occurs 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)
- **Cerebrovascular accident (CVA):** The risk of CVA is increased in patients with pancreatic cancer. (5.6)
- **Microangiopathic hemolytic anemia (MAHA):** The risk of MAHA is increased in patients with pancreatic cancer. (5.7)
- **Ocular disorders:** Discontinue TARCEVA for corneal perforation, ulceration or persistent severe keratitis. (5.8)
- **Hemorrhage in patients taking warfarin:** Regularly monitor INR in patients taking warfarin or other coumarin-derivative anticoagulants. (5.9)
- **Embryo-fetal toxicity:** Can cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception. (5.10, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (≥ 20%) with TARCEVA from a pooled analysis in patients with NSCLC across all approved lines of therapy, with and without EGFR mutations, and in patients with pancreatic cancer 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 <http://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

Lactation: Do not breastfeed (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Non-Small Cell Lung Cancer (NSCLC)

TARCEVA[®] is indicated for:

- The 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 receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen [see *Clinical Studies (14.1, 14.3)*].

Limitations of use:

- Safety and efficacy of TARCEVA have not been established in patients with NSCLC whose tumors have other EGFR mutations [see *Clinical Studies (14.1, 14.2)*].
- TARCEVA is not recommended for use in combination with platinum-based chemotherapy [see *Clinical Studies (14.4)*].

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 Selection of Patients with Metastatic NSCLC

Select patients for the 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, 14.2)*]. 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

Adverse Reactions		
Pulmonary [†]	Interstitial Lung Disease (ILD)	Discontinue TARCEVA
	During diagnostic evaluation for possible ILD	Withhold TARCEVA*
Hepatic [†]	Severe hepatic toxicity that does not improve significantly or resolve within three weeks	Discontinue TARCEVA
	In patients with pre-existing hepatic impairment or biliary obstruction for doubling of bilirubin or tripling of transaminases values over baseline	Withhold TARCEVA* and consider discontinuation
	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* and consider discontinuation
Renal [†]	For severe (CTCAE grade 3 to 4) renal toxicity	Withhold TARCEVA* and consider discontinuation
Gastrointestinal [†]	Gastrointestinal perforation	Discontinue TARCEVA
	For persistent severe diarrhea not responsive to medical management (e.g., loperamide)	Withhold TARCEVA*
Skin [†]	Severe bullous, blistering or exfoliating skin conditions	Discontinue TARCEVA
	For severe rash not responsive to medical management	Withhold TARCEVA*
Ocular [†]	Corneal perforation or severe ulceration	Discontinue TARCEVA
	For keratitis of (NCI-CTC version 4.0) grade 3-4 or for grade 2 lasting more than 2 weeks	Withhold TARCEVA*
	For acute/worsening ocular disorders such as eye pain	Withhold TARCEVA* and consider discontinuation
Drug Interactions		
CYP3A4 inhibitors [‡]	If severe reactions occur with concomitant use of strong CYP3A4 inhibitors [such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), voriconazole, or grapefruit or grapefruit juice] or when using concomitantly with an inhibitor of both CYP3A4 and CYP1A2 (e.g., ciprofloxacin)	Reduce TARCEVA by 50 mg decrements; avoid concomitant use if possible
CYP3A4 inducers [‡]	Concomitant use with CYP3A4 inducers, such as rifampin, rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital, or St. John's Wort	Increase TARCEVA by 50 mg increments at 2-week intervals to a maximum of 450 mg as tolerated. Avoid concomitant use if possible
Concurrent Cigarette Smoking ^{‡§}	Concurrent cigarette smoking	Increase TARCEVA 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
Proton Pump inhibitors	Separation of doses may not eliminate the interaction since proton pump inhibitors affect the pH of the upper GI tract for an extended period	Avoid concomitant use if possible

H ₂ -receptor antagonists	If treatment with an H ₂ -receptor antagonist such as ranitidine is required, separate dosing.	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
Antacids	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

† For additional information see *Warnings and Precautions* (5).

* Reduce TARCEVA by 50 mg decrements when restarting therapy following withholding treatment for a dose-limiting toxicity that has resolved to baseline or grade ≤ 1.

‡ For additional information see *Drug Interactions* (7).

§ For additional information see *Clinical Pharmacology* (12.3).

3 DOSAGE FORMS AND STRENGTHS

25 mg tablets: round, biconvex face and straight sides, white film-coated, printed in orange with “T” and “25” on one side and plain on other side.

100 mg tablets: round, biconvex face and straight sides, white film-coated, printed in gray with “T” and “100” on one side and plain on other side.

150 mg tablets: round, biconvex face and straight sides, white film-coated, printed in maroon with “T” and “150” on one side and plain on 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)].

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 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 not higher than that observed in the control arms.

5.7 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.

5.8 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)].

5.9 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)].

5.10 Embryo-fetal Toxicity

Based on animal data and 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 exposures approximately 3 times the exposure at the recommended human daily dose of 150 mg. Advise pregnant women of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during therapy and for one month after the last dose of TARCEVA [see *Use in Specific Populations* (8.1) and (8.3), *Clinical Pharmacology* (12.1)].

6 ADVERSE REACTIONS

The following serious adverse reactions, which may include fatalities, are discussed in greater detail in other sections of the labeling:

- Interstitial Lung Disease (ILD) [see *Warnings and Precautions* (5.1)]
- Renal Failure [see *Warnings and Precautions* (5.2)]
- Hepatotoxicity with or without Hepatic Impairment [see *Warnings and Precautions* (5.3)]
- Gastrointestinal Perforation [see *Warnings and Precautions* (5.4)]
- Bullous and Exfoliative Skin Disorders [see *Warnings and Precautions* (5.5)]
- Cerebrovascular Accident [see *Warnings and Precautions* (5.6)]
- Microangiopathic Hemolytic Anemia with Thrombocytopenia [see *Warnings and Precautions* (5.7)]
- Ocular Disorders [see *Warnings and Precautions* (5.8)]
- Hemorrhage in Patients Taking Warfarin [see *Warnings and Precautions* (5.9)]

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