DRUG NAME: Dacomitinib

SYNONYM(S): PF-00299804[1]

COMMON TRADE NAME(S): VIZIMPRO®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Dacomitinib is a second-generation tyrosine kinase inhibitor (TKI). It selectively and irreversibly binds to the kinase domains EGFR/HER1, HER2 and HER4, which inhibits tyrosine kinase autophosphorylation, resulting in reduction of tumour growth and tumour regression. Dacomitinib has activity against the EGFR activating mutations exon 19 deletion and exon 21 L858R substitution.[1-4]

PHARMACOKINETICS:

Oral Absorption	bioavailability 80%; steady state within 14 days	
Distribution	extensively distributed throughout the body	
	cross blood brain barrier?	yes (equal brain/plasma concentrations based on animal data)
	volume of distribution	1889 L
	plasma protein binding	98%
Metabolism	hepatic via CYP 2D6 (major) and CYP 3A4 (minor) pathways	
	active metabolite(s)[2,5]	major: O-desmethyl dacomitinib (similar activity to dacomitinib); other: oxidative metabolites (unknown activity)
	inactive metabolite(s)	no information found
Excretion	mainly fecal elimination	
	urine	3% (<1% parent drug)[2,6]
	feces	79% (20% parent drug)[2,6]
	terminal half life	dacomitinib: 70 h (54 to 80 h)[2,3] O-desmethyl dacomitinib: 73 h[3]
	clearance	24.9 L/h[4]

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Lung cancer, non-small cell

*Health Canada approved indication

Other uses:

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SPECIAL PRECAUTIONS:

Special populations:
- Patients who are ***female, non-Asian,*** or ***65 years of age or older*** may experience more serious adverse events than other patients.[2]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test. Dacomitinib is not clastogenic in mammalian *in vivo* chromosome tests. Results of mammalian *in vitro* chromosome tests are conflicting.[2,4]

Fertility: Preimplantation loss has been demonstrated in animals exposed to EGFR inhibitors. In animal studies, female test subjects experienced reversible epithelial atrophy of the cervix and vagina at exposures 0.3 times the human therapeutic exposure of dacomitinib. In male test subjects, reversible decreased secretion in the prostate gland was reported at exposures 0.6 times the human therapeutic exposure.[2-4]

Pregnancy: Based on its mechanism of action, dacomitinib is expected to cause fetal harm. In animal models, disruption of the EGFR signalling pathway is associated with embryo-fetal toxicity (e.g., increased fetal loss, postnatal death, developmental anomalies, and visceral abnormalities). Pregnant test subjects in animal studies experienced less maternal weight gain, reduced fetal body weights, and increased post-implantation loss. Women of reproductive potential and men with female partners of reproductive potential should use effective contraception while on dacomitinib and for at least two months after treatment has been discontinued.[2,3]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should wait at least two months after the last dose of dacomitinib before breastfeeding.[2]

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*** (44%, severe, ≤1%)[2,6]
	leukopenia (14%, severe <1%)
	lymphopenia (42-47%, severe 6-7%)[2,6]
cardiac	chest pain (10%)[6]
eye	***keratitis*** (2%, severe ≤2%); see paragraph following **Side Effects** table
	visual disorders (19-24%, severe <1%)[2,6]; includes blepharitis, dry eye, infectious and noninfectious conjunctivitis, keratitis
gastrointestinal	*emetogenic potential:* minimal[6]
	constipation (13%)
	diarrhea (87%, severe 8-11%); see paragraph following **Side Effects** table
	nausea (19%, severe 1%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	stomatitis (45-70%, severe 4%)[2,6]; includes cheilitis, dry mouth, mucosal inflammation, mouth/oropharyngeal pain, mouth ulcer
	vomiting (9%)
general disorders and administration site conditions	asthenia (13%, severe 2%)
	fatigue (9%)
hepatobiliary	***hepatotoxicity*** (1%); sometimes fatal
infections and infestations	***paronychia*** (61-62%, severe 7-8%)[1,2]; see paragraph following **Side Effects** table
	upper respiratory tract infection (12%, severe 1%)
investigations	alkaline phosphatase increase (22%, severe <1%)
	ALT increase (40%, severe 1%)
	AST increase (35%, severe <1%)
	bilirubin increase (16%, severe <1%)
	creatinine increase 24%[4]
	weight decrease (26%, severe 5%)
metabolism and nutrition	appetite decrease (31%, severe 3%)
	dehydration (1%)
	hyperglycemia (36%, severe 1%)
	hypoalbuminemia (44%)
	hypocalcemia (33%, severe 1%)
	hypokalemia (29%, severe 7%)
	hypomagnesemia (22-23%, severe <1%)[2,6]
	hyponatremia (26%, severe 3%)
musculoskeletal and connective tissue	back pain (8%)[1]
	musculoskeletal pain (12%, <1%)
	pain in extremity (14%)
nervous system	dysgeusia (7%)
psychiatric	insomnia (11%, severe <1%)
respiratory, thoracic and mediastinal	cough (21%)
	dyspnea (13%, severe 2%)
	interstitial lung disease/pneumonitis (≤3%, severe ≤1%)[2,6]; see paragraph following **Side Effects** table
	nasal symptoms (19%)[6]
	pleural effusion (3%, severe 2%)[1]
skin and subcutaneous tissue	***alopecia*** (23%, severe <1%)
	dermatitis acneiform/papulopustular rash (49%, severe 14%)[1]; see paragraph following **Side Effects** table

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	dry skin (28-30%, severe 1-2%)[1,2]
	hypertrichosis (1%)
	nail disorder (66%, severe 8%); see paragraph following **Side Effects** table
	palmar-plantar erythrodysesthesia syndrome (15%, severe ≤2%)[1,2]; see paragraph following **Side Effects** table
	pruritus (20-21%, severe <1%)[2,6]
	rash (6-78%, severe 2-21%)[1,2]; including dermatitis, maculopapular, pustular
	skin exfoliation (3-7%)[2,6]; see paragraph following **Side Effects** table
	skin fissures (9%)
	Stevens Johnson syndrome (severe <1%)
vascular	hypertension (6%, severe 1%)[1]

Adapted from standard reference[2] unless specified otherwise.

Diarrhea is reported in 87% of patients receiving dacomitinib. Onset of diarrhea usually occurs within the first week of treatment, with the worst episodes of diarrhea developing within the first 2 weeks. The median duration of any grade diarrhea is reported as 20 weeks, while grade 3 or greater diarrhea usually lasts for only 1 week. Close monitoring and early intervention is essential in preventing the development of more severe diarrhea which can result in dehydration, renal impairment, and severe electrolyte imbalance. Rarely, fatalities have been reported. Patients with severe diarrhea may require dose interruption, dose reduction, or discontinuation of therapy. Recommendations for management of diarrhea[2,9,10]:

- initiate adequate hydration and anti-diarrheal agents (e.g., loperamide) at the first sign of diarrhea and continue until 12 hours after the last loose bowel movement;
- escalate anti-diarrheal medication to the highest recommended dose if necessary (e.g., maximum 20 mg loperamide per day)[10,11]; and,
- monitor for dehydration and administer intravenous fluids and electrolytes as required.

Interstitial lung disease (ILD)/pneumonitis has occurred in up to 3% of patients. Average onset of ILD/pneumonitis is 16 weeks. Average duration for any grade ILD/pneumonitis is 21 weeks, but three weeks for grade 3 or greater reactions. Withhold dacomitinib during diagnostic assessment and permanently discontinue treatment for any grade confirmed ILD/pneumonitis.[2]

Keratitis, including severe cases, has been reported. Most cases present around week 40 of treatment. The median duration of all grade keratitis is 17 weeks, with severe keratitis usually persisting for 10 weeks. Prompt referral to an ophthalmologist is recommended for all patients presenting with symptoms suggestive of keratitis. Withhold dacomitinib for grade 2 or greater keratitis; treatment may be resumed at a reduced dose once symptoms have resolved to grade 1 or less.[2]

Hand-foot skin reaction (also known as palmar-plantar erythrodysesthesia and PPE) usually appears within the first 4 weeks of treatment and may worsen in the subsequent two weeks. Symptoms often last for 15 weeks, with grade 3 or greater symptoms lasting about 2 weeks. Dacomitinib dose interruption/reduction and/or treatment with antibiotics, topical steroids, and emollients may be required to manage the reaction.[2] Recommendations for the prevention and management of hand-foot skin reaction:

- avoid tight-fitting shoes or repetitive rubbing pressure to hands and feet, such as that produced by strenuous activities.
- apply lanolin-containing creams (eg, Bag Balm®, Udderly Smooth®) liberally and frequently to affected areas,[12] and
- use protective clothing and sunscreen when exposed to sun.[2]

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Papulopustular rash is a common dermatologic toxicity associated with EGFR inhibition. This may be caused by agents with specific EGFR inhibition, multikinase inhibition with EGFR inhibition, or indirect EGFR inhibition. The incidence and severity may vary, depending on the selectivity and the type of EGFR binding. Erythematous papules and pustules usually erupt on the face, scalp, "v" shaped area of the chest, and upper trunk.[13-15] The rash is often pruritic and painful and secondary bacterial infection may occur.[15-17] The rash develops within the first three weeks of therapy, and is preceded by sensory disturbance, erythema, and edema. Tender papules evolve into pustules and then crust over by 3-4 weeks. Rash severity and intensity usually decreases after 6-8 weeks although dry skin, erythema, and scattered telangiectasias may persist for months.[18-20] Ultraviolet radiation may exacerbate skin eruptions and hyperpigmentation.[20] Most patients will experience gradual or partial improvement despite continued EGFR inhibitor therapy.[20] Preventative measures plus prompt reactive intervention may reduce the severity of the reaction and maintain dose intensity of the EGFR inhibitor. Preventative measures may include: moisturizing with a thick emollient, avoiding hot showers, minimizing ultraviolet radiation and sun exposure, and using broad-spectrum sunscreen.[20] Treatment options may include topical/oral steroids and antibiotics.[15,21-23] As the rash is clinically and histologically distinct from acne, topical acne medication is not recommended.[18] Severe rash may require dose interruption and modification.[15,22] Withhold dacomitinib for life-threatening bullous, blistering or exfoliating conditions, including ***Stevens Johnson syndrome***. Restarting dacomitinib treatment at a reduced dose may be considered upon resolution of symptoms to grade 1 or less.[2]

Paronychia and other ***nail disorders*** have been reported in up to 68% patients, with a median onset of 48 days. Besides paronychia, reported nail disorders may include in-grown nail, nail discolouration, onychoclasis, and onycholysis. Dacomitinib dose reduction, interruption, or discontinuation may be required. Preventative measures and good skin care may help to reduce the frequency and severity of paronychia[2,9]:

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

Topical antibiotics/antiseptics and/or steroids may be helpful for management of mild cases. For management of moderate or severe cases, topical or systemic antibiotics and/or steroids, and silver nitrate applications may be used.[2]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
dextromethorphan[2]	dextromethorphan C_{max} increased by 855%, AUC increased by 874%	strong inhibition of CYP 2D6 by dacomitinib	avoid concurrent use
antacids (magnesium/aluminum hydroxide)[2]	no significant influence on dacomitinib pharmacokinetics[2]	reduced solubility of dacomitinib with increasing pH	antacids may be taken with dacomitinib if needed[2]; if using H_2-blockers, consider taking dacomitinib at least 6 hours before or 10 hours after the H_2-blocker[3]
paroxetine[2]	dacomitinib AUC increased by 37%	strong CYP 2D6 inhibition by paroxetine	not considered clinically relevant; dose adjustment not required
rabeprazole[2]	dacomitinib C_{max} decreased by 51%, AUC decreased by 39%	reduced solubility of dacomitinib with increasing pH	avoid concurrent use

Dacomitinib is a ***substrate of CYP 2D6***. Concurrent administration with CYP 2D6 inhibitors did not cause clinically significant changes in dacomitinib pharmacokinetics; therefore, no dose adjustment of dacomitinib is required.[2]

Dacomitinib is a ***strong inhibitor of CYP 2D6***. Avoid concurrent use with CYP 2D6 substrates if possible. If not possible, modification of the substrate may be required to prevent toxicity or loss of efficacy of the substrate.[2]

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In vitro, dacomitinib is a ***substrate*** of P-glycoprotein (***P-gp***) and breast cancer resistance protein (***BCRP***), and may ***inhibit*** the drug transporters ***P-gp***, ***BCRP***, and organic cation transporter 1 (***OCT 1***), as well as the uridine-diphosphate glucuronosyltransferase 1A1 (***UGT 1A1***) enzyme. Clinical significance is unknown.[2,3]

SUPPLY AND STORAGE:

Oral: Pfizer Canada ULC supplies dacomitinib as 15 mg, 30 mg, and 45 mg film-coated immediate-release tablets. Tablets contain lactose. Store at room temperature.[2]

Additional Information: Dacomitinib tablets are packaged in unit dose blister cards and in bulk bottles.[2]

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:

45 mg PO once daily.[2]

Administer with food or on an empty stomach. To avoid fluctuations in plasma levels, dacomitinib administration should be consistent from day to day (i.e., same time of day and either always fasted or always with the same type of meal).[2]

Concurrent radiation:

no information found

Dosage in renal failure:[2]

CrCl ≥ 30 mL/min: no adjustment required
CrCl < 30 mL/min: no information found

$$\text{calculated creatinine clearance} = \frac{\text{N* x (140 - Age) x weight in kg}}{\text{serum creatinine in micromol/L}}$$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure:[2,6]

mild or moderate impairment (bilirubin ≤ 3 times ULN and any AST/Child-Pugh class A or B): no adjustment required
severe impairment (bilirubin > 3 times ULN and any AST/Child-Pugh class C): no information found

Dosage in dialysis:

no information found

Children:

safety and efficacy have not been established

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