Osimertinib: Drug information

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

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

Brand Names: US

Tagrisso

Brand Names: Canada

Tagrisso

Pharmacologic Category

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

Dosing: Adult

Note: Confirm tumor T790M EGFR mutation status prior to treatment initiation (in the absence of tumor biopsy, a plasma specimen may be utilized).

Non-small cell lung cancer, metastatic (T790M EGFR mutation-positive): Oral: 80 mg once daily until disease progression or unacceptable toxicity (Janne 2015; Mok 2017)

Missed doses: If a dose is missed, do not make up the missed dose, take the next dose as scheduled.

Dosage adjustment for concomitant strong CYP3A4 inducers: Avoid concomitant use. If coadministration with a strong CYP3A4 inducer cannot be avoided, increase osimertinib dose to 160 mg once daily. Reduce osimertinib dose to 80 mg once daily 3 weeks after discontinuation of the strong CYP3A4 inducer.

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

Note: Renal function may be estimated using the Cockcroft Gault formula.

CrCl 15 to 89 mL/minute: No dosage adjustment necessary.

End-stage renal disease (ESRD): There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

Dosing: Hepatic Impairment

Mild (total bilirubin ≤ULN and AST >ULN **or** total bilirubin 1 to 1.5 times ULN and any AST) or moderate (total bilirubin 1.5 to 3 times ULN and any AST) impairment: No dosage adjustment necessary.

Severe impairment (total bilirubin 3 to 10 times ULN and any AST): There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

Dosing: Adjustment for Toxicity

Cardiotoxicity:

QTc interval >500 msec on at least 2 separate ECGs: Withhold treatment until QTc interval is <481 msec or recovers to baseline (if baseline QTc ≥481 msec) and then resume at a dose of 40 mg once daily.

QTc interval prolongation with signs/symptoms of life-threatening arrhythmia: Permanently discontinue.

Symptomatic heart failure or asymptomatic left ventricular dysfunction that persists for 4 weeks or longer: Permanently discontinue.

Pulmonary toxicity: Interstitial lung disease/pneumonitis: Permanently discontinue.

Other toxicities: Grade 3 or higher adverse reaction: Withhold treatment for up to 3 weeks. If improves to grade 2 or lower within 3 weeks, resume at either 80 mg once daily or 40 mg once daily. If not improved within 3 weeks, permanently discontinue.

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

Tablet, Oral:

Tagrisso: 40 mg, 80 mg

Generic Equivalent Available (US) No

Prescribing and Access Restrictions Available through specialty pharmacies and distributors. Further information may be obtained from the manufacturer, Astra Zeneca, at 1-844-275-2360 or at https://www.tagrisso.com.

Administration Oral: May be administered with or without food.

For patients who have difficulty swallowing tablets, disperse tablet in 60 mL of noncarbonated water (only), stir until tablet is dispersed into small pieces (will not dissolve completely) and immediately swallow. Rinse container with 120 to 240 mL of water and immediately drink. For nasogastric administration, disperse the tablet in 15 mL of noncarbonated water; use an additional 15 mL of water to transfer residue to the syringe. Administer the 30 mL of liquid via the nasogastric tube and flush appropriately (with ~30 mL of water). Do not crush, heat, or ultrasonicate during preparation.

Hazardous Drugs Handling Considerations

Hazardous agent (meets NIOSH 2016 criteria). This medication is not on the NIOSH (2016) list; however, it meets the criteria for a hazardous drug. Drugs are classified as hazardous based on their properties; the properties of a hazardous drug include one or more of the following characteristics: carcinogenic, teratogenic (or other developmental toxicity), reproductive toxicity, organotoxic at low doses, genotoxic, and/or new agents with structural or toxicity profiles similar to existing hazardous agents.

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 (NIOSH 2016). 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 epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an approved test, in patients who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy

Medication Safety Issues

Sound-alike/look-alike issues:

Osimertinib may be confused with olaparib, ospemifene.

Tagrisso may be confused with Targretin, Tasigna.

High-alert medication:

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

Adverse Reactions

>10%:

Central nervous system: Fatigue (14%), headache (10%)

Dermatologic: Skin rash (41%, including erythematous rash, macular rash, maculopapular rash, papular rash, pustular rash, erythema, folliculitis, acne vulgaris, dermatitis, dermatitis acneiform), xeroderma (31%), nail disease (25%), pruritus (14%)

Endocrine & metabolic: Hyponatremia (26%), hypermagnesemia (20%)

Gastrointestinal: Diarrhea (42%), nausea (17%), decreased appetite (16%), constipation (15%), stomatitis (12%)

Hematologic & oncologic: Lymphocytopenia (63%, grades 3/4: 3%), thrombocytopenia (54%, grades 3/4: 1%), anemia (44%, grades 3/4: <1%), neutropenia (33%, grades 3/4: 3%)

Neuromuscular & skeletal: Back pain (13%)

Ophthalmic: Eye disorder (19%, including dry eyes, blurred vision, keratitis, cataract, eye irritation, blepharitis, eye pain, increased lacrimation, vitreous floaters, <1% other ocular toxicity)

Respiratory: Cough (14%)

1% to 10%:

Cardiovascular: Venous thromboembolism (7%, including deep vein thrombosis, internal jugular thrombosis), cerebrovascular accident (3%), prolonged Q-T interval on EKG (≤3%; prolonged from baseline), pulmonary embolism (≤2%), reduced ejection fraction (<2%), cardiomyopathy (≤1%)

Respiratory: Pneumonia (≤4%; grade 3/4: 2%), interstitial pneumonitis (3%)

Contraindications

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

Canadian labeling: Additional contraindications (not in US labeling): Hypersensitivity to osimertinib or any component of the formulation.

Warnings/Precautions

Concerns related to adverse effects:

• Bone marrow suppression: Lymphopenia, thrombocytopenia, neutropenia, and anemia may occur (usually grades 1 and 2) with osimertinib.

• Cardiovascular toxicity: Cardiomyopathy (cardiac failure, congestive heart failure, pulmonary edema, decreased ejection fraction, or stress cardiomyopathy) has been observed; some events were fatal. In patients who had baseline and at least one follow up assessment, a left ventricular ejection fraction (LVEF) decline of ≥10% and a drop to below 50% was noted. Assess LVEF prior to treatment, while on treatment in patients with cardiac risk factors, and in patients who develop cardiac signs/symptoms during treatment. Permanently discontinue for symptomatic heart failure or persistent, asymptomatic left ventricular dysfunction that does not resolve within 4 weeks. Prolongation of the QTc interval may occur; QTc >500 msec and an increase from baseline of >60 msec have been reported, although no QTc-related arrhythmias have been reported. Patients with a baseline QTc of ≥470 were excluded from clinical trials. Monitor ECG and electrolytes periodically in patients with a history of congenital long QTc syndrome, heart failure, electrolyte abnormalities, and/or those taking concurrent medications known to prolong the QTc interval. Permanently discontinue in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia.

• Dermatologic toxicity: Skin reactions, including rash, dry skin, and itching may occur. Nail toxicity may also occur.

• Fertility effects: Osimertinib may impair fertility; effects may be reversible in females.

• Gastrointestinal toxicity: Diarrhea (usually grades 1 and 2) was observed in almost half the patients receiving osimertinib.

• Ocular toxicity: Keratitis has been reported (rarely) in clinical trials. Promptly refer patients for ophthalmologic evaluation if signs/symptoms of keratitis (eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) develop.

• Pulmonary toxicity: Interstitial lung disease (ILD) and pneumonitis was observed in clinical studies; some events were fatal. Withhold treatment with worsening respiratory symptoms (dyspnea, cough, fever) which may be indicative of ILD; permanently discontinue if ILD is confirmed.

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.

Other warnings/precautions:

• Appropriate use: Confirm the presence of a T790M epidermal growth factor receptor (EGFR) mutation in tumor sample or plasma specimen prior to treatment initiation. Mutation status should be determined from tumor sample; if tumor was not biopsied, a plasma sample may be used. Circulating tumor cells from plasma sample may be used as a surrogate marker for detection of T790M in tumor tissue (Remon 2017). If mutation is not detected in plasma sample, re-evaluate the feasibility of tumor biopsy for tissue testing. Information on diagnostic tests approved for detection of T790M mutations may be found at www.fda.gov/companiondiagnostics.

Metabolism/Transport Effects

Substrate of BCRP, CYP3A4 (major), P-glycoprotein; **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential; **Inhibits** BCRP

Drug Interactions

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

BCG (Intravesical): Immunosuppressants may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCG (Intravesical): Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCRP/ABCG2 Substrates: Osimertinib may increase the serum concentration of BCRP/ABCG2 Substrates. *Risk C: Monitor therapy*

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

Coccidioides immitis Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioides immitis Skin Test. *Risk C: Monitor therapy*

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

CYP3A4 Inducers (Strong): May decrease the serum concentration of Osimertinib. *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*

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

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. *Risk C: Monitor therapy*

Dipyrone: May enhance the adverse/toxic effect of Myelosuppressive Agents. Specifically, the risk for agranulocytosis and pancytopenia may be increased *Risk X: Avoid combination*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

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*

Fingolimod: Immunosuppressants may enhance the immunosuppressive effect of Fingolimod. Management: Avoid the concomitant use of fingolimod and other immunosuppressants when possible. If combined, monitor patients closely for additive immunosuppressant effects (eg, infections). *Risk D: Consider therapy modification*

Highest Risk QTc-Prolonging Agents: Moderate Risk QTc-Prolonging Agents may enhance the QTc-prolonging effect of Highest Risk QTc-Prolonging Agents. *Risk X: Avoid combination*

Hydroxychloroquine: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk X: Avoid combination*

Ivabradine: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk X: Avoid combination*

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. *Risk D: Consider therapy modification*

MiFEPRIStone: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk X: Avoid combination*

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*

Moderate Risk QTc-Prolonging Agents: May enhance the QTc-prolonging effect of other Moderate Risk QTc-Prolonging Agents. Management: Avoid such combinations when possible. Use should be accompanied by close monitoring for evidence of QT prolongation or other alterations of cardiac rhythm. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Nivolumab: Immunosuppressants may diminish the therapeutic effect of Nivolumab. *Risk D: Consider therapy modification*

Ocrelizumab: May enhance the immunosuppressive effect of Immunosuppressants. *Risk C: Monitor*

therapy

PAZOPanib: BCRP/ABCG2 Inhibitors may increase the serum concentration of PAZOPanib. *Risk X: Avoid combination*

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Probucol: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk X: Avoid combination*

Promazine: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk X: Avoid combination*

QTc-Prolonging Agents (Indeterminate Risk and Risk Modifying): May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk C: Monitor therapy*

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. *Risk D: Consider therapy modification*

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*

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. *Risk C: Monitor therapy*

St John's Wort: May decrease the serum concentration of Osimertinib. *Risk X: Avoid combination*

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Tertomotide: Immunosuppressants may diminish the therapeutic effect of Tertomotide. *Risk C: Monitor therapy*

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

Tofacitinib: Immunosuppressants may enhance the immunosuppressive effect of Tofacitinib. Management: Concurrent use with antirheumatic doses of methotrexate or nonbiologic disease modifying antirheumatic drugs (DMARDs) is permitted, and this warning seems particularly focused on more potent immunosuppressants. *Risk X: Avoid combination*

Topotecan: BCRP/ABCG2 Inhibitors may increase the serum concentration of Topotecan. *Risk D: Consider therapy modification*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at

least 3 months after immunosuppressants. *Risk X: Avoid combination*

Vinflunine: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk X: Avoid combination*

Xipamide: May enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk C: Monitor therapy*

Pregnancy Implications Based on data from animal reproduction studies and the mechanism of action, use during pregnancy is expected to cause fetal harm. Women of reproductive potential should use effective contraception during therapy and for 6 weeks after the last dose. Males with female partners of reproductive potential should also use effective contraception during therapy and for 4 months after the last dose.

Breast-Feeding Considerations It is not known if osimertinib is present in breast milk. Because of the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended by the manufacturer during therapy and for 2 weeks after the last dose.

Monitoring Parameters T790M epidermal growth factor receptor (EGFR) mutation status (prior to treatment). Monitor ECG and electrolytes periodically (in patients with a history of congenital long QTc syndrome, heart failure, electrolyte abnormalities, and/or those taking concurrent medications known to prolong the QTc interval). Assess LVEF prior to treatment, and while on treatment in patients with cardiac risk factors, and assess in patients who develop cardiac signs/symptoms. Monitor for signs/symptoms of interstitial lung disease or pneumonitis, dermatologic, and gastrointestinal toxicity.

Mechanism of Action Osimertinib is an irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor which binds to select mutant forms of EGFR, including T790M, L858R, and exon 19 deletion at lower concentrations than wild-type. Osimertinib exhibits less activity against wild-type EGFR (as compared to other EGFR inhibitors) and is selective for sensitizing mutations and the T790M resistance mutation, which is the most common mechanism of resistance to EGFR tyrosine kinase inhibitors (Janne 2015).

Pharmacodynamics/Kinetics

Distribution: V_{ss}/F: 997 L

Protein binding: Binding is likely high

Metabolism: Hepatic; predominantly oxidation (via CYP3A) and dealkylation to 2 active metabolites (AZ7550 and AZ5104)

Bioavailability: AUC is increased by 19% with a high-fat, high-calorie meal

Half-life, elimination: Mean (estimated): 48 hours

Time to peak: Median: 6 hours (range: 3 to 24 hours)

Excretion: Feces (68%; ~2% as unchanged drug); Urine (14%; ~2% as unchanged drug)

Pricing: US

Tablets (Tagrisso Oral)

40 mg (30): $17028.90

80 mg (30): $17028.90

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

Tagrisso (AT, CZ, DE, DK, EE, FR, GB, HK, HR, IL, JP, KR, LT, NO, PT, RO, SI, SK)

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