**Drug Monograph**

Drug Name | Mechanism of Action and Pharmacokinetics | Indications and Status | Adverse Effects | Dosing | Administration Guidelines | Special Precautions | Interactions | Recommended Clinical Monitoring | Supplementary Public Funding | References | Disclaimer

## A - Drug Name

# daBRAFenib

**COMMON TRADE NAME(S):** Tafinlar®

back to top

## B - Mechanism of Action and Pharmacokinetics

Dabrafenib is an inhibitor of RAF kinases, including BRAF. It acts on BRAF mutations which result in a constitutively active MAPK pathway (including RAS, RAF, MEK and ERK) and stimulated cell growth.

| | | |
|---|---|---|
| Absorption | Decreased exposure was observed with repeat dosing (auto-induction of metabolism) and also with high fat foods. Food also delays dabrafenib absorption. | |
| | Bioavailability | 95%; decreased with food |
| | Peak plasma levels | Achieved at 2 hours |
| Distribution | PPB | 96.3 to 99.9% (dabrafenib and metabolites) |
| Metabolism | Main enzymes involved | CYP3A4 and CYP2C8 |
| | Active metabolites | Yes (hydroxy-dabrafenib, desmethyl-dabrafenib) |
| | Inactive metabolites | Yes (carboxy-dabrafenib) |
| Elimination | Feces | 71% |

| | |
|---|---|
| Urine | 23% |
| Half-life | 8 h (unchanged drug); 10 h (hydroxy metabolite); 21-22 h (carboxy and desmethyl metabolites) |

back to top

## C - Indications and Status

**Health Canada Approvals:**

- Melanoma
- 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 events observed in the phase III monotherapy study of treatment-naïve patients with unresectable or metastatic melanoma, unless otherwise indicated. Clinically important, severe or life-threatening adverse events from other trials or post-marketing may also be included. Consult the DABRTRAM regimen monograph when used in combination.

| ORGAN SITE | SIDE EFFECT* (%) | ONSET** |
|---|---|---|
| Cardiovascular | Atrial fibrillation (2%) | E |
| | Cardiotoxicity (ejection fraction decreased) (when combined with trametinib: 5%) | E D |
| | Hypertension (when combined with trametinib: 6% severe) | E |
| | Hypotension (<1%) | E |
| | Other (<1%) (worsening valve disease) | E |
| | QT interval prolonged (rare) | E |
| | Venous thromboembolism (when combined with trametinib: 2%) | E |

| | | |
|---|---|---|
| Dermatological | Alopecia (29%) | D |
| | Erythema nodosum or panniculitis (1%) | E D |
| | Hand-foot syndrome (20%) | E |
| | Other (39%) (hyperkeratosis) | E |
| | Photosensitivity (3%) | E |
| | Rash (18%) (when combined with trametinib: Stevens-Johnson syndrome, rare) | E |
| Gastrointestinal | Anorexia (12%) | E |
| | Constipation (13%) | E |
| | Diarrhea (14%) | E |
| | GI perforation (rare) (when combined with trametinib) | E |
| | Nausea, vomiting (27%) | I |
| General | Fatigue (22%) (when combined with trametinib: 5% severe) | E |
| | Fever (non-infection related - 31%) (when combined with trametinib: 63%, severe 5%) | E |
| | Flu-like symptoms (4%) | E |
| | Sarcoidosis (rare) (when combined with trametinib) | E |
| Hematological | Hemorrhage (15%) (when combined with trametinib: <1% severe, including intracranial hemorrhage into metastases) | E |
| | Myelosuppression (when combined with trametinib: 10% neutropenia, 5% severe) | E |
| Hepatobiliary | ↑ LFTs (12%) (< 2% severe) (when combined with trametinib: 6% severe) | E |
| | Pancreatitis (<1%) | E D |
| Hypersensitivity | DRESS syndrome (rare) (when combined with trametinib) | E D |
| | Hypersensitivity (1%) | I |
| Metabolic / Endocrine | Abnormal electrolyte(s) (5%) (↓PO4, ↓Na) | E |
| | Hyperglycemia (7%) (3% severe) | E |
| Musculoskeletal | Musculoskeletal pain (32%) | E |
| | Rhabdomyolysis (when combined with trametinib: <1%) | E |
| Neoplastic | Other (25%) (skin papilloma) | D |
| | Secondary malignancy (9%) (cuSCC; new primary melanoma: 1%, non-cutaneous malignancies: 2%) | D L |
| Nervous System | Headache (34%) | E |

| | | |
|---|---|---|
| Ophthalmic | Retinopathy (including retinal detachment and chorioretinopathy) (when combined with trametinib: 1%) | E D |
| | Uveitis (1%) | E |
| Renal | Nephritis (<1%) | E |
| | Renal failure (2%) | E |
| Respiratory | Cough (14%) | E |
| | Pharyngitis (16%) (nasopharyngitis) | 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 dabrafenib include hyperkeratosis, headache, musculoskeletal pain, fever, alopecia, nausea, vomiting, skin papilloma, fatigue, hand-foot syndrome and rash.

**Combination therapy** with trametinib had higher incidences or greater severity of ↑ LFTs, chills, fever, diarrhea, peripheral edema, bleeding, neutropenia, uveitis, muscle spasms, panniculitis, renal failure and hypertension compared to monotherapy. **Severe cutaneous adverse reactions (SCARs)**, including Stevens-Johnson syndrome (SJS) and life-threatening or fatal drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported during combination therapy.

**Sarcoidosis**, mostly involving the skin, lung, eye and lymph nodes, has been reported during combination therapy. Assess carefully as sarcoidosis may mimic signs of disease progression. If sarcoidosis diagnosis is confirmed, treatment should be considered.

**Febrile events** include severe febrile drug reactions with rigors/chills, dehydration, hypotension and renal failure. Median time to initial onset of febrile events was 2 to 4 weeks and the incidence is higher in combination with trametinib. The incidence and severity of pyrexia are increased when dabrafenib is used in combination therapy with trametinib. Dose modification is required (refer to Dosing section).

**Interstitial/granulomatous nephritis** has also been reported.

Paradoxical activation of MAP-3 kinase signalling has been reported in BRAF wild-type cells with exposure to BRAF inhibitors, which may promote growth of wild-type melanoma or **non-cutaneous malignancies**. **Cutaneous Squamous Cell Carcinoma** (cuSCC) has been reported in up to 11% of patients on monotherapy and usually occurred in the first 2 months of treatment (4 to 7 months with combination therapy). New **primary melanoma** (1%) has also been reported in the first 3 to 4 months. Management of cuSCC and new primary melanoma included excision without dose adjustment. RAS associated malignancies (eg colorectal or pancreatic adenocarcinoma) have been reported in the clinic; risk benefit should be considered before continuing with treatment.

Initiation and changes in **hyperglycemia** management may be required in some patients.

Decreases in systolic and diastolic **blood pressure** were reported in the phase III trial. The average decreases were -4 to -7.5 mmHg SBP and -2 to -3.6 mmHg DBP during the first 18 weeks of treatment.

**Pancreatitis**, generally occuring soon after treatment initation, has been reported during clinical trials (< 1% with monotherapy, 2% in combination) and post-marketing surveillance. Unexplained abdominal pain should be investigated appropriately.

Fatal **venous thromboembolic events** and major **hemorrhagic events** (including intracranial or gastric hemorrhage) have been reported when dabrafenib was given in combination with trametinib.

**Fatal cerebral hemorrhage** has been reported in patients who developed **brain metastases** while on the combination treatment; the risk may be increased in patients on anti-platelet or anticoagulant drugs.

back to top

## E - Dosing

Refer to protocol by which patient is being treated.

A validated test is required to identify BRAF V600 mutation status.

Prophylaxis with antipyretics +/- oral corticosteroids may be required if prior severe febrile reactions with dabrafenib.

***Adults:***

Consult the DABRTRAM regimen monograph when used in combination.

**Oral:** 150 mg BID

***Dosage with Toxicity:***

| Dose Level | Dabrafenib Dose (mg BID) |
|---|---|
| 0 | 150 |
| -1 | 100 |

| | |
|---|---|
| -2 | 75 |
| -3 | 50 |
| -4 | Discontinue |

Recommended dose modifications for monotherapy and combination therapy with trametinib; also refer to the regimen monograph DABRTRAM for dose modifications for combination therapy:

| Toxicity | Dabrafenib Dose |
|---|---|
| ↓ LVEF below LLN and > 20% decrease from baseline | Hold until resolution, then restart at the same or reduced dose level. |
| Symptomatic cardiac failure | Hold until resolution, then restart at the same or reduced dose level. |
| Fever of 38.5-40°C without complications | Hold until resolution; monitor creatinine and for signs and symptoms of infection. Restart at same dose or by ↓ 1 dose level.<br><br>Prophylaxis with antipyretics +/- oral corticosteroids may be required if prior severe febrile reactions. |
| Fever > 40°C or any fever with complications due to rigors, hypotension, dehydration or renal failure | Monitor creatinine and for signs and symptoms of infection.<br><br>Discontinue.<br><br>OR<br><br>Hold until ≤ Grade 1, then restart by ↓ 1 dose level.<br><br>Prophylaxis with antipyretics +/- oral corticosteroids may be required if prior severe febrile reactions. |
| Intolerable Grade 2 or ≥ Grade 3 rash | Hold until ≤ Grade 1, then restart by ↓1 dose level. |
| Intolerable Grade 2 or ≥ Grade 3 rash that does not improve within 3 weeks of holding treatment | Discontinue. |
| Uveitis that responds to local ocular therapies | Continue treatment without dose modifications and monitor. |
| Uveitis that does not improve despite local ocular therapy | Hold until resolved, then restart by ↓ 1 dose level. |

| | |
|---|---|
| Pancreatitis | Discontinue.<br><br>OR<br><br>Hold until resolved, then restart by ↓ 1 dose level; monitor carefully. |
| Cutaneous squamous cell carcinoma or new primary melanoma | No dose modification or interruptions recommended. |
| RAS associated malignancy | Consider risk benefit before making decision to continue treatment. |
| Severe cutaneous adverse reactions (e.g. Stevens-Johnson syndrome, DRESS) | Discontinue. |
| Other Grade 1 or tolerable Grade 2 | No change; monitor. |
| Other Grade 2 (intolerable) or Grade 3 | Hold until ≤ Grade 1, then restart by ↓ 1 dose level. |
| Other Grade 4 or Grade 3 that does not improve to ≤ Grade 1 | Discontinue<br><br>OR<br><br>Hold until ≤ Grade 1, then restart by ↓ 1 dose level. |

***Dosage with Hepatic Impairment:***

Hepatic metabolism and biliary secretion are the main routes of dabrafenib elimination; hepatic impairment may lead to increased exposure and toxicities. Population pharmacokinetics in mild hepatic impairment suggest no dose adjustment is required, but no data are available for moderate to severe hepatic impairment.

| Hepatic Impairment | Dabrafenib Dose |
|---|---|
| Mild | No dose adjustment required. |
| Moderate | No data. |
| Severe | No data. |

***Dosage with Renal Impairment:***

There are no clinical data in patients with severe renal impairment. With mild to moderate impairment, population pharmacokinetics suggest that no adjustments are required.

| Creatinine Clearance (mL/min) | Dabrafenib Dose |
|---|---|
| 30-89 | No dose adjustment needed. |
| < 30 | No data found. Use with caution. |

***Dosage in the elderly:***

No dose adjustment required. In unresectable or metastatic melanoma, more serious adverse events were observed in elderly patients (≥ 65 years); peripheral edema and decreased appetite were reported more frequently.

***Dosage based on gender:***

Compared to male patients, female patients treated with combination therapy had higher incidences of treatment-related adverse events (AEs) and treatment-related serious adverse events.

***Dosage based on ethnicity:***

Dabrafenib clearance is similar in Asian and Caucasian cancer patients with similar liver function.

***Children:***

Not recommended for use in children and adolescents < 18 years of age; safety and efficacy have not been established in this population. Adverse growth effects and renal toxicity have been observed in developing animals.

back to top

## F - Administration Guidelines

- Dabrafenib doses should be given approximately 12 hours apart on an empty stomach, at least 1 hour before or 2 hours after a meal.
- When given in combination, trametinib should be administered once daily with either the morning or evening dose of dabrafenib.
- Capsules should be swallowed whole with a full glass of water.
- If a dose is missed and it is less than 6 hours until the next dose, skip it and give the next dose as scheduled. Do not give extra doses to make up for a missed dose.
- Grapefruit, starfruit, Seville oranges, their juices or products should be avoided during treatment.
- Store at room temperature (15-30°C).

back to top

## G - Special Precautions

### Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

### Other Warnings/Precautions:

- Dabrafenib should not be used in patients with BRAF wild-type or unknown disease. BRAF mutation must be confirmed using a validated test before starting dabrafenib treatment.
- Dabrafenib monotherapy has not been studied in patients who have had previous treatment with BRAF inhibitors.
- Exercise caution in patients with risk factors for QT prolongation or Torsades de pointes (low potassium/magnesium, congenital QT prolongation, or history of arrhythmia, CHF, anti-arrhythmics, other QTc prolonging agents, prior anthracyclines), diabetes, autonomic neuropathy.
- Patients were excluded from clinical trials if they had abnormal heart valve morphology ≥ grade 2.
- Monitor for hemolytic anemia in patients with G6PD deficiency as dabrafenib contains a sulfonamide moiety.
- Use combination therapy with caution in patients at risk of bleeding as severe or fatal events have been reported. The risk may be increased with concomitant use of antiplatelet/anticoagulant therapy or in patients who develop brain metastases while on treatment.

**Other Drug Properties:**

- Carcinogenicity:
  Cutaneous squamous cell carcinoma, new primary melanoma and non-cutaneous malignancies have been observed in patients treated with dabrafenib.
- Phototoxicity: Yes

**Pregnancy and Lactation:**

- Mutagenicity: No
- Clastogenicity: No
- Embryotoxicity: Yes
- Fetotoxicity: Yes
- Teratogenicity: Yes
  - Dabrafenib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **2 weeks** after the last dose when given as monotherapy, or for at least **16 weeks** after the last dose of trametinib when given in combination.
  - Efficacy of hormonal contraceptives is likely to be decreased; use effective alternative methods of contraception.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.
- Fertility effects: Likely
  No fertility data in humans. Adverse effects on male reproductive organs have been seen in animals. Fertility effects may be irreversible.

back to top

## H - Interactions

Dabrafenib is primarily metabolized by CYP3A4 and CYP2C8; drug interactions are probable with inhibitors of these enzymes. Dabrafenib is a moderate to strong inducer of CYP3A4, and may also induce CYP2C9 (weak), CYP2B6, CYP2C8, CYP2C19, UGTs and P-gp. It is an *in vitro* inhibitor of OATP1B1 and OATP1B3. The inhibitory effects of dabrafenib and its metabolites on OAT1, OAT3 and BCRP do not contribute to significant drug-drug interactions.

Drugs that alter upper GI pH (e.g. PPIs, H2 receptor anagonists, antacids) are not expected to reduce dabrafenib bioavailability to a clinically significant level.

| AGENT | EFFECT | MECHANISM | MANAGEMENT |
|---|---|---|---|
| CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, | ↓ dabrafenib concentration and/or efficacy | ↑ metabolism of dabrafenib into its metabolites | Avoid strong CYP3A4 inducers if possible |

| | | | |
|---|---|---|---|
| phenobarbital, St. John's Wort, etc) | | | |
| CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit) | ↑ dabrafenib and metabolite exposure (up to 82% ↑) and/or toxicity | ↓ metabolism of dabrafenib | Avoid strong CYP3A4 inhibitors if possible |
| CYP3A4 substrates (e.g. cyclosporine, pimozide, tacrolimus, triazolo-benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors) | ↓ substrate exposure (up to 74% ↓) and/or efficacy | ↑ metabolism of substrates | Caution; monitor for efficacy. Avoid hormonal contraceptives as dabrafenib can decrease their efficacy. |
| CYP 2C8 inducers (e.g. rifampin) | ↓ dabrafenib concentration and/or efficacy | ↑ metabolism of dabrafenib into its metabolites | Avoid strong CYP2C8 inducers if possible |
| CYP 2C8 inhibitors (e.g. gemfibrozil) | ↑ dabrafenib AUC (up to 47% ↑) and metabolite exposure and/or toxicity | ↓ metabolism of dabrafenib | Avoid strong CYP2C8 inhibitors if possible |
| 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 | Additive | Avoid if possible |

| | | | |
|---|---|---|---|
| OATP1B1 and 1B3 substrates (e.g. statins, angiotensin receptor blockers, SN-38) | Potentially ↑ substrate concentration and/or toxicity | ↓ metabolism of OATP1B1 or 1B3 substrates | Caution |
| Substrates of CYP2B6, 2C8, 2C9, 2C19, UGTs and Pgp (e.g. warfarin, paclitaxel, amiodarone, bupropion, celecoxib, some PPIs, digoxin) | Potentially ↓ substrate concentration (warfarin AUC up to 37% ↓) and/or efficacy | ↑ metabolism of substrates | Use alternative medications if possible; if must use together, monitor for efficacy. |

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 |
|---|---|
| CBC | Baseline, at each visit and as clinically indicated (when combined with trametinib) |
| Liver function tests | Baseline, every 1 to 2 months, (every 4 weeks for 6 months after starting combined treatment with trametinib) |
| Renal function tests and electrolytes, including phosphate | Baseline, every 1 to 2 months, during and after febrile events |
| Skin examination for cutaneous squamous cell carcinoma and new primary melanoma | Baseline, every 2 months during treatment, continue every 2-3 months for 6 months after the last dose |
| Non-cutaneous malignancies | Baseline, periodic or as clinically indicated during treatment, and up |

| | |
|---|---|
| | to 6 months after the last dose |
| Blood glucose | Baseline, every 1 to 2 months, more regularly (at each visit) in patients with diabetes or hyperglycemia |
| Blood pressure | Baseline and as clinically indicated |
| Clinical toxicity assessment for febrile events, pancreatitis, musculoskeletal pain, ocular, dermatologic and cardiac effects, hypersensitivity, bleeding, (inflammatory and neurologic effects when combined with trametinib) | At each visit |

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

**Suggested Clinical Monitoring**

| Monitor Type | Monitor Frequency |
|---|---|
| INR for patients receiving warfarin | Baseline and as clinically indicated |

back to top

## J - Supplementary Public Funding

**Exceptional Access Program (EAP Website)**

- daBRAfenib - As monotherapy for the treatment of patients with BRAF V600 mutation-positive unresectable melanoma or metastatic disease, according to specific criteria
- daBRAfenib - In combination with trametinib for the treatment of BRAF V600 mutation-positive, unresectable or metastatic melanoma, according to specific clinical criteria
- daBRAfenib - For the adjuvant treatment of resected Stage III cutaneous melanoma according to clinical criteria

back to top

## K - References

Prescribing Information: Tafinlar® (dabrafenib). GlaxoSmithKline Inc. (US), May 2013.

Product Monograph: Tafinlar® (dabrafenib). Novartis Pharmaceuticals Canada Inc., March 19, 2021.

**June 2021** Updated indications and status, adverse effects, dosing and special precautions 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.*

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back to top