

CYP3A4 and CYP1A2 inhibitors

CYP3A4 inhibitors

- Erlotinib is metabolized predominantly by CYP3A4, and inhibitors of CYP3A4 would be expected to increase exposure to the drug. In one study, co-treatment with the potent CYP3A4 inhibitor ketoconazole increased erlotinib AUC by 2/3.¹
- Caution should be used during co-treatment with erlotinib and CYP3A4 inhibitors, and in some situations, a decreased dose of erlotinib may be required. Other inhibitors to consider using with caution during co-treatment with erlotinib include, but are not limited to¹:

atazanavir	indinavir	nelfinavir
ritonavir	saquinavir	clarithromycin
telithromycin	troleandomycin (TAO)	itraconazole
ketoconazole	voriconazole	nefazodone
grapefruit	grapefruit juice	

- **Grapefruit** and **grapefruit juice** can reduce the activity of CYP3A4 enough to significantly increase the bioavailability of drugs metabolized by CYP3A4.²

CYP3A4 and CYP1A2 inhibitors

- Erlotinib is metabolized to a lesser extent by CYP1A2. Inhibitors of both CYP3A4 and CYP1A2 would be expected to increase exposure to the drug. When erlotinib was administered with the potent inhibitor of both CYP3A4 and CYP1A2 ciprofloxacin, the erlotinib exposure (AUC) and maximum concentration (C_{max}) increased by 39% and 17%, respectively.¹
- Caution should be used during co-treatment with erlotinib and inhibitors of both CYP3A4 and CYP1A2, and in some situations, a decreased dose of erlotinib may be required.¹

Please see important safety information inside and accompanying full prescribing information.



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Tarceva dosing and indications

- Patients should be instructed to take Tarceva on an empty stomach at least one hour before or two hours after the ingestion of food.¹
- Tarceva patients who smoke cigarettes should be advised to stop smoking. Cigarette smoking has been shown to reduce Tarceva exposure.¹
- The exact dose recommended for smokers is unknown; however, a cautious increase in the dose of Tarceva, not exceeding 300 mg, may be considered while monitoring the patients' safety.¹
- Efficacy and long-term safety (>14 days) of a dose higher than the recommended starting dose in smokers have not been established. The dose should be reduced immediately to the indicated starting dose if the patient stops smoking.¹



Do not take
Tarceva
with food

Tarceva in non-small cell lung cancer (NSCLC)

- The recommended once-daily dose of Tarceva monotherapy for the treatment of advanced NSCLC is **150 mg taken orally on an empty stomach**.^{1,*}

Tarceva monotherapy is indicated for:

- the maintenance treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.
- the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.

Results from two, multicenter, placebo-controlled, randomized, Phase III 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.

Tarceva in first-line advanced pancreatic cancer

- The recommended once-daily dose of Tarceva for the treatment of advanced pancreatic cancer is **100 mg taken orally on an empty stomach in combination with gemcitabine**.^{1,*}
- Tarceva in combination with gemcitabine is indicated for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.

* Administering Tarceva above the recommended daily dosage may result in an unacceptable incidence of adverse events.¹



Important safety information

- There have been 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.
- Cases of hepatic failure, hepatorenal syndrome, acute renal failure (all including fatalities), and renal insufficiency have been reported during use of Tarceva.
- Gastrointestinal perforation (including fatalities) has been reported in patients receiving Tarceva.
- 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.
- In the pancreatic cancer trial, other serious adverse reactions associated with Tarceva plus gemcitabine and which may have included fatalities, were myocardial infarction/ischemia, cerebrovascular accident and microangiopathic hemolytic anemia with thrombocytopenia.
- Corneal perforation and ulceration have been reported during use of Tarceva.
- International Normalized Ratio (INR) elevation and infrequent reports of bleeding events, including gastrointestinal and non-gastrointestinal bleeding, have been reported in clinical studies.
- Tarceva is pregnancy category D. When receiving Tarceva therapy, women should be advised to avoid pregnancy or breastfeeding.
- The most common adverse reactions in patients with NSCLC receiving single-agent Tarceva 150 mg were rash and diarrhea.
- The most common adverse reactions in patients with pancreatic cancer receiving Tarceva 100 mg plus gemcitabine were fatigue, rash, nausea, anorexia and diarrhea.

References: 1. Tarceva [package insert]. Melville, NY: OSI Pharmaceuticals Inc; 2010. 2. Huang SM, Lesko LJ. Drug-drug, drug-dietary supplement, and drug-citrus fruit and other food interactions: what have we learned? *J Clin Pharmacol.* 2004;44(6):559-569.



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CYP3A4 inducers

- Erlotinib is metabolized predominantly by CYP3A4, and drugs that are CYP3A4 inducers may increase clearance of erlotinib. Pre- or co-treatment with the CYP3A4 inducer rifampicin increased erlotinib clearance threefold and reduced AUC by 2/3.¹
- Thus, alternate treatments lacking CYP3A4-inducing activity should be considered. In the absence of an alternative, erlotinib dose modification should be considered during co-treatment with CYP3A4 inducers such as, but not limited to¹:

rifabutin

rifampicin

rifapentine

carbamazepine

phenobarbital

phenytoin

St. John's Wort

- St. John's Wort increases the activity of CYP3A4, effectively decreasing the bioavailability of drugs metabolized by the same system.¹
- If the erlotinib dose is adjusted upward, the dose will need to be reduced upon discontinuation of rifampicin or other inducers.¹

Please see important safety information on page 3 and enclosed full prescribing information.

Visit Tarceva.com for additional information and resources.

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