Drug Monograph

A - Drug Name

osimertinib

COMMON TRADE NAME(S): Tagrisso®

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B - Mechanism of Action and Pharmacokinetics

Osimertinib is an irreversible inhibitor of both Epidermal Growth Factor Receptor (EGFR) with activity in clinically relevant sensitizing mutations as well as T790M.

Absorption	Bioavailability	70%
	Peak plasma levels	median t_{max} of 6 (3-24) hours
	Effects with food	Food does not alter osimertinib bioavailability to a clinically significant extent. The drug may be taken with or without food.
	Time to reach steady state	15 days
Distribution	Extensive tissue distribution	
	PPB	94.7%
	Cross blood brain barrier?	Brain penetration and activity in the CNS have been observed in animal studies.

Metabolism	Main enzymes involved	CYP3A4 and CYP3A5
	Active metabolites	yes (10% of osimertinib exposure at steady state)
	Inactive metabolites	yes
Elimination	Feces	68% (~1% unchanged)
	Urine	14% (~1% unchanged)
	Half-life	44 hours

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C - Indications and Status

Health Canada Approvals:

- Non-small cell lung cancer

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

Extravasation Potential: Not applicable

The following table lists adverse effects that occurred in previously untreated patients, or previously treated patients (marked with #), in phase III trials treated with osimertinib. Adverse events from other trial data or severe / post-marketing events may also be included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Cardiotoxicity (3%)	E D
	QT interval prolonged (1%) (> 500 msec)	E
	Venous thromboembolism (1%)	E D
Dermatological	Dry skin (36%)	E
	Erythema multiforme (rare)	E
	Nail disorder (35%)	E D
	Rash, pruritus (58%) (1% severe)	E
	Stevens-Johnson syndrome (rare)	E
	Toxic epidermal necrolysis (rare)	E
Gastrointestinal	Anorexia (18%) #	E
	Constipation (14%) #	E
	Diarrhea (58%) (2% severe)	E
	Mucositis (31%)	E
	Nausea, vomiting (16%) #	E
General	Fatigue (16%) #	E
Hematological	Myelosuppression ± infection, bleeding (6%) (severe)	E
	Other - Aplastic anemia (rare)	E
Hepatobiliary	↑ LFTs (1%) (severe) #	E
Musculoskeletal	Musculoskeletal pain (10%) #	E
Nervous System	Headache (10%) #	E
Ophthalmic	Conjunctivitis (8%) # (related to ocular surface events)	E
	Keratitis (<1%)	E
Renal	Creatinine increased (9%)	E
Respiratory	Cough, dyspnea (17%) #	E
	Epistaxis (6%) #	E
	Other (bronchiolitis obliterans organizing pneumonia; rare)	E
	Pneumonitis (4%)	E D
Vascular	Vasculitis (cutaneous; rare)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for osimertinib include diarrhea, rash, pruritus, dry skin, nail disorder, mucositis, anorexia, cough, dyspnea, fatigue, nausea, vomiting and constipation.

Skin effects observed with osimertinib have mainly been mild in nature, including rash, dry skin pruritus and nail effects. Regular application of moisturizers to skin and nails, practice of good hand hygiene, and keeping hands dry help prevent and control skin and nail adverse effects. Rare, post-marketing case reports of erythema multiforme, toxic epidermal necrolysis, or non-fatal Stevens-Johnson syndrome have been reported with osimertinib.

QTc interval prolongation has been observed and may lead to an increased risk of ventricular arrhythmias, including Torsade de pointes, although no QT-associated arrhythmias were reported in clinical trials. A pharmacokinetic/ pharmacodynamic analysis with osimertinib predicted a concentration-dependent increase in QTc prolongation.

Left ventricular dysfunction has been reported. Across clinical trials, 3% of patients had decreases in LVEF ≥ 10% and drops in LVEF to below 50%. Three percent of patients reported cardiomyopathy events, including 1 case of fatal congestive heart failure.

Interstitial lung disease (ILD) and/or pneumonitis were reported in 4% of patients with a median onset of about 3 months, and may be fatal. Patients with a history of or active ILD, or those with radiation pneumonitis requiring steroids were excluded from clinical trials.

Ocular surface events (i.e. conjunctivitis, blepharitis and dry eye) were usually mild and rarely required dose modification. **Keratitis** has been rarely reported.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

A validated test is required to identify EGFR mutation-positive status prior to adjuvant or first-line locally advanced/metastatic NSCLC treatment.

A validated test is required to confirm EGFR T790M mutation-positive status prior to treatment of NSCLC that has progressed on or after EGFR TKI.

Electrolyte abnormalities should be corrected prior to treatment.

Adults:

Oral: 80 mg Daily

Dosage with Toxicity:

Dose Level	Osimertinib Dose (mg/day)
0	80
-1	40
-2	Discontinue

Toxicity	Dose Modification
ILD/pneumonitis	Hold and investigate. Discontinue permanently if confirmed.
Asymptomatic LVEF < 50% and absolute decrease of 10% from baseline	Hold for up to 4 weeks. If recovery to baseline, restart. If no recovery to baseline, discontinue permanently.
QTc interval > 500 msec on at least 2 separate ECGs	Hold until QTc interval is < 481 msec or recovery to baseline if baseline is ≥ 481 msec. Then restart at 1 dose level ↓.
QTc interval prolonged with signs/symptoms of serious arrhythmia (e.g. Torsade de pointes, polymorphic VT) OR Symptomatic congestive heart failure	Discontinue permanently.
Signs & symptoms suggestive of keratitis	Refer promptly to an ophthalmology specialist. For ≥ grade 3 toxicity, also refer to action below.
Signs and symptoms suggestive of aplastic anemia	Hold if suspected; discontinue if confirmed.
Signs and symptoms of Stevens-Johnson syndrome, Toxic epidermal necrolysis	Hold if suspected; discontinue if confirmed.
Signs and symptoms of erythema multiforme	Hold if suspected; consider discontinuing if confirmed. (Discontinue for erythema multiforme major.)

Other ≥ grade 3 toxicity	Hold for up to 3 weeks. If recovery to ≤ grade 2, restart at the same dose or at 1 dose level ↓. If no recovery, discontinue permanently.

Dosage with Hepatic Impairment:

Hepatic Impairment	Osimertinib Dose
Mild (total bilirubin ≤ ULN and AST > ULN OR total bilirubin 1-1.5 x ULN and any AST) or Moderate (total bilirubin 1.5 to 3 x ULN and any AST)	No dosage adjustment required.
Severe	No data; use with caution.

Dosage with Renal Impairment:

Renal Impairment (Creatinine Clearance)	Osimertinib Dose
Mild to moderate (30 to <60 mL/min)	No dosage adjustment required.
Severe (15 to < 30 mL/min)	No dosage adjustment required. Use with caution.
End-stage renal disease (<15 mL/min) or dialysis	No data.

Dosage in the elderly:

No dosage adjustment is required.

No overall differences in efficacy or predicted steady state exposure of osimertinib were observed between patients ≥ 65 years of age and younger patients.

Patients ≥ 65 years of age experienced more ≥ Grade 3 adverse reactions compared to younger patients and had more reported adverse reactions that led to drug dose interruptions or reductions.

Dosage based on ethnicity:

No dosage adjustment required due to ethnicity.

In clinical trials, the incidence of ILD was higher in Japanese patients compared to other Asian and non-Asian patients.

Children:

Safety and efficacy are not established in children under 18 years.

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F - Administration Guidelines

- Osimertinib may be taken orally with or without food at the same time each day.
- The tablet should be swallowed whole with water and not crushed, split or chewed.
- If a dose is missed, it may be taken within 12 hours. If there are less than 12 hours until the next dose, the missed dose should be skipped and the next dose should be taken at the scheduled time.
- If the patient has difficulty swallowing, the tablet may be dispersed in 50 ml of non-carbonated water (room temperature) and swallowed immediately. An additional 50 ml of water should be added to capture drug residue and immediately swallowed. No other liquids should be added.
- For nasogastric administration, the tablet may be dispersed in 15 mL of noncarbonated water; using an additional 15 mL of water for residue rinses. The 30 mL of liquid should be administered within 30 minutes via the nasogastric tube and flush appropriately as per the nasogastric tube manufacturer's instructions.
- Store tablets at room temperature (15-30^{o}C).

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G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or to ingredients in the formulation or component in the container

Other Warnings/Precautions:

- Not recommended in patients with congenital long QT syndrome or those taking other medications know to prolong QTc
- Patients at risk for prolonged QTc such as those with cardiac disease, history of arrhythmias, electrolyte disturbances or conditions leading to electrolyte disturbances, bradycardia, acute neurological events, diabetes mellitus and autonomic neuropathy should be monitored closely and electrolyte abnormalities corrected prior to treatment.
- Patients with abnormal LVEF, significant cardiac history, significant rhythm and conduction abnormalities, or resting QTc > 470 msec were excluded from clinical trials.
- Exercise caution in patients with cardiac risk factors and those with conditions that can affect LVEF.
- Patients with a history of ILD/pneumonitis, evidence of clinically active ILD or those with radiation pneumonitis requiring steroids were excluded from clinical trials.
- Ocular events have been reported. Contact lens use is a risk factor for ocular toxicity, including keratitis. Caution should be used when driving or operating machinery in patients who experience visual disturbances.

Other Drug Properties:

- Carcinogenicity: Unknown
  Carcinogenicity studies have not been performed.

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Fetotoxicity: Yes
  Osimertinib is not recommended for use in pregnancy.
  - Adequate contraception should be used by patients who can become pregnant and their partners during treatment, and for at least **2 months** after the last dose.
  - Adequate contraception should be used by patients who produce sperm and their partners during treatment, and for at least **4 months** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.
- Fertility effects: Documented in animals

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H - Interactions

Osimertinib is metabolized primarily by CYP3A4/5. It does not inhibit P-gp, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, MATE2K and OCT2.

Strong CYP3A4 inhibitors decreased the osimertinib maximum plasma concentration (Cmax) by approximately 20% and increased the area under the curve (AUC) by approximately 24%. Given the inter-patient variability of 46% in the osimertinib exposure in the population PK analysis, this change of 24% is not clinically significant.

Clinical pharmacokinetic interactions with CYP3A4 substrates are unlikely.

There are no interactions with gastric pH modifying agents.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Strong CYP3A4 inducers (i.e. phenytoin, rifampin, carbamazepine, St. John's Wort, etc)	↓ osimertinib concentration and/or efficacy (e.g. rifampin ↓ osimertinib exposure by 78%)	↑ metabolism of osimertinib	Avoid. If coadministration is unavoidable, closely monitor therapy and increase osimertinib dose to 160mg daily during concurrent use. Continue this dose for 3 weeks after discontinuation of the strong CYP3A4 inducer. Then, resume osimertinib dose at 80mg daily.
Moderate CYP3A4 inducers (i.e. bosentan, efavirenz, etravirine, phenobarbital, primidone)	↓ osimertinib concentration and/or efficacy	↑ metabolism of osimertinib	Monitor therapy if co-administered. No dose adjustments required.
BCRP and P-gp substrates (e.g. certain HMG-CoA reductase inhibitors, digoxin, fexofenadine, dabigatran)	↑ substrate concentration and/or toxicity	osimertinib is a competitive inhibitor of BCRP	Monitor closely when co-administered with substrates with narrow therapeutic indices.

Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	↑ risk of QT prolongation and arrhythmias	Additive	Avoid if possible; closely monitor if co-administered
Drugs that disrupt electrolyte levels (i.e. loop/thiazide diuretics, laxatives, amphotericin B, high dose corticosteroids)	↑ risk of QT prolongation and arrhythmias	Additive	Avoid if possible; closely monitor if co-administered

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline, at each visit, and as clinically indicated
Liver function tests	Baseline, at each visit, and as clinically indicated
Renal function tests	Baseline and at each visit; more frequent in patients with severe renal impairment
Electrolytes (calcium, potassium and magnesium), especially in patients at risk of electrolyte abnormalities	Baseline, at each visit, and as clinically indicated
ECG	Baseline and as clinically indicated
LVEF; in patients with cardiac risk factors or those who develop cardiac signs/symptoms during treatment	Baseline, during treatment* and as clinically indicated
Clinical toxicity assessment for GI, skin, and respiratory effects, signs and symptoms of CHF, thromboembolism and ocular effects	At each visit

*LVEF was monitored every 12 weeks while on treatment in some clinical trials

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- osimertinib - For the treatment of locally advanced (not amenable to curative therapies) or metastatic non-small cell lung cancer (NSCLC) according to clinical criteria
- osimertinib - For adjuvant therapy after tumour resection in patients with stage IB-IIIA (AJCC 7th edition, or equivalent) NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858 R) substitution mutations

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K - References

Lacouture ME, Sibaud V, Gerber PA, et al. Prevention and management of dermatological toxicities related to anticancer agents: ESMO Clinical Practice Guidelines. Ann Oncol 2021 Feb;32(2):157-70.

Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, et al.; AURA3 Investigators. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med. 2017 Feb 16;376(7):629-40.

Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2018 Jan 11;378(2):113-25.

Prescribing information: Tagrisso (osimertinib). AstraZeneca Pharmaceuticals (USA), May 2023.

Product monograph: Tagrisso (osimertinib). AstraZeneca Canada Ltd., March 2023.

Wu YL, Tsuboi M, He J, et al. Osimertinib in resected EGFR-mutated non-small-cell lung cancer. N Engl J Med . 2020 Oct 29;383(18):1711-23.

December 2023 Modified Adverse effects, Dose modifications, Special precautions, Pregnancy/lactation, Interactions, and Monitoring sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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