# DRUG NAME: Osimertinib

**SYNONYM(S):** AZD9291[1], osimertinib mesylate[2]

**COMMON TRADE NAME(S):** TAGRISSO®

**CLASSIFICATION:** molecular targeted therapy

*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.*

## MECHANISM OF ACTION:

Osimertinib is a third-generation, oral, irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor. Osimertinib exhibits a nine-fold greater affinity for select EGFR-sensitizing and T790M-resistance mutations than to wild-type EGFR. *In vitro*, osimertinib inhibits the activity of HER2, HER3, HER4, ACK1, and BLK. Compared to first- and second-generation EGFR tyrosine kinase inhibitors, osimertinib's selectivity for mutated EGFR may enhance its effectiveness, while minimizing its toxicities.[2-4]

## PHARMACOKINETICS:

| | | |
|---|---|---|
| Oral Absorption | median time to peak concentration ~6 h (range 3-24 h), steady state ~15 days; bioavailability is not significantly affected by food | |
| Distribution | extensive tissue distribution | |
| | cross blood brain barrier? | yes[1,4] |
| | volume of distribution | 986 L |
| | plasma protein binding | predicted to be high based on physiochemical properties |
| Metabolism | hepatic; predominantly by CYP3A oxidation and dealkylation[3,5] | |
| | active metabolite(s) | AZ7550 (similar potency to osimertinib) and AZ5104 (higher potency against mutant and wild-type EGFR) |
| | inactive metabolite(s) | yes, unnamed |
| Excretion | primarily eliminated via the feces | |
| | urine | 14% (~2% unchanged) |
| | feces | 68% (~2% unchanged) |
| | terminal half life | 48 hours |
| | clearance | 14.2 L/h |

Adapted from standard reference[5] unless specified otherwise.

## USES:

***Primary uses:***

*Lung cancer, non-small cell

*Health Canada approved indication

***Other uses:***



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## SPECIAL PRECAUTIONS:

***Caution:***
- ***QT interval prolongation*** is reported; use caution in patients with congenital long QT syndrome or taking other medications known to prolong the QT interval or disrupt electrolyte levels[5]
- decreased ***left ventricular ejection fraction (LVEF)*** is reported; use caution in patients with cardiac risk factors and/or pre-existing conditions that may impair LVEF[5]

***Special populations:***
- patients 65 years and older may have a higher incidence of grade 3 and 4 adverse events compared to younger patients[5]
- Japanese patients may experience interstitial lung disease more frequently than other Asian or non-Asian patients[5]

***Carcinogenicity:*** no information found

***Mutagenicity:*** Not mutagenic in Ames test and in mammalian *in vitro* mutation test. Osimertinib is not clastogenic in mammalian *in vivo* chromosome tests.[6]

***Fertility:*** In animal studies, epithelial thinning in the uterus and vagina, anestrus, and corpora luteum degeneration were reported with an increased incidence following treatment; however, these effects appeared to be reversible. Osimertinib did not affect the female's ability to become pregnant, but caused early embryonic deaths. In males, degenerative changes occurred in the testes. Male fertility was reduced, as demonstrated by increased pre-implantation loss in untreated female subjects paired with treated males. It is unclear whether the reported effects on male fertility were reversible.[4,5]

***Pregnancy:*** In animal studies, embryolethality, reduced fetal growth, and neonatal death have been observed. Females of childbearing potential should use effective contraception during treatment and for two months after completing therapy. Male patients should use effective contraception during treatment and for four months after completing therapy.[5]

***Breastfeeding*** is not recommended during osimertinib treatment and for two weeks following the final dose, due to the potential secretion into breast milk.[4]

## SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[7,8]

| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| blood and lymphatic system/ febrile neutropenia | anemia (10%) |
| | leukopenia (3%) |
| | lymphopenia (1%) |
| | neutropenia (4%); usually grade 1 and 2, occurs early in treatment and appears to stabilize[3,5] |
| | thrombocytopenia (5%); occurs early in treatment and appears to stabilize |



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| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| cardiac (see paragraph following **Side Effects** table) | ***cardiomyopathy,*** including congestive heart failure, pulmonary edema (1-2%)[4,5] |
| | tachycardia (2%) |
| | palpitations (1%) |
| ear and labyrinth | tinnitus (2%) |
| | vertigo (1%) |
| eye (see paragraph following **Side Effects** table) | conjunctivitis (3%) |
| | ***keratitis*** (<1%) |
| | ***vision disorders*** including blepharitis, blurred vision, cataracts, irritation, increased lacrimation, dry eye (1-6%) |
| gastrointestinal | *emetogenic potential:* low[9] |
| | abdominal distension or pain (1-9%) |
| | constipation (15%, severe <1%) |
| | ***diarrhea*** (42%, severe 1%) |
| | dry mouth (5%) |
| | dyspepsia (2%) |
| | dysphagia (2%) |
| | gastroesophageal reflux disease (2%) |
| | nausea (17%, severe <1%) |
| | stomatitis (12%) |
| | vomiting (10%) |
| general disorders and administration site conditions | asthenia (8%) |
| | ***fatigue*** (14%, severe <1%) |
| | gait disturbance (2%) |
| | peripheral edema (8%) |
| | pyrexia (5%) |
| infections and infestations | bronchitis (2%) |
| | cystitis (2%) |
| | gastroenteritis (1%) |
| | herpes zoster (1%) |
| | influenza (2%) |
| | pharyngitis, nasopharyngitis (2-9%) |
| | pneumonia (3-4%) |
| | upper respiratory infection (2-7%) |
| | urinary tract infection (2-6%) |



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| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| investigations | alkaline phosphatase increase (3%) |
| | ALT increase (7%) |
| | AST increase (6%) |
| | bilirubin increase (2%) |
| | creatinine increase (3%) |
| | ***left ventricular ejection fraction decrease*** (2%); see paragraph following **Side Effects** table |
| | ***QT interval prolongation*** (3-4%, severe <1%); see paragraph following **Side Effects** table |
| | weight decrease (3%) |
| metabolism and nutrition | anorexia (16%, severe <1%) |
| | dehydration (2%) |
| | hyperglycemia (1%) |
| | hyperkalemia (2%) |
| | hypocalcemia (2%) |
| | hypokalemia (2%) |
| | hypomagnesemia (2%) |
| | hyponatremia (2%) |
| | hypophosphatemia (1%) |
| musculoskeletal and connective tissue | arthralgia (8%) |
| | back pain (13%, severe <1%) |
| | bone pain (2%) |
| | muscle spasm (6%) |
| | musculoskeletal pain including neck, chest, extremity pain (4-7%) |
| | myalgia (4%) |
| nervous system | cerebrovascular accident (<1%) |
| | dizziness (5%) |
| | dysgeusia (2%) |
| | headache (10%, severe <1%) |
| | intracranial hemorrhage (<1%) |
| | peripheral neuropathy (2%) |
| | tremor (1%) |
| psychiatric | depression, anxiety (1%) |
| | insomnia (7%) |
| renal and urinary | dysuria (2%) |
| | urinary frequency (4%) |

 

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| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| respiratory, thoracic and mediastinal | cough (14%, severe <1%) |
| | dysphonia (2%) |
| | dyspnea (8%) |
| | epistaxis (3%) |
| | hemoptysis (2%) |
| | hiccups (1%) |
| | ***interstitial lung disease/pneumonitis*** (1-4%, severe <1%)[4,5]; see paragraph following **Side Effects** table |
| | pneumothorax (2%) |
| skin and subcutaneous tissue (see paragraph following **Side Effects** table) | alopecia (3%) |
| | ***dry skin*** (31%) |
| | ***nail effects/paronychia*** (17-25%) |
| | night sweats (1%) |
| | palmar-plantar erythrodysesthesia syndrome (1%) |
| | pruritis (14%) |
| | ***rash***, including dermatitis acneiform, drug eruption, folliculitis, rash erythematous, maculo-papular (41%, severe <1%) |
| vascular | pulmonary embolism (4%) |
| | deep vein thrombosis (3%) |
| | hot flash (2%) |
| | hypertension (2%) |
| | hypotension (1%) |

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***Cardiomyopathy*** has been observed, including congestive heart failure, pulmonary edema, and decreased ejection fraction. Patients with known cardiac risk factors or patients who develop cardiac symptoms while on osimertinib require LVEF assessment. Hold osimertinib therapy in asymptomatic patients who experience an absolute decrease in LVEF of 10% from baseline or LVEF which falls below 50%. Consider permanently discontinuing osimertinib for symptomatic congestive heart failure or persistent, asymptomatic left ventricular dysfunction that does not resolve.[5]

Concentration-dependent ***QT interval prolongation*** is associated with osimertinib. Monitor ECG and correct electrolytes prior to starting osimertinib. Patients with a history of congenital long QT syndrome, heart failure, electrolyte abnormalities, and/or are receiving concurrent QT interval prolonging medication require monitoring throughout treatment. Interrupt treatment for QTc intervals of 500 ms or greater, and consider resuming at a reduced dose once the QTc interval is less than 481 ms or returns to baseline. If QT interval prolongation is accompanied by symptoms of life-threatening arrhythmia, permanently discontinue osimertinib.[5]

***Interstitial lung disease (ILD)*** and ***pneumonitis*** have been reported and are sometimes fatal. Median time to onset is 2.7 months. Withhold osimertinib and promptly investigate worsening respiratory symptoms indicative of ILD (e.g., dyspnea, cough, and fever). Permanently discontinue osimertinib if ILD is confirmed.[5]



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***Keratitis*** and other vision disorders such as conjunctivitis, blepharitis, and dry eye have been reported during osimertinib therapy. Median time to onset is 36 days. Contact lens use is an independent risk factor for ocular toxicity, including keratitis. Consider an ophthalmologic referral for patients who present with symptoms of keratitis including increased lacrimation, blurred vision, eye inflammation, pain, and/or red eye. Patients should promptly report any eye symptoms and exercise caution driving if they experience any visual disturbance.[4,5]

***Papulopustular rash*** is a common dermatologic toxicity associated with EGFR inhibitors. Erythematous papules and pustules erupt on the face, scalp, "v" shaped area of the chest, upper trunk, and less frequently on the extremities, lower back, abdomen, and buttocks.[10-12] Ultraviolet radiation may exacerbate skin eruptions and hyperpigmentation.[13] The rash is often pruritic and secondary bacterial infection may occur, further exacerbating cutaneous injury.[12,14,15] Because osimertinib is EGFR mutant selective, the adverse reactions related to osimertinib may be less severe than with previous generations of EGFR tyrosine kinase inhibitors, however management of these reactions remains the same. Pre-emptive skin care measures include moisturizing with a thick alcohol-free emollient, avoiding hot showers, minimizing sun exposure, and using broad-spectrum sunscreen.[13] Prophylactic treatment and prompt reactive intervention with topical/oral steroids and antibiotics may reduce the severity of skin reactions and help to maintain dose intensity.[12,16-18] However, the rash is clinically and histologically distinct from acne, and therefore, should not be treated with topical acne medication.[19] Severe rashes may require dose interruption or modification.[12,17]

***Paronychia*** occurs in 17% of patients treated with osimertinib. Paronychia typically occurs later in treatment (e.g., 4-8 weeks) and can cause severe pain. Preventative measures and good skin care may help to reduce the frequency and severity of paronychia. Suggest to:

- avoid trauma to nails or fingertips,
- avoid harsh chemicals such as soaps, detergents and nail products, and
- keep hands clean and dry.

Topical antiseptics, and/or steroids may be helpful for management of mild cases. For management of moderate to severe cases, systemic antibiotics, steroids, and silver nitrate applications may be used.[16,17]

## INTERACTIONS:

| AGENT | EFFECT | MECHANISM | MANAGEMENT |
|---|---|---|---|
| grapefruit juice | may increase plasma level of osimertinib | may inhibit CYP 3A4 metabolism of osimertinib in the intestinal wall | avoid grapefruit juice for 48 hours before and for duration of treatment[20] |
| itraconazole | osimertinib $C_{max}$ decreased by 20% and AUC increased by 24%[5,21] | strong inhibition of CYP 3A4 by itraconazole | no dose adjustment necessary; not considered clinically significant[5,21] |
| omeprazole | no clinically significant effect on osimertinib exposure[4] | reduced solubility of osimertinib with increasing pH | no action required[4] |
| rifampin | osimertinib $C_{max}$ decreased by 73% and AUC decreased by 78%[2] | strong induction of CYP 3A4 by rifampin | avoid concurrent use[5]; if unable to avoid, may consider increasing osimertinib dose to 160 mg daily[2,4] |
| rosuvastatin | rosuvastatin $C_{max}$ increased by 72% and AUC increased by 35%[22] | inhibition of BCRP by osimertinib | if unable to avoid, use lowest possible rosuvastatin dose and monitor for adverse effects of rosuvastatin[4,5] |
| simvastatin | no clinically significant effect on simvastatin pharmacokinetics[22] | inhibition of CYP 3A4 by osimertinib | no action required[4,22] |



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Concurrent therapy with drugs that prolong QT/QTc interval or disrupt electrolyte levels should be avoided if possible; periodic monitoring of ECG and electrolytes is suggested.[5]

Osimertinib is a substrate of CYP 3A4. Concurrent use with CYP 3A4 inducers may lead to reduced efficacy of osimertinib; avoid concurrent therapy. Osimertinib dose adjustments are not recommended when osimertinib is given concurrently with moderate or weak CYP 3A4 inducers.[4]

Osimertinib induces CYP 1A2 enzymes *in vitro*. Clinical significance is unknown.[4]

## SUPPLY AND STORAGE:

***Oral:*** AstraZeneca Canada Inc. supplies osimertinib as 40 mg and 80 mg tablets. Store at room temperature.[5]

***Additional information*[5]**:

- For patients who have difficulty swallowing, tablets may be dispersed in 50 mL of non-carbonated, room temperature water. Other liquids should not be used. Stir to disperse. Do not crush tablets or heat the solution to aid dispersion. Tablets will not completely dissolve. The resulting preparation should be consumed immediately. Following consumption of the dose, rinse the cup with 50 mL of water and consume the rinse solution immediately to ensure administration of the full dose.
- For nasogastric tube administration, follow the steps above but use a volume of 15 mL for initial dispersion plus 15 mL for the rinse and flush with water as appropriate. Complete administration within 30 minutes of the addition of tablets to water.

## DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Dosage may be reduced, delayed or discontinued in patients with toxicities.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

| | |
|---|---|
| *Oral:* | ***80 mg*** (range 40-80 mg) ***PO once daily***.[5]<br>May be taken with or without food.[5] |
| *Concurrent radiation:* | no information found |
| *Dosage in renal failure:* | CrCl >15 mL/min: no adjustment required[5]<br>CrCl <15 mL/min: no information found<br>calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$<br>* For males N=1.23; for females N=1.04 |
| *Dosage in hepatic failure:* | mild impairment: no adjustment required[5]<br>moderate/severe impairment: no information found |
| *Dosage in dialysis:* | no information found |



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***Children:*** safety and effectiveness not established[5]

## REFERENCES:


1. Bollinger MK, Agnew AS, Mascara GP. Osimertinib: A third-generation tyrosine kinase inhibitor for treatment of epidermal growth factor receptor-mutated non-small cell lung cancer with the acquired Thr790Met mutation. J Oncol Pharm Practice 2018;24(5):379-388.
2. AHFS Drug Information® (database on the Internet). Osimertinib mesylate. Lexi-Comp Inc., 8 March 2017. Available at: http://online.lexi.com. Accessed 4 September 2017.
3. Lexicomp Online® (database on the Internet). Osimertinib. Lexi-Comp Inc., 19 August 2017. Available at: http://online.lexi.com. Accessed 4 September 2017.
4. AstraZeneca Pharmaceuticals LP. TAGRISSO® full prescribing information. Wilmington, DE, USA; March 2017.
5. AstraZeneca Canada Inc. TAGRISSO® product monograph. Mississauga, Ontario; 6 July 2016.
6. FDA Medwatch. Pharmacology/Toxicology Review and Evaluation. Center for Drug Evaluation and Research (CDER): TAGRISSO® (osimertinib). FDA US Food and Drug Administration, June 2015. . Accessed 20 September 2017.
7. Chris Lee MD. BC Cancer Agency Lung Tumour Group. Personal communication. 30 October 2017.
8. Alysha Bharmal. Pharmacist. BC Cancer Agency Lung Tumour Group. Personal communication. 30 October 2017.
9. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 Mar 2012.
10. Hu JC, Sadeghi P, Pinter-Brown LC, et al. Cutaneous side effects of epidermal growth factor receptor inhibitors: Clinical presentation, pathogenesis, and management. J Am Acad Dermatol February 2007;56(2):317-326.
11. Payne AS, Savarese DMF. Cutaneous complications of molecularly targeted therapy and other biologic agents used for cancer therapy. In: 2017 UpToDate®; Basow,Denise S. (Ed); Waltham, Massachusetts: UpToDate®; Available at www.uptodate.com; updated 2Dec2016; accessed 1Feb2017.
12. Lacouture ME. Acneiform eruption secondary to epidermal growth factor receptor (EGFR) inhibitors. In: 2017 UpToDate®; Basow,Denise S. (Ed); Waltham, Massachusetts: UpToDate®; Available at www.uptodate.com; updated 7Dec2015; accessed 2Feb2017.
13. Balagula Y, Garbe C, Myskowski PL, et al. Clinical presentation and management of dermatological toxicities of epidermal growth factor receptor inhibitors. Int.J.Dermatol. 2011;50(2):129-146.
14. Melosky B, Burkes R, Rayson D, et al. Management of skin rash during EGFR-targeted monoclonal antibody treatment for gastrointestinal malignancies: Canadian recommendations. Curr Oncol 2009;16(1):16-26.
15. Baas JM, Krens LL, Guchelaar H-, et al. Recommendations on management of EGFR inhibitor-induced skin toxicity: A systematic review. Cancer Treat Rev 2012;38(5):505-514.
16. Lacouture ME, Anadkat MJ, Bensadoun RJ, et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer 2011;19:1079-1095.
17. Aw DC, Tan EH, Chin TM, et al. Management of epidermal growth factor receptor tyrosine kinase inhibitor-related cutaneous and gastrointestinal toxicities. Asia-Pac J Clin Oncol 2017:n/a-n/a.
18. Petrelli F, Borgonovo K, Cabiddu M, et al. Antibiotic prophylaxis for skin toxicity induced by anitepidermal growth factor receptor agents: a systemic review and meta-analysis. Br J Derm 2016;175:1166-1174.
19. Fabbrocini G, Panariello L, Caro G, et al. Acneiform rash induced by EGFR inhibitors: review of the literature and new insights. Skin Appendage Disord 2015;1(1):31-37.
20. Bailey DG. Compendium of Pharmaceuticals and Specialties. Drug Administration and Grapefruit. Ottawa: Canadian Pharmacists Association; 2017.
21. Vishwanathan K, Yang JC, Lee J, et al. Effect of itraconazole or rifampicin on the pharmacokinetics (PK) of osimertinib (AZD9291). J Clin Oncol 2016;34(15):e14100-e14100.
22. Harvey RD, Isambert N, Rafii S, et al. Effect of multiple-dose osimertinib (AZD9291) on the pharmacokinetics (PK) of simvastatin and rosuvastatin. J Clin Oncol 2016;34(15):e14098-e14098.




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