Erlotinib: Drug information

(For additional information see "Erlotinib: Patient drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

Special Alerts

Tarceva Maintenance Treatment Alert January 2016

Health Canada has notified health care professionals that based on a recent study, IUNO (B025460), the benefit-risk of *Tarceva* (erlotinib) as maintenance treatment in patients with advanced non–small cell lung cancer (NSCLC) whose tumors do not have an epidermal growth factor receptor (EGFR)–activating mutation is negative. The IUNO study compared the primary endpoint of overall survival using maintenance *Tarceva* therapy with *Tarceva* administered at the time of disease progression in patients with advanced NSCLC whose tumors did not harbor an EGFR-activating mutation (exon 19 deletion or exon 21 L858R mutation). Overall survival rate was not superior to that of patients randomized to receive maintenance *Tarceva*. The role of *Tarceva* as maintenance therapy in patients whose tumors do harbor an EGFR-activating mutation with locally advanced or metastatic NSCLC will be assessed by Health Canada. Health Canada, in collaboration with Hoffmann-La Roche Limited, will revise the Canadian prescribing and consumer information for *Tarceva* to reflect these updated data.

For additional information, refer to http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2016/56720a-eng.php,

Brand Names: US

Tarceva

Brand Names: Canada

Tarceva; Teva-Erlotinib

Pharmacologic Category

Antineoplastic Agent, Epidermal Growth Factor Receptor (EGFR) Inhibitor; Antineoplastic Agent, Tyrosine Kinase Inhibitor

Dosing: Adult

Non-small cell lung cancer (NSCLC), metastatic, in patients with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations: Oral: 150 mg once daily until disease progression or unacceptable toxicity (Capuzzo 2010; Rosell 2012; Shepherd 2005).

Pancreatic cancer: Oral: 100 mg once daily (in combination with gemcitabine); continue until disease progression or unacceptable toxicity (Moore 2007).

Dosage adjustment for concomitant CYP inhibitors/inducers:

CYP3A4 inhibitors (strong): Avoid concurrent use if possible; reduce erlotinib dose for severe adverse reactions if erlotinib is administered concomitantly with strong CYP3A4 inhibitors. Dose reduction should be done in decrements of 50 mg (after toxicity has resolved to baseline or ≤ grade 1).

Concomitant CYP3A4 and CYP1A2 inhibitor (eg, ciprofloxacin): Avoid concurrent use if possible; if concomitant use cannot be avoided, reduce dose in decrements of 50 mg if severe adverse reactions occur (after toxicity has resolved to baseline or ≤ grade 1).

CYP3A4 inducers: Avoid concurrent use if possible; if concomitant administration with CYP3A4 inducers cannot be avoided, increase erlotinib dose in 50 mg increments at 2-week intervals to a maximum of 450 mg; reduce erlotinib dose to recommended starting dose when CYP3A4 inducer is discontinued.

CYP1A2 inducers: Avoid concurrent moderate CYP1A2 inducers if possible. If unavoidable, increase dose at 2-week intervals in 50 mg increments to a maximum dose of 300 mg (with careful monitoring); immediately reduce erlotinib dose to recommended starting dose (based on indication) upon discontinuation of the moderate CYP1A2 inducer.

Dosage adjustment for concomitant smoking: Avoid tobacco smoking if possible. If unavoidable, increase dose at 2-week intervals in 50 mg increments to a maximum dose of 300 mg (with careful monitoring); immediately reduce erlotinib dose to recommended starting dose (based on indication) upon smoking cessation.

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

Renal impairment at treatment initiation: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied), although <9% of a single dose is excreted in the urine.

Renal toxicity during treatment:

Grades 3/4 renal toxicity: Withhold treatment and consider discontinuing. If treatment is resumed, reinitiate with a 50 mg dose reduction after toxicity has resolved to baseline or ≤ grade 1.

Renal failure associated with hepatorenal syndrome or due to dehydration: Withhold treatment until renal toxicity is resolved. If treatment is resumed, reinitiate with a 50 mg dose reduction after toxicity has resolved.

Dosing: Hepatic Impairment

Hepatic impairment at treatment initiation:

Total bilirubin > ULN or Child-Pugh classes A, B, and C: There are no dosage adjustments provided in the manufacturer's labeling; use with caution and monitor closely during treatment.

Total bilirubin >3 times ULN: Use extreme caution.

The following adjustments have also been studied: A reduced starting dose (75 mg once daily) has been

recommended in patients with hepatic dysfunction (AST ≥3 times ULN or direct bilirubin 1 to 7 mg/dL), with individualized dosage escalation if tolerated (Miller 2007); another study determined that pharmacokinetic and safety profiles were similar between patients with normal hepatic function and moderate hepatic impairment (O'Bryant 2012).

Hepatotoxicity during treatment:

Patients with normal hepatic function at baseline: If total bilirubin >3 times ULN and/or transaminases >5 times ULN: Interrupt therapy and consider discontinuing. If treatment is resumed, reinitiate with a 50 mg dose reduction after bilirubin and transaminases return to baseline.

Patients with baseline hepatic impairment or biliary obstruction: If bilirubin doubles or transaminases triple over baseline: Interrupt therapy and consider discontinuing. If treatment is resumed, reinitiate with a 50 mg dose reduction after bilirubin and transaminases return to baseline.

Severe hepatotoxicity that does not significantly improve or resolve within 3 weeks: Discontinue treatment.

Dosing: Adjustment for Toxicity

Dermatologic toxicity:

Bullous, blistering, or exfoliative skin toxicity (severe): Discontinue treatment.

Severe rash (unresponsive to medical management): Withhold treatment; may reinitiate with a 50 mg dose reduction after toxicity has resolved to baseline or ≤ grade 1.

Gastrointestinal toxicity:

Diarrhea: Manage with loperamide; in persistent, severe diarrhea (unresponsive to loperamide) or dehydration due to diarrhea, withhold treatment; may reinitiate with a 50 mg dose reduction after toxicity has resolved to baseline or ≤ grade 1.

Gastrointestinal perforation: Discontinue treatment.

Ocular toxicities:

Acute or worsening ocular toxicities (eg, eye pain): Interrupt and consider discontinuing treatment. If therapy is resumed, reinitiate with a 50 mg dose reduction after toxicity has resolved to baseline or ≤ grade 1.

Corneal perforation or severe ulceration: Discontinue treatment.

Keratitis (grade 3 or 4 or grade 2 persisting >2 weeks): Withhold treatment; may reinitiate with a 50 mg dose reduction after toxicity has resolved to baseline or ≤ grade 1.

Pulmonary symptoms: Acute onset (or worsening) of pulmonary symptoms (eg, dyspnea, cough, fever): Withhold treatment while evaluating for drug-induced interstitial lung disease; if resuming treatment, reinitiate with a 50 mg dose reduction after symptoms resolve to grade 1 or lower. Discontinue permanently with development of interstitial lung disease

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, Oral:

Tarceva: 25 mg [contains fd&c yellow #6 (sunset yellow)]

Tarceva: 100 mg, 150 mg

Generic Equivalent Available (US) No

Administration The manufacturer recommends administration on an empty stomach (at least 1 hour before or 2 hours after the ingestion of food). Avoid concomitant use with proton pump inhibitors (if possible). If taken with an H_2-receptor antagonist (eg, ranitidine), administer erlotinib 10 hours after the H_2-receptor antagonist dose and at least 2 hours prior to the next H_2- receptor dose. If an antacid is necessary, separate dosing by several hours.

For patients unable to swallow whole, tablets may be dissolved in 100 mL water and administered orally or via feeding tube (silicone-based); to ensure full dose is received, rinse container with 40 mL water, administer residue and repeat rinse; administer immediately after preparation (data on file, Genentech [contact product manufacturer to obtain current information]; Siu 2007; Soulieres 2004). If necessary, an oral suspension may be prepared (see Extemporaneously Prepared).

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends single gloving for administration of intact tablets or capsules. If manipulating tablets/capsules (eg, to prepare an oral suspension), NIOSH recommends double gloving, a protective gown, and preparation in a controlled device; if not prepared in a controlled device, respiratory and eye/face protection as well as ventilated engineering controls are recommended. NIOSH recommends double gloving, a protective gown, and (if there is a potential for vomit or spit up) eye/face protection for administration of an oral liquid/feeding tube administration (NIOSH 2016).

Use

Non-small cell lung cancer, metastatic: Treatment of metastatic non-small cell lung cancer (NSCLC) in tumors with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an approved test either as first-line, maintenance, or as second or greater line treatment after progression following at least 1 prior chemotherapy regimen.

Limitations of use: Use in combination with platinum-based chemotherapy is not recommended. Safety and efficacy of treatment for metastatic NSCLC with EGFR mutations other than exon 19 deletion or exon 21 (L858R) substitution have not been established.

Pancreatic cancer: First-line treatment of locally advanced, unresectable, or metastatic pancreatic cancer (in combination with gemcitabine)

Medication Safety Issues

Sound-alike/look-alike issues:

Erlotinib may be confused with afatinib, crizotinib, eribulin, gefitinib, imatinib, nintedanib, regorafenib, SUNItinib, vandetanib

Tarceva may be confused with Tresiba

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Adverse Reactions

Adverse reactions reported with monotherapy:

>10%:

Cardiovascular: Chest pain (≤18%)

Central nervous system: Fatigue (9% to 52%)

Dermatologic: Skin rash (49% to 85%; grade 3: 5% to 13%; grade 4: <1%; median onset: 8 days), xeroderma (4% to 21%), pruritus (7% to 16%), paronychia (4% to 16%), alopecia (14% to 15%), acne vulgaris (6% to 12%)

Gastrointestinal: Diarrhea (20% to 62%; grade 3: 2% to 6%; grade 4: <1%; median onset: 12 days), anorexia (9% to 52%), nausea (23% to 33%), decreased appetite (≤28%), vomiting (13% to 23%), mucositis (≤18%), stomatitis (11% to 17%), abdominal pain (3% to 11%), constipation (≤8%)

Genitourinary: Urinary tract infection (≤4%)

Hematologic & oncologic: Anemia (≤11%; grade 4: 1%)

Infection: Increased susceptibility to infection (4% to 24%)

Miscellaneous: Fever (≤11%)

Neuromuscular & skeletal: Weakness (≤53%), back pain (19%), arthralgia (≤13%), musculoskeletal pain (11%)

Ophthalmic: Conjunctivitis (12% to 18%), keratoconjunctivitis sicca (12%)

Respiratory: Cough (33% to 48%), dyspnea (41% to 45%; grades 3/4: 8% to 28%)

1% to 10%:

Cardiovascular: Peripheral edema (≤5%)

Central nervous system: Pain (≤9%), headache (≤7%), anxiety (≤5%), dizziness (≤4%), insomnia (≤4%), neurotoxicity (≤4%), paresthesia (≤4%), voice disorder (≤4%)

Dermatologic: Folliculitis (≤8%), nail disease (≤7%), exfoliative dermatitis (5%), hypertrichosis (5%), skin fissure (5%), acneiform eruption (4% to 5%), erythema (≤5%), dermatitis (4%), erythematous rash (≤4%), palmar-plantar erythrodysesthesia (≤4%), bullous dermatitis

Endocrine & metabolic: Weight loss (4% to 5%)

Gastrointestinal: Dyspepsia (≤5%), xerostomia (≤3%), taste disorder (≤1%)

Hematologic & oncologic: Lymphocytopenia (≤4%; grade 3: 1%), leukopenia (≤3%), thrombocytopenia (≤1%)

Hepatic: Hyperbilirubinemia (7%; grade 3: ≤1%), increased serum ALT (grade 2: 2% to 4%; grade 3: 1% to 3%), increased gamma-glutamyl transferase (≤4%), hepatic failure (≤1%)

Neuromuscular & skeletal: Muscle spasm (≤4%), musculoskeletal chest pain (≤4%), ostealgia (≤4%)

Otic: Tinnitus (≤1%)

Renal: Increased serum creatinine (≤1%), renal failure (≤1%),

Respiratory: Nasopharyngitis (≤7%), epistaxis (≤4%), pulmonary embolism (≤4%), respiratory tract infection (≤4%), pneumonitis (3%), pulmonary fibrosis (3%)

<1%: Interstitial pulmonary disease

Adverse reactions reported with combination (erlotinib plus gemcitabine) therapy:

>10%:

Cardiovascular: Edema (37%), thrombosis (grades 3/4: 11%)

Central nervous system: Fatigue (73% to 79%), depression (19%), dizziness (15%), headache (15%), anxiety (13%)

Dermatologic: Skin rash (70%), alopecia (14%)

Gastrointestinal: Nausea (60%), anorexia (52%), diarrhea (48%), abdominal pain (46%), vomiting (42%), weight loss (39%), stomatitis (22%), dyspepsia (17%), flatulence (13%)

Hepatic: Increased serum ALT (grade 2: 31%, grade 3: 13%, grade 4: <1%), increased serum AST (grade 2: 24%, grade 3: 10%, grade 4 <1%), hyperbilirubinemia (grade 2: 17%, grade 3: 10%, grade 4: <1%)

Infection: Increased susceptibility to infection (39%)

Miscellaneous: Fever (36%)

Neuromuscular & skeletal: Ostealgia (25%), myalgia (21%), neuropathy (13%), rigors (12%)

Respiratory: Dyspnea (24%), cough (16%)

1% to 10%:

Cardiovascular: Cardiac arrhythmia (<5%), syncope (<5%), deep vein thrombosis (4%), cerebrovascular accident (3%; including cerebral hemorrhage), myocardial infarction (2%)

Gastrointestinal: Intestinal obstruction (<5%), pancreatitis (<5%)

Hematologic & oncologic: Hemolytic anemia (<5%), microangiopathic hemolytic anemia with thrombocytopenia (1%)

Renal: Renal insufficiency (<5%), renal failure (1%)

Respiratory: Interstitial pulmonary disease (<3%)

<1%: Bullous dermatitis, exfoliative dermatitis, hepatic failure

Mono- or combination therapy: <1%, postmarketing, and/or case reports: Acute peptic ulcer with hemorrhage, bronchiolitis, corneal perforation, corneal ulcer, decreased lacrimation, episcleritis, gastritis, gastrointestinal hemorrhage, gastrointestinal perforation, hearing loss, hematemesis, hematochezia, hepatorenal syndrome, hepatotoxicity, hirsutism, hyperpigmentation, hypokalemia, increased eyelash thickness, increased growth in number of eyelashes, keratitis, melena, misdirected growth of eyelashes, myopathy (in combination with statin therapy), ocular inflammation, peptic ulcer, rhabdomyolysis (in combination with statin therapy), skin photosensitivity, skin rash (acneiform; sparing prior radiation field), Stevens-Johnson syndrome, toxic epidermal necrolysis, tympanic membrane perforation, uveitis

Contraindications

There are no contraindications listed in the manufacturer's US labeling.

Canadian labeling: Hypersensitivity to erlotinib or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

• Cardiovascular events: Cerebrovascular accidents, MI, and myocardial ischemia have been reported (some fatal).

• Dermatologic toxicity: Bullous, blistering, and/or exfoliating skin conditions, some suggestive of Stevens-Johnson or toxic epidermal necrolysis (TEN), have been reported (some fatal). An acne-like rash commonly appears on the face, back, and upper chest. Generalized or severe acneiform, erythematous or maculopapular rash may occur. Skin rash may correlate with treatment response and prolonged survival (Saif 2008); management of skin rashes that are not serious should include alcohol-free lotions, topical antibiotics, or topical corticosteroids, or if necessary, oral antibiotics and systemic corticosteroids; avoid sunlight. Reduce dose or temporarily interrupt treatment for severe skin reactions; discontinue treatment for bullous, blistering, or exfoliative skin toxicity.

• Gastrointestinal (GI) perforation: GI perforation (including fatalities) has been reported; risk for perforation is increased with concurrent anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane based-chemotherapy, and patients with history of peptic ulcers or diverticular disease. Permanently discontinue in patients who develop perforation.

• Hematologic effects: Microangiopathic hemolytic anemia (MAHA) with thrombocytopenia has been reported (rarely) with erlotinib in combination with gemcitabine.

• Hemorrhage: Elevated INR and bleeding events (including fatal hemorrhage) have been reported

when erlotinib was administered concomitantly with warfarin; monitor prothrombin time and INR closely.

• Hepatotoxicity: Hepatic failure and hepatorenal syndrome have been reported (some fatal), particularly in patients with baseline hepatic impairment (although have also been observed in patients with normal hepatic function). Monitor liver function (transaminases, bilirubin, and alkaline phosphatase); patients with any hepatic impairment (total bilirubin >ULN; Child-Pugh class A, B, or C) should be closely and more frequently monitored, including those with hepatic disease due to tumor burden. Increased monitoring of liver function is required in patients with preexisting hepatic impairment or biliary obstruction. Dosage reduction, interruption, or discontinuation may be necessary for changes in hepatic function. Use with extreme caution in patients with total bilirubin >3 times ULN. Interrupt therapy if total bilirubin is >3 times ULN or transaminases are >5 times ULN in patients without preexisting hepatic impairment. In patients with baseline hepatic dysfunction or biliary obstruction, interrupt therapy if bilirubin doubles or transaminases triple from baseline values.

• Ocular toxicity: Corneal perforation and ulceration have been reported; decreased tear production, abnormal eyelash growth, keratoconjunctivitis sicca, or keratitis have also been reported and are known risk factors for corneal ulceration/perforation. Interrupt or discontinue treatment in patients presenting with eye pain or other acute or worsening ocular symptoms. Consider a baseline ophthalmologic exam and reassess for ocular toxicities at 4 to 8 weeks after treatment initiation (Renouf 2012).

• Pulmonary toxicity: Rare, sometimes fatal, interstitial lung disease (ILD) has occurred; symptoms include acute respiratory distress syndrome, interstitial pneumonia, obliterative bronchiolitis, pneumonitis (including radiation and hypersensitivity), pulmonary fibrosis, and pulmonary infiltrates. The onset of symptoms has been within 5 days to more than 9 months after treatment initiation (median: 39 days). Interrupt treatment for unexplained new or worsening pulmonary symptoms (dyspnea, cough, and fever); permanently discontinue for confirmed ILD.

• Renal impairment: Acute renal failure (some fatal), renal insufficiency, and hepatorenal syndrome have been reported, either secondary to hepatic impairment at baseline or due to severe dehydration; use with caution in patients with or at risk for renal impairment. Monitor closely for dehydration; monitor renal function and electrolytes in patients at risk for dehydration. If severe renal impairment develops, interrupt therapy until toxicity resolves.

Disease-related concerns:

• NSCLC: Some factors which correlate positively with response to EGFR-tyrosine kinase inhibitor (TKI) therapy in NSCLC include patients who have never smoked, EGFR mutation, and patients of Asian origin. EGFR mutations, specifically exon 19 deletions and exon 21 mutation (L858R), are associated with better response to erlotinib in patients with NSCLC (Riely 2006). Erlotinib treatment is not recommended in patients with NSCLC with *K-ras* mutations; they are not likely to benefit from erlotinib treatment (Eberhard 2005; Miller 2008). *K-ras* mutations correlated with poorer outcome with EGFR-TKI therapy in patients with NSCLC (Jackman 2009; Masarelli 2007; Shepherd 2005). The cobas EGFR mutation test has been approved to detect EGFR mutation for NSCLC treatment.

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

• Drugs affecting gastric pH: Avoid concomitant use with proton pump inhibitors. If taken with an H_2-receptor antagonist (eg, ranitidine), administer erlotinib 10 hours after the H_2-receptor antagonist dose and at least 2 hours prior to the next H_2-receptor dose. If an antacid is necessary, separate dosing by several hours.

Special populations:

• Smokers: Erlotinib levels may be lower in patients who smoke; advise patients to stop smoking. Smokers treated with 300 mg/day exhibited steady-state erlotinib levels comparable to former- and never-smokers receiving 150 mg/day (Hughes 2009).

Other warnings/precautions:

• Appropriate use: Concurrent erlotinib plus platinum-based chemotherapy is not recommended for treatment of locally-advanced or metastatic NSCLC due to a lack of clinical benefit. Treatment in patients with metastatic NSCLC with EGFR mutations other than exon 19 deletion or exon 21 (L858R) substitution has not been evaluated. Select patients for metastatic NSCLC treatment based on EGFR exon 19 deletions and exon 21 mutation (L858R) in tumor or plasma specimens; if these mutations are not detected in plasma specimen, tumor tissue (if available) may be tested.

• Lactose intolerance: Product may contain lactose; avoid use in patients with Lapp lactase deficiency, glucose-galactose malabsorption, or glucose intolerance.

Metabolism/Transport Effects

Substrate of CYP1A2 (minor), CYP3A4 (major); **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential; **Inhibits** UGT1A1

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Antacids: May decrease the serum concentration of Erlotinib. Management: Separate the administration of erlotinib and any antacid by several hours in order to minimize the risk of a significant interaction. *Risk D: Consider therapy modification*

Aprepitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Bosentan: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Ciprofloxacin (Systemic): May increase the serum concentration of Erlotinib. Management: Avoid use of this combination when possible. When the combination must be used, monitor the patient closely for the development of severe adverse reactions, and if such severe reactions occur, reduce the erlotinib dose (in 50 mg decrements). *Risk D: Consider therapy modification*

Conivaptan: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

CYP3A4 Inducers (Moderate): May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May decrease the serum concentration of Erlotinib. Management: Avoid combination if possible. If combination must be used, increase erlotinib dose by 50 mg increments every 2 weeks as tolerated, to a maximum of 450 mg/day. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of Erlotinib. Management: Avoid use of this combination when possible. When the combination must be used, monitor the patient closely for the development of severe adverse reactions, and if such severe reactions occur, reduce the erlotinib dose (in 50 mg decrements). *Risk D: Consider therapy modification*

Dabrafenib: May decrease the serum concentration of CYP3A4 Substrates. Management: Seek alternatives to the CYP3A4 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Enzalutamide: May decrease the serum concentration of CYP3A4 Substrates. Management: Concurrent use of enzalutamide with CYP3A4 substrates that have a narrow therapeutic index should be avoided. Use of enzalutamide and any other CYP3A4 substrate should be performed with caution and close monitoring. *Risk D: Consider therapy modification*

FluvoxaMINE: May increase the serum concentration of Erlotinib. Management: Avoid use of this combination when possible. When the combination must be used, monitor the patient closely for the development of severe adverse reactions, and if such severe reactions occur, reduce the erlotinib dose (in 50 mg decrements). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Fosphenytoin-Phenytoin: Erlotinib may increase the serum concentration of Fosphenytoin-Phenytoin. Fosphenytoin-Phenytoin may decrease the serum concentration of Erlotinib. Management: Avoid use of erlotinib with phenytoin when possible. If required, increase erlotinib dose by 50 mg increments at 2 week intervals, as tolerated, to a max of 450 mg/day. *Risk X: Avoid combination*

Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

Grapefruit Juice: May increase the serum concentration of Erlotinib. Management: Avoid use of this combination when possible. When the combination must be used, monitor the patient closely for the development of severe adverse reactions, and if such severe reactions occur, reduce the erlotinib dose (in 50 mg decrements). *Risk D: Consider therapy modification*

H2-Antagonists: May decrease the serum concentration of Erlotinib. Management: Avoid H2-antagonists in patients receiving erlotinib when possible. If concomitant treatment cannot be avoided, erlotinib should be dosed once daily, 10 hours after and at least 2 hours before H2-antagonist dosing. *Risk D: Consider therapy modification*

Idelalisib: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

Irinotecan Products: UGT1A1 Inhibitors may increase serum concentrations of the active metabolite(s) of Irinotecan Products. Specifically, concentrations of SN-38 may be increased. UGT1A1 Inhibitors may increase the serum concentration of Irinotecan Products. *Risk X: Avoid combination*

Leflunomide: May decrease the serum concentration of Erlotinib. Management: Avoid the concomitant use of erlotinib and leflunomide if possible. If concomitant use is unavoidable, increase the erlotinib dose by 50 mg increments at 2-week intervals to a maximum of 300 mg. *Risk D: Consider therapy modification*

MiFEPRIStone: May increase the serum concentration of CYP3A4 Substrates. Management: Minimize doses of CYP3A4 substrates, and monitor for increased concentrations/toxicity, during and 2 weeks following treatment with mifepristone. Avoid cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus. *Risk D: Consider therapy modification*

Mitotane: May decrease the serum concentration of CYP3A4 Substrates. Management: Doses of CYP3A4 substrates may need to be adjusted substantially when used in patients being treated with mitotane. *Risk D: Consider therapy modification*

Netupitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Palbociclib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Proton Pump Inhibitors: May decrease the serum concentration of Erlotinib. *Risk X: Avoid combination*

Sarilumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Siltuximab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Simeprevir: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

St John's Wort: May decrease the serum concentration of Erlotinib. Management: Avoid combination if possible. If combination must be used, increase erlotinib dose by 50 mg increments every 2 weeks as tolerated, to a maximum of 450 mg/day. *Risk D: Consider therapy modification*

Stiripentol: May increase the serum concentration of CYP3A4 Substrates. Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided due to the increased risk for adverse effects and toxicity. Any CYP3A4 substrate used with stiripentol requires closer monitoring. *Risk D: Consider therapy modification*

Teriflunomide: May decrease the serum concentration of Erlotinib. Management: Avoid the concomitant use of erlotinib and teriflunomide if possible. If concomitant use is unavoidable, increase the erlotinib dose by 50 mg increments at 2-week intervals to a maximum of 300 mg. *Risk D: Consider therapy modification*

Tocilizumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Warfarin: Erlotinib may increase the serum concentration of Warfarin. *Risk C: Monitor therapy*

Food Interactions Erlotinib bioavailability is increased with food. Grapefruit or grapefruit juice may decrease metabolism and increase erlotinib plasma concentrations. Management: Take on an empty stomach at least 1 hour before or 2 hours after the ingestion of food. Avoid grapefruit and grapefruit juice. Maintain adequate nutrition and hydration, unless instructed to restrict fluid intake.

Pregnancy Implications Adverse events were observed in animal reproduction studies. Erlotinib crosses the placenta (Ji 2015; Jovelet 2015). Information related to the use of erlotinib in pregnancy is limited (Ji 2015; Rivas 2012; Zambelli 2008). Based on the mechanism of action, erlotinib may cause fetal harm if administered in pregnancy. Advise females of reproductive potential to use effective contraception during

treatment and for at least 1 month after the last erlotinib dose.

Breast-Feeding Considerations It is not known if erlotinib is excreted in breast milk. Due to the potential for serious adverse reactions in the nursing infant (including bullous and exfoliative skin disorders, diarrhea, hepatotoxicity, interstitial lung disease, microangiopathic hemolytic anemia with thrombocytopenia, and ocular disorders) lactating women should not breastfeed during treatment and for 2 weeks after the final erlotinib dose.

Dietary Considerations Avoid grapefruit and grapefruit juice.

Monitoring Parameters

Liver function tests (transaminases, bilirubin, and alkaline phosphatase [periodic], monitor more frequently with worsening liver function); renal function tests (periodic) and serum electrolytes (in patients at risk for dehydration; periodic); prothrombin time and INR (in patients on concomitant warfarin therapy); EGFR mutation status in patients with NSCLC adenocarcinoma (Keedy 2011); the cobas EGFR mutation test has been approved to detect EGFR mutation for first-line NSCLC treatment, smoking status.

Consider a baseline ophthalmologic exam and reassess for ocular toxicities at 4 to 8 weeks after treatment initiation (Renouf 2012). Monitor hydration status; monitor for signs/symptoms of pulmonary toxicity, dermatologic toxicity, and ocular toxicity.

Mechanism of Action Reversibly inhibits overall epidermal growth factor receptor (HER1/EGFR) - tyrosine kinase activity. Intracellular phosphorylation is inhibited which prevents further downstream signaling, resulting in cell death. Erlotinib has higher binding affinity for EGFR exon 19 deletion or exon 21 L858R mutations than for the wild type receptor.

Pharmacodynamics/Kinetics

Absorption: Oral: ~60% on an empty stomach; food increases to ~100%

Distribution: 232 L

Protein binding: 93% to albumin and $alpha_1$-acid glycoprotein

Metabolism: Hepatic, via CYP3A4 (major), CYP1A1 (minor), CYP1A2 (minor), and CYP1C (minor)

Bioavailability: ~100% when given with food; ~60% without food

Half-life elimination: 36.2 hours

Time to peak, plasma: 4 hours

Excretion: Primarily as metabolites: Feces (83%; 1% as unchanged drug); urine (8%; <1% as unchanged drug)

Pricing: US

Tablets (Tarceva Oral)

25 mg (30): $3022.66

100 mg (30): $8302.25

150 mg (30): $9390.44

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names Birlotib (LK); Erlonix (BD); Erlotec (LK); Etopul (VN); Orlicert (BD); Tarcenib (BD); Tarceva (AE, AR, AT, AU, BE, BG, BH, BR, CH, CL, CN, CO, CR, CU, CY, CZ, DE, DK, DO, EC, EE, ES, FI, FR, GB, GR, GT, HK, HN, HR, HU, IE, IL, IS, IT, JO, JP, KR, KW, LB, LK, LT, LU, LV, MT, MX, MY, NI, NL, NO, NZ, PA, PE, PH, PL, PT, PY, QA, RO, RU, SE, SG, SI, SK, SV, TH, TR, TW, UY, VN); Tartseva (UA)

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