

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, oral
Initial U.S. Approval: 2004

RECENT MAJOR CHANGES

Table with 2 columns: Description of change and Date. Includes Warnings and Precautions for Gastrointestinal Perforation, Bullous Skin Disorders, Ocular Disorders, Renal Failure, Hepatotoxicity, and Hepatic Impairment.

INDICATIONS AND USAGE

- TARCEVA is a kinase inhibitor indicated for the treatment of:
- Locally advanced or metastatic non-small cell lung cancer (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)

DOSAGE AND ADMINISTRATION

- The dose for NSCLC is 150 mg/day. (2.1)
The dose for pancreatic cancer is 100 mg/day. (2.2)
All doses of TARCEVA should be taken at least one hour before or two hours after food. (2.1, 2.2)
Reduce in 50 mg decrements, when necessary. (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)-like events, including fatalities have been infrequently reported. Interrupt TARCEVA if acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever occur. Discontinue TARCEVA if ILD is diagnosed. (5.1)
Cases of acute renal failure (including fatalities), and renal insufficiency have been reported. Interrupt TARCEVA in the

- event of dehydration. Monitor renal function and electrolytes in patients at risk of dehydration. (5.2)
Cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported. Monitor periodic liver function testing. Interrupt or discontinue TARCEVA if liver function changes are severe. (5.3)
Monitor patients with hepatic impairment closely. Interrupt or discontinue TARCEVA if changes in liver function are severe (5.4)
Gastrointestinal perforations, including fatalities, have been reported. Discontinue TARCEVA. (5.5)
Bullous and exfoliative skin disorders, including fatalities, have been reported. Interrupt or discontinue TARCEVA (5.6)
Myocardial infarction/ischemia has been reported, including fatalities, in patients with pancreatic cancer. (5.7)
Cerebrovascular accidents, including a fatality, have been reported in patients with pancreatic cancer. (5.8)
Microangiopathic Hemolytic Anemia with thrombocytopenia has been reported in patients with pancreatic cancer. (5.9)
Corneal perforation and ulceration have been reported. Interrupt or discontinue TARCEVA (5.10)
Women should be advised to avoid pregnancy while on TARCEVA. Treatment should only be continued if the potential benefit to the mother outweighs the risk to the fetus. (5.11)
International Normalized Ratio (INR) elevations and bleeding events, some associated with concomitant warfarin administration have been reported. Monitor patients taking warfarin or other coumarin-derivative anticoagulants. (5.12)

ADVERSE REACTIONS

The most common adverse reactions (>50%) in NSCLC are rash, diarrhea, anorexia and fatigue. (6.1)
The most common adverse reactions (>50%) in pancreatic cancer are fatigue, rash, nausea and anorexia. (6.2)

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

DRUG INTERACTIONS

- CYP3A4 inhibitors may increase erlotinib plasma concentrations. (7)
CYP3A4 inducers may decrease erlotinib plasma concentrations. (7)
CYP1A2 inducers may decrease erlotinib plasma concentrations. (7)
Erlotinib solubility is pH dependent. Drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and hence its absorption. (7)
Cigarette smoking decreases erlotinib plasma concentrations (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: [04/2009]

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Non-Small Cell Lung Cancer (NSCLC)

TARCEVA monotherapy is indicated for 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 (14.1)*].

Results from two, multicenter, placebo-controlled, randomized, Phase 3 trials conducted in first-line patients with locally advanced or metastatic NSCLC showed no clinical benefit with the concurrent administration of TARCEVA with platinum-based chemotherapy [carboplatin and paclitaxel or gemcitabine and cisplatin] and its use is not recommended in that setting [see *Clinical Studies (14.3)*].

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 (14.4)*].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose - NSCLC

The recommended daily dose of TARCEVA for non-small cell lung cancer is 150 mg taken at least one hour before or two hours after the ingestion of food. Treatment should continue until disease progression or unacceptable toxicity occurs. There is no evidence that treatment beyond progression is beneficial.

2.2 Recommended Dose – Pancreatic Cancer

The recommended daily dose of TARCEVA for pancreatic cancer is 100 mg taken at least one hour before or two hours after the ingestion of food, in combination with gemcitabine (see the gemcitabine package insert). Treatment should continue until disease progression or unacceptable toxicity occurs.

2.3 Dose Modifications

In patients who develop an acute onset of new or progressive pulmonary symptoms, such as dyspnea, cough or fever, treatment with TARCEVA should be interrupted pending diagnostic evaluation. If Interstitial Lung Disease (ILD) is diagnosed, TARCEVA should be discontinued and appropriate treatment instituted as necessary [see *Warnings and Precautions (5.1)*]. Discontinue TARCEVA for hepatic failure or gastrointestinal perforation. Interrupt or discontinue TARCEVA in patients with dehydration who are at risk for renal failure, in patients with severe bullous, blistering or exfoliative skin conditions, or in patients with acute /worsening ocular disorders [see *Warnings and Precautions (5.3, 5.4, 5.5, 5.6, 5.10)*].

Diarrhea can usually be managed with loperamide. Patients with severe diarrhea who are unresponsive to loperamide or who become dehydrated may require dose reduction or temporary interruption of therapy. Patients with severe skin reactions may also require dose reduction or temporary interruption of therapy.

When dose reduction is necessary, the TARCEVA dose should be reduced in 50 mg decrements.

In patients who are taking TARCEVA with a strong CYP3A4 inhibitor such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), voriconazole, or grapefruit or grapefruit juice, a dose reduction should be considered if severe adverse reactions occur. Similarly, in patients who are taking TARCEVA with an inhibitor of both CYP3A4 and CYP1A2 like ciprofloxacin, a dose reduction of TARCEVA should be considered if severe adverse reactions occur [see *Drug Interactions (7)*].

Pre-treatment with the CYP3A4 inducer rifampicin decreased erlotinib AUC by about 2/3 to 4/5. Use of alternative treatments lacking CYP3A4 inducing activity is strongly recommended. If an alternative treatment is unavailable, an increase in the dose of TARCEVA should be considered as tolerated at two week intervals while monitoring the patient's safety. The maximum dose of TARCEVA studied in combination with rifampicin is 450 mg. If the TARCEVA dose is adjusted upward, the dose will need to be reduced immediately to the indicated starting dose upon discontinuation of rifampicin or other inducers. Other CYP3A4 inducers include, but are not limited to rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital and St. John's Wort. These too should be avoided if possible [see *Drug Interactions* (7)].

Cigarette smoking has been shown to reduce erlotinib exposure. Patients should be advised to stop smoking. If a patient continues to smoke, a cautious increase in the dose of TARCEVA, not exceeding 300 mg may be considered, while monitoring the patient's safety. However, efficacy and long-term safety (> 14 days) of a dose higher than the recommended starting doses have not been established in patients who continue to smoke cigarettes. If the TARCEVA dose is adjusted upward, the dose should be reduced immediately to the indicated starting dose upon cessation of smoking [see *Clinical Pharmacology* (12.3)].

Erlotinib is eliminated by hepatic metabolism and biliary excretion. Although erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh B), patients with hepatic impairment (total bilirubin > ULN or Child-Pugh A, B and C) should be closely monitored during therapy with TARCEVA [see *Warnings and Precautions* (5.4)]. Treatment with TARCEVA should be used with extra caution in patients with total bilirubin > 3 x ULN. TARCEVA dosing should be interrupted or discontinued if changes in liver function are severe such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside normal range. In the setting of worsening liver function tests, before they become severe, dose interruption and/or dose reduction with frequent liver function test monitoring should be considered. TARCEVA dosing should be interrupted or discontinued if total bilirubin is >3 x ULN and/or transaminases are >5 x ULN in the setting of normal pretreatment values [see *Warnings and Precautions* (5.3, 5.4), *Adverse Reactions* (6.3) and *Use in Specific Populations* (8.6)].

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 Pulmonary Toxicity

There have been infrequent reports of serious Interstitial Lung Disease (ILD)-like events, including fatalities, in patients receiving TARCEVA for treatment of NSCLC, pancreatic cancer or other advanced solid tumors. In the randomized single-agent NSCLC study [see *Clinical Studies* (14.1)], the incidence of ILD-like events (0.8%) was the same in both the placebo and TARCEVA groups. In the pancreatic cancer study - in combination with gemcitabine - [see *Clinical Studies* (14.3)], the incidence of ILD-like events was 2.5% in the TARCEVA plus gemcitabine group vs. 0.4% in the placebo plus gemcitabine group.

The overall incidence of ILD-like events in approximately 4900 TARCEVA-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) was approximately 0.7%. Reported diagnoses in patients suspected of having ILD-like events included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome and lung infiltration. Symptoms started from 5 days to more than 9 months (median 39 days) after initiating TARCEVA therapy. In the lung cancer trials most of the cases were associated with confounding or contributing factors such as concomitant/prior chemotherapy, prior radiotherapy, pre-

In the event of an acute onset of new or progressive unexplained pulmonary symptoms such as dyspnea, cough, and fever, TARCEVA therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, TARCEVA should be discontinued and appropriate treatment instituted as needed [see *Dosage and Administration* (2.3)].

5.2 Renal Failure

Cases of hepatorenal syndrome, acute renal failure (including fatalities), and renal insufficiency have been reported. Some were secondary to baseline hepatic impairment while others were associated with severe dehydration due to diarrhea, vomiting, and/or anorexia or concurrent chemotherapy use. In the event of dehydration, particularly in patients with contributing risk factors for renal failure (eg, pre-existing renal disease, medical conditions or medications that may lead to renal disease, or other predisposing conditions including advanced age), TARCEVA therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patient. Periodic monitoring of renal function and serum electrolytes is recommended in patients at risk of dehydration [see *Adverse Reactions* (6.3) and *Dosage and Administration* (2.3)].

5.3 Hepatotoxicity

Cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported during use of TARCEVA, particularly in patients with baseline hepatic impairment. Therefore, periodic liver function testing (transaminases, bilirubin, and alkaline phosphatase) is recommended. In the setting of worsening liver function tests, dose interruption and/or dose reduction with frequent liver function test monitoring should be considered. TARCEVA dosing should be interrupted or discontinued if total bilirubin is >3 x ULN and/or transaminases are >5 x ULN in the setting of normal pretreatment values [see *Adverse Reactions* (6.3) and *Dosage and Administration* (2.3)].

5.4 Patients with Hepatic Impairment

In a pharmacokinetic study in patients with moderate hepatic impairment (Child-Pugh B) associated with significant liver tumor burden, 10 out of 15 patients died on treatment or 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 suggesting severe hepatic impairment. Treatment with TARCEVA should be used with extra caution in patients with total bilirubin >3 x ULN. Patients with hepatic impairment (total bilirubin $>ULN$ or Child-Pugh A, B and C) should be closely monitored during therapy with TARCEVA. TARCEVA dosing should be interrupted or discontinued if changes in liver function are severe such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside normal range [see *Clinical Pharmacology* (12.3) and *Dosage and Administration* (2.3)].

5.5 Gastrointestinal Perforation

Gastrointestinal perforation (including fatalities) has been reported in patients receiving TARCEVA. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane-based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. [see *Adverse Reactions* (6.3)]. Permanently discontinue TARCEVA in patients who develop gastrointestinal perforation.

5.6 Bullous and Exfoliative Skin Disorders

Bullous, blistering and exfoliative skin conditions have been reported including cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis, which in some cases were fatal [see *Adverse Reactions* (6.3)]. Interrupt or discontinue TARCEVA treatment if the patient develops severe bullous, blistering or exfoliating conditions.

5.7 Myocardial infarction/ischemia

In the pancreatic carcinoma trial, six patients (incidence of 2.3%) 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 1.2%) and one died due to myocardial infarction.

5.8 Cerebrovascular accident

In the pancreatic carcinoma trial, six patients in the TARCEVA/gemcitabine group developed cerebrovascular accidents (incidence: 2.3%) One of these was

5.9 Microangiopathic Hemolytic Anemia with Thrombocytopenia

In the pancreatic carcinoma trial, two patients in the TARCEVA/gemcitabine group developed microangiopathic hemolytic anemia with thrombocytopenia (incidence: 0.8%). Both patients received TARCEVA and gemcitabine concurrently. In comparison, in the placebo/gemcitabine group there were no cases of microangiopathic hemolytic anemia with thrombocytopenia.

5.10 Ocular Disorders

Corneal perforation and ulceration have been reported during use of TARCEVA. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with TARCEVA treatment and are known risk factors for corneal ulceration/perforation [see *Adverse Reactions (6.3)*].

Interrupt or discontinue TARCEVA therapy if patients present with acute/worsening ocular disorders such as eye pain.

5.11 Use in Pregnancy

Pregnancy Category D

Women of childbearing potential should avoid becoming pregnant while being treated with TARCEVA. Erlotinib administered to rabbits during organogenesis at doses that result in plasma drug concentrations of approximately 3 times those in humans (AUCs at 150 mg daily dose) was associated with embryo/fetal lethality and abortion. When erlotinib was administered to female rats prior to mating and through the first week of pregnancy, at doses 0.3 or 0.7 times the clinical dose of 150 mg, on a mg/m² basis, there was an increase in early resorptions that resulted in a decrease in the number of live fetuses [see *Use in Specific Populations (8.1)*].

5.12 Elevated International Normalized Ratio and Potential Bleeding

International Normalized Ratio (INR) elevations and infrequent reports of bleeding events including gastrointestinal and non-gastrointestinal bleedings have been reported in clinical studies, some associated with concomitant warfarin administration. Patients taking warfarin or other coumarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR [see *Adverse Reactions (6.3)*].

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety evaluation of TARCEVA is based on 856 cancer patients who received TARCEVA as monotherapy, 308 patients who received TARCEVA 100 or 150 mg plus gemcitabine, and 1228 patients who received TARCEVA concurrently with other chemotherapies.

There have been reports of serious events, including fatalities, in patients receiving TARCEVA for treatment of NSCLC, pancreatic cancer or other advanced solid tumors [see *Warnings and Precautions (5) and Dosage and Administration (2.3)*].

6.1 Non-Small Cell Lung Cancer

Adverse reactions, regardless of causality, that occurred in at least 10% of patients treated with single-agent TARCEVA at 150 mg and at least 3% more often than in the placebo group in the randomized trial of patients with NSCLC are summarized by NCI-CTC (version 2.0) Grade in Table 1.

The most common adverse reactions in patients receiving single-agent TARCEVA 150 mg were rash and diarrhea. Grade 3/4 rash and diarrhea occurred in 9% and 6%, respectively, in TARCEVA-treated patients. Rash and diarrhea each resulted in study discontinuation in 1% of TARCEVA-treated patients. Six percent and 1% of patients needed dose reduction for rash and diarrhea, respectively. The median time to onset of rash was 8 days, and the median time to onset of diarrhea was 12 days.

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