DRUG NAME: Dabrafenib

SYNONYM(S): dabrafenib mesylate[1], GSK2118436[2]

COMMON TRADE NAME(S): TAFINLAR®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Dabrafenib is an oral, small molecule inhibitor of BRAF serine-threonine kinase. BRAF mutations result in the activation of the mitogen-activated protein kinase (MAPK) pathway and may promote tumour cell growth. Dabrafenib inhibits the MAPK pathway in BRAF mutated cells, leading to regression and decreased proliferation of the cells.[1,3]

PHARMACOKINETICS:

Oral Absorption	bioavailability (95%); absorption delayed after food (AUC reduced by 31%, C_{max} reduced by 51%)	
Distribution	peak plasma level: 2 h	
	cross blood brain barrier?	no information found
	volume of distribution	70.3 L
	plasma protein binding	99.7% ; metabolites 96.3-99.9%
Metabolism	hepatic metabolism via CYP3A4 and CYP2C8; hydroxy- and desmethyl- metabolites have similar exposure and BRAF inhibitory activity as dabrafenib; carboxy- metabolite is less active but has a greater than 10 times higher exposure compared to dabrafenib and the other two metabolites	
	active metabolite(s)	hydroxy-dabrafenib, desmethyl-dabrafenib, carboxy-dabrafenib
	inactive metabolite(s)	no information found
Excretion	primarily fecal elimination	
	urine	23%
	feces	71%
	terminal half life	dabrafenib (8h); hydroxy-metabolite (10 h); desmethyl- and carboxy-metabolites (21-22 h)
	clearance	34.6 L/h
Elderly	patients ≥ 75 years of age had a 40% increase in carboxy- and desmethyl-dabrafenib plasma levels compared to patients less than 75 years	

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:

*Melanoma

*Lung cancer, non-small cell

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to dabrafenib[1]
- patients with wild-type BRAF melanoma[1]

Caution:
- ***QTc prolongation*** has been observed with dabrafenib; use with caution in patients who may be at an increased risk of developing torsade de pointes.[1]
- ***Secondary malignancies***, including ***cutaneous squamous cell carcinoma***, ***new primary melanoma,*** and ***non-cutaneous malignancies*** have been reported with dabrafenib; dermatologic evaluations should be performed prior to treatment and regularly during treatment.[1]
- ***Renal failure*** has been reported; monitor serum creatinine prior to treatment and regularly thereafter.[4]

Special populations:
- ***Elderly patients*** (65 years or older) reported a higher incidence of adverse events that led to dose reductions or interruptions as compared with younger patients.[1]
- Safety and efficacy in ***children and adolescents*** less than 18 years of age has not been established; developmental toxicities have been reported in animal studies.[1]

Carcinogenicity: No carcinogenicity studies have been conducted. Secondary malignancies, including cutaneous squamous cell carcinoma, new primary melanomas and non-cutaneous malignancies have been reported with dabrafenib usage.[1]

Mutagenicity: Not mutagenic in Ames test and in mammalian *in vitro* mutation test. Dabrafenib is not clastogenic in a mammalian *in vivo* chromosome test.[1]

Fertility: In animal studies, testicular degeneration/depletion and a reduction in the number of ovarian corpora lutea have been reported.[1]

Pregnancy: FDA Pregnancy Category D.[5] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
Human studies have not been conducted but fetal harm is expected based on the mechanism of action. Embryotoxicity and teratogenicity have been reported in animal studies. Shorter bone lengths and renal toxicity have been observed in juvenile animals. Women of childbearing potential should use contraception during treatment and for 4 weeks after discontinuation of therapy. Dabrafenib may decrease the efficacy of hormonal contraceptives; alternate contraceptive measures are recommended.[1]

Breastfeeding is not recommended due to the potential secretion into breast milk.[1]

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.[6]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (12-28%, severe 4%)[5,7]
	lymphocytopenia (40%, severe 6%)[5]
	leucopenia (21%)[5]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	neutropenia (9%, severe 2%)[5]
	thrombocytopenia (8%)[5]
cardiac	atrial fibrillation (2%)
eye	uveitis, including iritis (1%)[1,5]
gastrointestinal	*emetogenic potential: low*[8]
	abdominal pain (21%)[5]
	constipation (8-13%, severe 2%)
	diarrhea (11-28%, severe 1%)[5,7]
	nausea (20-27%, severe 1-2%)[5,7]
	pancreatitis (1-10%)[1,5]
	vomiting (15-20%, severe 1%)[1,5]
	xerostomia (6%)[5]
general disorders and administration site conditions	asthenia (5-19%, severe <1%)
	chills (11-17%, severe <1%)[1,5]
	fatigue (22-40%, severe 1%)[1,5]
	flu-like reaction (2-4%)[1,5]
	peripheral edema (17%)[5]
	pyrexia (24-31%, severe 1-3%)[5,7]; see paragraph following **Side Effects** table
immune system	hypersensitivity, manifesting as bullous rash (<10%)[5]
infections and infestations	nasopharyngitis (10%)[5]
	urinary tract infection (9%)[5]
investigations	alkaline phosphatase increase (19-26%)[5]
	ALT increase (11%)[5]
	AST increase (15%)[5]
	creatinine increase (7-9%, severe <1%)[4,5]; see paragraph following **Side Effects** table
	GGT increase (38%)[5]
	QTc prolongation (2%)[5]
metabolism and nutrition	appetite loss (12-19%, severe 2%)[1,5]
	dehydration (2%)[5]
	hypercalcemia (4%)[5]
	hyperglycemia (5-56%, severe 1-8%)
	hyperkalemia (15%)[5]
	hypoalbuminemia (23%)[5]
	hypocalcemia (9%)[5]
	hypokalemia (23%)[5]
	hypomagnesemia (6%)[5]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hyponatremia (3-36%, severe 2%)[1,5]
	hypophosphatemia (5-41%, severe 2-6%)
musculoskeletal and connective tissue	arthralgia (17-34%, severe 2%)[1,5]
	back pain (10-12%, severe 1%)[5,7]
	limb pain (12-19%, severe <1%)[1,5]
	muscle spasm (4%)[5]
	myalgia (11-23%)[5]
neoplasms; see paragraph following **Side Effects** table	***basal cell carcinoma*** (2%)[5]
	cutaneous squamous cell carcinoma (6-19%, severe 4-7%)[5]
	new melanoma (1-2%)[1,5]
	non-cutaneous malignancies (2%)
nervous system	dizziness (9%)[5]
	headache (21-34%, severe 2%)[1,7]
psychiatric	insomnia (8%)[5]
renal and urinary	interstitial nephritis (<1%)[5]
	renal failure (1-4%)[4]; see paragraph following **Side Effects** table
respiratory, thoracic and mediastinal	cough (10-21%)[1,5]
skin and subcutaneous tissue	acneiform eruption (4%)[5]
	actinic keratosis (9%)
	alopecia (12-29%, severe <1%)[1,7]
	dermatological reaction (68%)[5]
	dry skin (6-10%)[1,5]
	erythema (2-6%)[1,5]
	hyperkeratosis (26-39%, severe 1-2%)
	night sweats (6%)[5]
	palmar-plantar erthyrodysesthesia (15-20%, severe 2%); may require dose reduction/interruption
	photosensitivity (3%)
	pruritus (10-13%)[5,7]
	rash (17-53%)[1,5]
	seborrhoeic keratosis (8%)
	skin lesion (5%)
	skin papilloma (5-27%)[1,5]
vascular	hemorrhage (2%)[5]
	hypotension (<1%)

Adapted from standard reference[1] unless specified otherwise.

Malignancies, including cutaneous squamous cell carcinoma (CuSCC), new primary melanomas, and non-cutaneous malignancies have been reported with dabrafenib. Skin examination should be performed prior to, during, and after treatment has ended. Cutaneous squamous cell carcinoma and new primary melanomas may be managed by dermatological excision; dose interruptions or modifications are not recommended. Non-cutaneous, new primary/recurrent malignancies (e.g. colorectal adenocarcinoma, pancreatic adenocarcinoma) have been reported with dabrafenib and should be managed according to standard clinical practice. Patients should be evaluated for signs and symptoms of non-cutaneous malignancies prior to, during and after therapy for up to 6 months or until start of another chemotherapy treatment.[1]

Pyrexia and serious non-infectious febrile events have been reported with dabrafenib. Interrupt dabrafenib for temperatures greater than or equal to 38.5ºC or fever of any severity accompanied by rigors, chills, dehydration, hypotension or renal failure in the absence of infection. Once fever is resolved, treatment may be restarted at the same or a reduced dose; prophylactic anti-pyretics may be required.[1]

Renal failure is reported in 1-4% of patients on dabrafenib monotherapy and may be associated with pyrexia and/or dehydration. Incidence may be increased when dabrafenib is given in combination with other treatments (i.e., trametinib). Granulomatous/tubulointerstitial nephritis has been reported rarely. The mechanism for injury appears to be tubular and interstitial damage related to BRAF inhibition. Renal function should be closely monitored for early detection of dysfunction, particularly during and following severe events of pyrexia.[4,9,10]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
midazolam[1]	decreased midazolam C_{max} by 61% and AUC by 74%	induction of CYP3A4 by dabrafenib	monitor for decreased midazolam effect
ketoconazole[1]	increased dabrafenib Cmax by 26% and AUC by 57%; also, increased hydroxy-metabolite AUC by 48%; increased desmethyl-metabolite AUC by 61%, and decreased carboxy-metabolite AUC by 33%	inhibition of CYP3A4 by ketoconazole	avoid concurrent use if possible

Dabrafenib is a substrate and inducer of CYP3A4 and CYP2C8.[1,2] Strong CYP3A4 or CYP2C8 inhibitors may increase the exposure of dabrafenib and metabolites; monitor for increased adverse reactions or consider alternate therapy.[1,5] Co-administration with strong CYP3A4 or CYP2C8 inducers may decrease dabrafenib exposure; avoid concurrent therapy.[1] Dabrafenib may increase the metabolism of CYP3A4 substrates and decrease their effectiveness; avoid concurrent therapy if possible. Dabrafenib may decrease the serum concentrations of estrogens and progestins in hormonal contraceptives,[5,11] and decrease their efficacy; alternate contraceptive methods should be used.[1,12]

Dabrafenib may induce other enzymes including CYP2B6, CYP2C9 and CYP2C19.[1]

Dabrafenib is associated with QTc interval prolongation. Avoid concurrent therapy with drugs associated with QTc prolongation and/or torsades de pointes, if possible.[1] If unavoidable, monitor for QT prolongation or cardiac arrhythias.[5]

Dabrafenib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) *in vitro*; impact on dabrafenib pharmacokinetics is minimal.[1]

The solubility and bioavailability of dabrafenib may be reduced with drugs that alter the pH of the upper GI tract; clinical significance is unknown.[1]

SUPPLY AND STORAGE:

Oral: Novartis Pharmaceuticals Canada Inc. supplies dabrafenib as 50 mg and 75 mg capsules. Store at room temperature. Monogramming ink on capsule shells contain propylene glycol.[13]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

	BCCA usual dose noted in ***bold, italics***
	Cycle Length:
Oral[1,14,15]:	***150 mg (range 50-150mg) PO twice daily*** (in the morning and in the evening, approximately 12 hours apart). Administer on an empty stomach (one hour before or two hours after a meal).
Concurrent radiation:	no information found
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"
Dosage in renal failure:	no adjustment required for mild to moderate renal impairment[1]; no information found for severe renal impairment
Dosage in hepatic failure:	no adjustment required for mild hepatic impairment[1]; no information found for moderate to severe hepatic impairment
Dosage in dialysis:	no information found

Children: no information found

REFERENCES:

1. GlaxoSmithKline Inc. TAFINLAR® product monograph. Mississauga, Ontario; 15 July 2013.
2. Trinh VA, Davis JE, Anderson JE, et al. Dabrafenib therapy for advanced melanoma. Ann Pharmacother 2014;48(4):519-529.
3. Hauschild A, Grob J, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380:358-365.
4. Novartis Pharmaceuticals Canada Inc. TAFINLAR® product monograph. Dorval, Quebec; 7 December 2016.
5. Lexi-Drugs® (database on the Internet). Dabrafenib. Lexi-Comp Inc., 1 June 2014. Available at: http://online.lexi.com. Accessed 16 June 2014.
6. Winson Cheung MD. Personal communication. BC Cancer Agency Skin and Melanoma Tumour Group; 26 November 2014.
7. Ascierto PA, Minor D, Ribas A, et al. Phase II trial (BREAK-2) of the BRAF inhibitor dabrafenib (GSK2118436) in patients with metastatic melanoma. J of Clin Oncol 2013.
8. 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.
9. Wanchoo R, Jhaveri KD, Deray G, et al. Renal effects of BRAF inhibitors: a systematic review by the Cancer and the Kidney International Network. Clin Kidney J 2016;9(2):245-251.
10. Jansen YJ, Janssens P, Hoorens A, et al. Granulomatous nephritis and dermatitis in a patient with BRAF V600E mutant metastatic melanoma treated with dabrafenib and trametinib. Melanoma Res 2015;25(2):245-251.

11. MICROMEDEX® 2.0 Drug Interactions (database on the Internet). Dabrafenib mesylate. Truven Health Analytics, updated periodically. Available at: http://www.micromedexsolutions.com/. Accessed 11 August 2014.
12. AHFS Drug Information® (database on the Internet). Dabrafenib mesylate. Lexi-Comp Inc., 27 March 2014. Available at: http://online.lexi.com. Accessed 16 June 2014.
13. Novartis Pharmaceuticals Canada Inc. TAFINLAR® product monograph. Dorval, Quebec; 31 July 2015.
14. BC Cancer Agency Skin and Melanoma Tumour Group. (USMAVDAB) BCCA Protocol Summary for the treatment of BRAF V600 Mutation-Positive Unresectable or Metastatic Melanoma using Dabrafenib. Vancouver, British Columbia: BC Cancer Agency; 1 December 2014.
15. BC Cancer Agency Skin and Melanoma Tumour Group. (USMAVDT) BCCA Protocol Summary for the Treatment of BRAF V600 Mutation-Positive Unresectable or Metastatic Melanoma Using daBRAFenib and Trametinib. Vancouver, British Columbia: BC Cancer Agency; 1 August 2016.