Drug Monograph

A - Drug Name

dacomitinb

COMMON TRADE NAME(S): Vizimpro™

back to top

B - Mechanism of Action and Pharmacokinetics

Dacomitinib is an irreversible, second generation inhibitor of EGFR-tyrosine kinase. Dacomitinib demonstrates activity against EGFR/HER1, HER2, HER4, and mutated EGFR with deletions in exon 19 or the L858R substitution in exon 21.

Absorption	Bioavailability	80%
	Effects with food	Administration with a high fat meal increased AUC by 14% and Cmax by 24%. Food has no clinically important effects.
	Peak plasma levels	5 to 6 hours (range: 2 to 24 hours)
	Time to reach steady state	14 days
Distribution	Dacomitinib has extensive distribution throughout the body.	
	PPB	~98%
Metabolism	Oxidation and glutathione conjugation are the major metabolic pathways. Formation of the active metabolite, O-desmethyl dacomitinib, is mostly via CYP2D6; CYP3A4 contributes to the formation of minor oxidative metabolites.	

Any use of the information is subject, at all times, to CCO's Terms and Conditions.

	Active metabolites	Yes
Elimination	Half-life	54 to 80 hours (plasma)
	Feces	79% (20% unchanged)
	Urine	3% (<1% unchanged)

back to top

C - Indications and Status

Health Canada Approvals:

- Non-small cell lung cancer (NSCLC)

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

back to top

D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

The following table lists adverse effects that occurred in ≥ 10% of patients in a Phase III study of unresectable locally advanced or metastatic NSCLC patients. It also includes severe and life-threatening adverse effects.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Dermatological	Alopecia (23%)	E
	Dry skin (30%)	E
	Hand-foot syndrome (15%) (severe 2%)	E
	Nail disorder (66%) (severe 8%)	D
	Rash, pruritus (77%) (severe 24%)	E D
Gastrointestinal	Anorexia, weight loss (31%) (severe 5%)	E D
	Diarrhea (87%) (severe 8%)	E

Any use of the information is subject, at all times, to CCO's Terms and Conditions.

	Mucositis (70%)	E
	Nausea, vomiting (19%)	E
General	Fatigue (13%)	E
Hepatobiliary	↑ LFTs (24%) (severe 1%)	E D
Metabolic / Endocrine	Abnormal electrolyte(s) (33%) (↓Mg, K, Na, or Ca, severe 7%)	E
Musculoskeletal	Musculoskeletal pain (12%)	E
Nervous System	Insomnia (11%)	E
Ophthalmic	Conjunctivitis (24%) (including keratitis, may be severe)	E D
Respiratory	Cough, dyspnea (21%)	E
	Interstitial lung disease (2%)	D

* "*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 dacomitinib include diarrhea, rash, pruritus, mucositis, nail disorder, abnormal electrolyte(s), anorexia, weight loss, dry skin, ↑ LFTs, conjunctivitis and alopecia.

Diarrhea has been reported in patients while taking dacomitinib. Serious cases were reported in 1.8% of patients; this was fatal in 0.3% of patients. The median onset was 1 week (2 weeks for worst episode). The median duration was 20 weeks (1 week for Grade ≥ 3). Diarrhea has been associated with acute renal insufficiency and severe electrolyte imbalance.

Increased transaminases have occurred with dacomitinib. The median onset was 12 weeks. The median duration was 12 weeks (1 week for Grade ≥ 3). Isolated reports of hepatotoxicity and hepatic failure, including 1 fatal outcome, have been reported.

Keratitis has occurred in 1.8% of patients with 0.3% of cases being serious. The median onset was 40 weeks. The median duration was 17 weeks (10 weeks for Grade ≥ 3).

Interstitial Lung Disease (ILD) and **pneumonitis** have been reported in patients receiving dacomitinib. The median onset was 16 weeks. The median duration was 21 weeks (3 weeks for Grade ≥ 3).

Severe rash and **exfoliative skin conditions**, including exfoliative rash, skin exfoliation, erythema multiforme and bullous dermatitis, have been reported. Rash and exfoliative skin reactions may be worse in areas with sun exposure; use of sunscreen and protective clothing is advised. The median onset of any rash and erythematous skin conditions was approximately 2 weeks (7 weeks onset of the worst episode). The median duration was 44 weeks (3 weeks for Grade ≥ 3). The median onset of any exfoliative skin conditions was 8 weeks (9 weeks onset of the worst episode). The median duration was 7 weeks (2 weeks for Grade ≥ 3).

Any use of the information is subject, at all times, to CCO's Terms and Conditions.

Paronychia has been reported in 60.7% of patients; Grade 3 paronychia occurred in 7.9% of patients. The median onset was 7 weeks (10 weeks onset to the worst episode). The median duration was 45 weeks (3 weeks for Grade ≥ 3). Topical antibiotics/antiseptics and/or steroid may be beneficial for mild cases. For moderate to severe paronychia, topical or systemic antibiotics and/or steroids as well as periodic silver nitrate application may be useful.

Hand-foot syndrome (HFS) has occurred in 15.2% of patients in clinical trials. The median onset was 4 weeks (6 weeks onset to the worst episode). The median duration was 15 weeks (2 weeks for Grade ≥ 3).

back to top

E - Dosing

Refer to protocol by which the patient is being treated.

Use only in patients with EGFR exon 19 deletion or exon 21 L858R substitution mutations confirmed using a validated test.

Use of sunscreen and protective clothing is advised for patients who are exposed to the sun.

Prophylactic treatment with doxycycline and a low-potency corticosteroid (e.g., aclometasone, hydrocortisone) may be beneficial in reducing the impact of dermatologic adverse events (Lacouture et al 2010, Lacouture et al 2016).

Start proactive management of diarrhea at the first sign of diarrhea, especially within the first 2 weeks of starting treatment, including adequate hydration combined with antidiarrheal medications; continue until bowel movements have stopped for 12 hours.

Adults:

Oral: 45 mg Daily

Dosage with Toxicity:

Dose Level	Dacomitinib Dose (mg/day)
0	45
-1	30
-2	15
-3	Discontinue

Any use of the information is subject, at all times, to CCO's Terms and Conditions.

Toxicity	Grade	Action
Diarrhea	Grade 1	Continue dose. Treat with anti-diarrheal medications (e.g., loperamide) and oral fluids.
	Grade 2	Continue dose. Treat with anti-diarrheal medications (e.g., loperamide) and oral fluids. If not improved to Grade ≤ 1 within 24 hours, hold dose. Then resume at same dose.* If recurs, hold dose. Then consider 1 dose level ↓.*
	Grade ≥ 3	Hold dose. Treat with anti-diarrheal medications (e.g., loperamide), oral / IV fluids, and / or electrolytes. Resume at 1 dose level ↓.*
Skin-related adverse reactions	Grade 1 or 2	Continue dose. Treat as clinically indicated (e.g. antibiotics, topical steroids, and/or emollients). If Grade 2 rash persists, hold dose. Then resume at the same dose level or at 1 dose level ↓.*
	Grade ≥ 3	Hold dose. Treat as clinically indicated (e.g. broad spectrum oral or intravenous antibiotics and topical steroids). Resume at 1 dose level ↓.*
Keratitis	Grade 2, 3 or 4	Hold dose. Refer patient to ophthalmologist. Resume at 1 dose level ↓.*
Other toxicity	Intolerable Grade 2	Hold dose. Resume at 1 dose level ↓.*
	Grade ≥ 3	Hold dose. Resume at 1 dose level ↓.*

Any use of the information is subject, at all times, to CCO's Terms and Conditions.

Interstitial Lung Disease (ILD)/Pneumonitis	Any	Hold dose if suspected. Discontinue if confirmed.

*Do not restart treatment until toxicity resolved to Grade ≤ 1; for other Grade ≥ 3 toxicity, treatment may be restarted if toxicity resolved to Grade ≤ 2.

Dosage with Hepatic Impairment:

No starting dose adjustments required when administering dacomitinib to patients with mild, moderate or severe hepatic impairment (Child-Pugh class A, B or C).

Dosage with Renal Impairment:

Renal Impairment	Dacomitinib Starting Dose
Mild or Moderate (CrCl ≥ 30 mL/min)	No dose adjustment required.
Severe (CrCl < 30 mL/min)	No data available.

Dosage in the elderly:

No starting dose adjustment required in patients ≥ 65 years of age. Patients ≥ 65 years experienced more serious adverse events (AEs), more Grade 3 AEs, and more permanent treatment discontinuations due to AEs compared to patients < 65 years. Higher incidences of decreased appetite, rash, mucosal inflammation and asthenia were observed in patients ≥ 65 years of age compared to younger patients.

Dosage based on gender:

Gender has no effect on the steady state clearance of dacomitinib based on population pharmacokinetic analyses.

In clinical trials, female patients experienced more Grade 3 AEs, dose reductions, dose interruptions, and treatment discontinuation. The following adverse events were reported at a greater frequency by female patients than male patients: weight decreased, conjunctivitis and alopecia.

Any use of the information is subject, at all times, to CCO's Terms and Conditions.

Dosage based on ethnicity:

There was no clinically relevant difference between Asian and non-Asian ethnicity in the steady state clearance of dacomitinib in population pharmacokinetic analyses.

In clinical trials, non-Asians experienced more serious adverse events. Non-Asian patients reported more frequently the following AEs: rash, dry skin, dyspnea, mucosal inflammation, asthenia, and skin fissures. The following AEs were experienced more frequently in Asian patients: diarrhea, dermatitis acneiform, decreased appetite, stomatitis, paronychia, weight decreased, upper respiratory tract infection, AST increased, ALT increased and mouth ulceration.

Children:

Safety and efficacy in children have not been established.

back to top

F - Administration Guidelines

- Administer dacomitinib with or without food, under consistent conditions (i.e. always on an empty stomach or always after the same type of meal).
- Tablets should be swallowed whole. Do not chew or crush the tablets.
- If a dose is missed, the dose should be skipped and the next dose should be taken at the next scheduled time.
- If the patient vomits after taking the dose, they should not take an extra dose. The next dose should be taken on the next day at the usual time.
- Store at room temperature (15 to 30ºC) in the original package.

back to top

Any use of the information is subject, at all times, to CCO's Terms and Conditions.

G - Special Precautions

Contraindications:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container

Other Warnings/Precautions:

- Patients experiencing fatigue should exercise caution when driving or operating machinery.
- The safety of dacomitinib in patients with cardiac impairment or with a history or presence of brain or meningeal metastases is not known.
- Tablets contain lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

Other Drug Properties:

- Carcinogenicity: Unknown
  Carcinogenicity studies have not been performed.

Pregnancy and Lactation:

- Genotoxicity: No
- Fetotoxicity: Documented in animals
  Dacomitinib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **2 months** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended during treatment and for at least **2 months** after the last dose.
- Fertility effects: Unknown
  Fertility studies have not been performed.

back to top

H - Interactions

Dacomitinib is metabolized by CYP2D6. However, dacomitinib dose adjustment is not required when it is concurrently administered with a CYP2D6 inhibitor.

Dacomitinib is a strong inhibitor of CYP2D6; in vitro, O-desmethyl dacomitinib may inhibit CYP2D6. Dose modification may be required when dacomitinib is coadministered with CYP2D6 substrates.

In vitro, dacomitinib may inhibit the activity of P-gp (GI), BCRP (systemically and GI), OCT1, and UGT1A1 at clinically relevant concentrations.

Any use of the information is subject, at all times, to CCO's Terms and Conditions.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Proton pump inhibitors (i.e. dexlansoprazole, esomeprazole, omeprazole, lansoprazole, pantoprazole, and rabeprazole)	↓ dacomitinib concentration and/or efficacy	↓ dacomitinib solubility and/or absorption due to increased pH caused by PPI.	Avoid use of PPIs. Antacids may be used, if required. If needed, administer dacomitinib at least 2 hours before or 10 hours after H2-blockers.
CYP2D6 substrates (e.g. dextromethorphan, beta-blockers, tramadol, nortriptyline, mirtazapine, serotonin-H3 antagonists)	↑ CYP2D6 substrate concentration (9.6x ↑ in dextromethorphan exposure) and/or toxicity	Dacomitinib is a strong CYP2D6 inhibitor.	Avoid use with substrates with narrow therapeutic indices (e.g. procainamide, pimozide, and thioridazine). For other CYP2D6 substrates, follow respective labels. Use alternatives for drugs with active metabolites formed by CYP2D6.

back to top

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.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests	Baseline and as clinically indicated
Renal function tests, especially in patients at risk of dehydration	Baseline and as clinically indicated
Electrolytes, including potassium, calcium and magnesium, especially in patients at risk of dehydration	Baseline and as clinically indicated
Clinical toxicity assessment for GI (including dehydration), skin/nail, ocular, and respiratory effects (including pneumonitis)	As clinically indicated

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

Any use of the information is subject, at all times, to CCO's Terms and Conditions.

version

back to top

K - References

Dacomitinib. DynaMed drug monograph. Record No. T1558463008461. DynaMed, Ipswich, MA: EBSCO Information Services. Jan 16, 2020.

Dacomitinib: UpToDate® drug information (v24.0). Accessed Feb 7, 2020.

Lacouture ME, Keefe DM, Sonis S, et al. A phase II study (ARCHER 1042) to evaluate prophylactic treatment of dacomitinib-induced dermatologic and gastrointestinal adverse events in advanced non-small-cell lung cancer. Ann Oncol. 2016;27(9):1712–1718.

Lacouture, ME, Mitchell EP, Piperdi B et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. J Clin Oncol 2010; 28: 1351-7.

Lavacchi D, Mazzoni F, Giaccone G. Clinical evaluation of dacomitinib for the treatment of metastatic non-small cell lung cancer (NSCLC): current perspectives. Drug Design, Development and Therapy 2019:13 3187–3198.

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Antiemesis: Version 1.2019, 2019.

Prescribing Information: Vizimpro (dacomitinib). Pfizer Inc, US. Sept 2018.

Product Monograph: Vizimpro (dacomitinib). Pfizer Canada ULC. July 29, 2021.

June 2022 Updated indications (to new format), dosage with hepatic impairment, and interactions sections

back to top

L - Disclaimer

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

Any use of the information is subject, at all times, to CCO's Terms and Conditions.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an “as-is” basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person’s use of the information in the Formulary.

back to top

Any use of the information is subject, at all times, to CCO’s Terms and Conditions.