NOVARTIS

# **RAFINLAR** (Dabrafenib)

50 and 75 mg capsules

Professional Information

Document status: Final

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**SCHEDULING STATUS:** **S4**

## 1. NAME OF THE MEDICINE

**RAFINLAR 50 mg** capsules

**RAFINLAR 75 mg** capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**RAFINLAR 50 mg** contains 59.25 mg Dabrafenib mesylate equivalent to 50 mg of free base.

**RAFINLAR 75 mg** contains 88.88 mg Dabrafenib mesylate equivalent to 75 mg of free base.

For the full list of excipients, see **section 6.1.**

## 3. PHARMACEUTICAL FORM

**RAFINLAR 50 mg**

Opaque, size 2 capsules composed of a dark red body and dark red cap containing a white to slightly coloured solid. Capsule shells imprinted with GS TEW and 50 mg.

**RAFINLAR 75 mg**

Opaque, size 1 capsules composed of a dark pink body and dark pink cap containing a white to slightly coloured solid. Capsule shells imprinted with GS LHF and 75 mg.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

*Unresectable or metastatic melanoma*

RAFINLAR in combination with trametinib is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

RAFINLAR as a monotherapy is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation.

RAFINLAR is not indicated for the treatment of patient with wild-type BRAF melanoma.

*Adjuvant treatment of melanoma*

RAFINLAR in combination with trametinib is indicated for the adjuvant treatment of adult patients with Stage III melanoma with BRAF V600 mutation, following complete resection.

*Advanced non-small cell cancer (NSCLC)*

RAFINLAR in combination with trametinib is indicated for the treatment of patients with advanced non-small cell cancer (NSCLC) with BRAF V600 mutation.

*Low-grade glioma*

RAFINLAR in combination with trametinib is indicated for the treatment of paediatric patients 6 years of age and older and weighing at least 26 kg with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

*Unresectable or metastatic solid tumours*

RAFINLAR in combination with trametinib is indicated for the treatment of adult and paediatric patients 6 years of age and older and weighing at least 26 kg with unresectable or metastatic solid tumours with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.

**4.2 POSOLOGY AND METHOD OF ADMINISTRATION**

Treatment with RAFINLAR should be initiated by a medical practitioner experienced in the use of anticancer therapies.

*Adult patients*

RAFINLAR in combination with trametinib should not be used in patients with wild-type BRAF solid tumours. RAFINLAR should not be used in patients with wild-type BRAF melanoma or wild-type BRAF non-small cell adenocarcinoma.

Confirmation of BRAF V600 mutation using an approved/validated test is required for selection of patients appropriate for RAFINLAR monotherapy.

The recommended dose of RAFINLAR in adult patients is 150 mg given orally twice daily (corresponding to a total daily dose of 300 mg) independent of body weight. RAFINLAR should be taken either at least one hour before or at least two hours after a meal leaving an interval of approximately 12 hours between doses. RAFINLAR should be taken at similar times every day.

If a dose of RAFINLAR is missed, it should not be taken if it is less than six hours until the next scheduled dose.

**Dose adjustments**

The management of adverse events/adverse drug reactions may require treatment interruption, dose reduction, or treatment discontinuation (see Table 4-1, 4-2 and Table 5).

Dose modifications or interruptions are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma.

For pyrexia management guidance see section below.

Recommended dose level reductions are in Table 4-1. Doses below 50 mg twice daily are not recommended.

**Table 4-1: Recommended RAFINLAR dose level reductions in adult patients**

| **Dose Level reductions** | **Recommended Starting Dosage** |
|---|---|
| Starting dose | 150 mg orally twice daily |
| First dose reduction | 100 mg orally twice daily |
| Second dose reduction | 75 mg orally twice daily |
| Third reduction | 50 mg orally twice daily |
| *Permanently discontinue if unable to tolerate RAFINLAR 50 mg capsule* | |

*Paediatric patients*

The recommended dosage for RAFINLAR capsules in paediatric patients who weigh at least 26 kg, is based on body weight (Table 4-2). A recommended dose of RAFINLAR capsules for patients who weigh less than 26 kg has not been established.

**Table 4-2 Recommended weight-based dosing for RAFINLAR capsules in paediatric patients**

| **Body weight** | **Recommended starting dosage** |
|---|---|
| 26 to 37 kg | 75 mg orally twice daily |
| 38 to 50 kg | 100 mg orally twice daily |
| 51 kg or greater | 150 mg orally twice daily |

Recommended dose level reductions for RAFINLAR capsules in paediatric patients are provided in Table 4-3.

**Table 4-3 Recommended dose reductions for RAFINLAR capsules in paediatric patients**

| Dose level reduction | Recommended starting dosage | | |
|---|---|---|---|
| | ***75 mg orally twice daily*** | ***100 mg orally twice daily*** | ***150 mg orally twice daily*** |
| First dose reduction | 50 mg orally twice daily | 75 mg orally twice daily | 100 mg orally twice daily |
| Second dose reduction | - | 50 mg orally twice daily | 75 mg orally twice daily |
| Third dose reduction | - | - | 50 mg orally twice daily |
| *Permanently discontinue if unable to tolerate maximum of three dose reductions or a RFINLAR 50 mg capsule orally twice daily* | | | |

*Duration of treatment*

The recommended duration of treatment for patients with unresectable or metastatic melanoma or solid tumours or NSCLC is until disease progression or unacceptable toxicity.

In the adjuvant melanoma setting, the treatment duration is limited to a maximum of 1 year.

The recommended duration of treatment for paediatric patients with LGG is until loss of clinical benefit or until unacceptable toxicity. There are limited data in patients older than 18 years of age with LGG who require first systemic therapy. Therefore, continued treatment into adulthood should be based on benefits and risks to the individual patient as assessed by the physician.

The recommended dose modification schedule is provided in Table 5. When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered. The RAFINLAR dose should not exceed 150 mg twice daily.

**Table 5 RAFINLAR dose modification schedule (excluding pyrexia)**

| **Grade (CTC-AE)*** | **Dose Modifications** |
|---|---|
| Grade 1 or Grade 2 (Tolerable) | Continue treatment and monitor as clinically indicated. |
| Grade 2 (Intolerable) or Grade 3 | Interrupt therapy until toxicity is grade 0 – 1 and reduce by one dose level when resuming therapy. |
| Grade 4 | Discontinue permanently, or interrupt therapy until Grade 0 to 1 and reduce by one dose level when resuming therapy. |

** The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE).*

If treatment related toxicities occur when RAFINLAR is used in combination with trametinib then both treatments should be simultaneously dose reduced, interrupted or discontinued with the exceptions shown below.

*Pyrexia management*

Therapy with RAFINLAR should be interrupted (RAFINLAR when used as monotherapy, and both RAFINLAR and trametinib when used in combination) if the patient's temperature is ≥ 38 ºC. In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Treatment with anti-pyretics should be initiated. Patients should be evaluated for signs and symptoms of infection (see section 4.4).

RAFINLAR, or both RAFINLAR and trametinib when used in combination, should be restarted if patient is symptom free for at least 24 hours either:

- At the same dose level.
- Or, reduced by one dose level, if pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure.

The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient.

Exception where dose modification is necessary for only RAFINLAR, only:

*Uveitis management*

No dose modifications are required if effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, withhold RAFINLAR until resolution of ocular inflammation and then restart RAFINLAR reduced by one dose level.

**Special populations**

*Renal impairment*

No dose adjustment is required for patients with mild or moderate renal impairment. Based on the population pharmacokinetic analysis, mild and moderate renal impairment had no significant effect on RAFINLAR oral clearance or on the concentrations of its metabolites. There are no clinical data in patients with severe renal impairment and the potential need for dose adjustment cannot be determined. RAFINLAR should be used with caution in patients with severe renal impairment**.**

*Hepatic impairment*

No dose adjustment is required for patients with mild hepatic impairment. Based on the population pharmacokinetic analysis, mild hepatic impairment had no significant effect on RAFINLAR oral clearance or on the concentrations of its metabolites. There are no clinical data in patients with moderate to severe hepatic impairment and the potential need for dose adjustment cannot be determined. Hepatic metabolism and biliary secretion are the primary routes of elimination of RAFINLAR and its metabolites, and patients with moderate to severe hepatic impairment may have increased exposure. RAFINLAR should be used with caution in patients with moderate or severe hepatic impairment.

*Paediatric patients (below the age of 18 years)*

The safety and efficacy of RAFINLAR in paediatric patients who weigh less than 26 kg or are younger than 6 years of age has not been established. RAFINLAR is not recommended in this age group.

*Geriatric patients (65 years of age or older)*

No dosage adjustment is required in patients over 65 years.

**4.3 Contraindications**

- Hypersensitivity to the active substance, dabrafenib or to any of the excipients.
- Pregnancy and lactation (see section 4.6)

**4.4 Special Warnings and Precautions for Use**

*Pyrexia*

Pyrexia was reported in clinical trials with RAFINLAR monotherapy. In a Phase III clinical trial in patients with melanoma, the incidence and severity of pyrexia were increased when RAFINLAR was used in combination with trametinib (57 % [119/209], 7 % Grade 3) as compared to RAFINLAR monotherapy (33 % [69/211], 2 % Grade 3). In a Phase II trial in patients with NSCLC the incidence and severity of pyrexia were increased slightly when RAFINLAR was used in combination with trametinib (45 % [37/82], 1 % Grade 3) as compared to RAFINLAR monotherapy (37 % [31/84], 2 % Grade 3). In patients with melanoma who received the combination dose of

RAFINLAR 150 mg twice daily and trametinib 2 mg once daily and developed pyrexia, approximately half of the first occurrences of pyrexia happened within the first month of therapy. About one-third of the patients receiving combination therapy who experienced pyrexia had three or more events. Pyrexia may be accompanied by severe rigors, dehydration and hypotension which in some cases can lead to acute renal insufficiency. Serum creatinine and other evidence of renal function should be monitored during and following severe events of pyrexia**.** Serious non-infectious febrile events have been observed. These events responded well to dose interruption and/or dose reduction and supportive care in clinical trials.

A cross-study comparison in 1,810 patients treated with combination therapy demonstrated a reduction in the incidence of high-grade pyrexia and other pyrexia-related adverse outcomes when both RAFINLAR and trametinib were interrupted, compared to when only RAFINLAR was interrupted. Therefore, interruption of both RAFINLAR and trametinib is recommended if the patient's temperature is ≥ 38 ºC, and in case of recurrence, therapy can also be interrupted at the first symptom of pyrexia (see sections 4.2 and 5.1).

*Cutaneous Squamous Cell Carcinoma (cuSCC)*

Cases of cuSCC (which include those classified as keratoacanthoma or mixed keratoacanthoma subtype) have been reported in patients treated with RAFINLAR as monotherapy and in combination with trametinib. In a Phase III study in patients with melanoma, 10 % (22/211) of patients receiving RAFINLAR monotherapy developed cuSCC, with a median time to onset of the first occurrence of approximately 8 weeks. In patients who received RAFINLAR in combination with trametinib, 3 % (6/209) of patients developed cuSCC and events occurred later, with the median time to onset of the first occurrence of 20 to 32 weeks. More than 90 % of patients on RAFINLAR who developed cuSCC continued on treatment without dose modification. In a Phase II trial in patients with NSCLC, 18 % (15/84) of patients receiving RAFINLAR monotherapy developed cuSCC, with a median time to onset of the first occurrence of approximately 11 weeks. In patients who received RAFINLAR in combination with trametinib, only 2 % (2/82) of patients developed cuSCC.

Skin examination should be performed prior to initiation of RAFINLAR and during treatment with RAFINLAR every 2 months throughout therapy. Monitoring should continue every 2 to 3 months for 6 months following discontinuation of RAFINLAR or until initiation of another anti-neoplastic therapy.

Cases of cuSCC should be managed by dermatological excision and RAFINLAR treatment should be continued without any dose adjustment. Patients should be instructed to immediately inform their medical practitioner if new lesions develop**.**

*New primary melanoma*

New primary melanomas have been reported in patients treated with RAFINLAR. In clinical trials in unresectable or metastatic melanoma these were identified within the first 5 months of therapy and did not require treatment modification other than excision. Monitoring for skin lesions should occur as described for cuSCC.

*Non-cutaneous secondary/recurrent malignancy*

*In vitro* experiments have demonstrated paradoxical activation of MAP-kinase signalling in BRAF wild type cells with RAS mutations when exposed to BRAF inhibitors, which may lead to increased risk of non-cutaneous malignancies in patients treated with RAFINLAR. Cases of RAS-driven malignancies have been seen with BRAF inhibitors. Patients should be monitored as clinically appropriate. The benefits and risks before continuing treatment with RAFINLAR should be considered in patients with a non-cutaneous malignancy that has a RAS mutation.

Following discontinuation of RAFINLAR, monitoring for non-cutaneous secondary/recurrent malignancies should continue for up to 6 months or until initiation of another anti-neoplastic therapy.

*Pancreatitis*

Pancreatitis has been reported in RAFINLAR-treated patients. One of the events occurred on the first day of dosing of a melanoma patient and recurred following re-challenge at a reduced dose. Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase. Patients should be closely monitored when re-starting RAFINLAR after an episode of pancreatitis.

*Uveitis*

Treatment with RAFINLAR has been associated with the development of uveitis (including iritis). Patients should be monitored for visual signs and symptoms (such as, change in vision, photophobia and eye pain) during therapy.

*Haemorrhage*

Haemorrhagic events, including major haemorrhagic events have occurred in patients taking RAFINLAR in combination with trametinib. If patients develop symptoms of haemorrhage they should immediately seek medical care**.**

*Venous thromboembolism (VTE)*

VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE) can occur when RAFINLAR is used in combination with trametinib. Patients should be advised to immediately seek medical care if they develop symptoms of VTE**.**

*Skin toxicity:*

*Severe cutaneous adverse reactions*

Cases of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported during treatment with RAFINLAR in combination with trametinib. Before initiating treatment, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of SCARs appear, RAFINLAR and trametinib should be withdrawn**.**

*Hemophagocytic lymphohistiocytosis (HLH)*

In post-marketing experience, HLH has been observed with RAFINLAR in combination with trametinib. If HLH is suspected, treatment should be interrupted. If HLH is confirmed, treatment should be discontinued and appropriate management of HLH should be initiated.

*Tumour Lysis Syndrome (TLS)*

Cases of TLS, including fatal cases, have been reported in patients treated with RAFINLAR in combination with trametinib (see section 4.8). Risk factors for TLS include rapidly growing tumours, a high tumour burden, renal dysfunction, and dehydration. Patients with risk factors for TLS should be closely monitored, prophylaxis should be considered (e.g. intravenous hydration and treatment of high uric acid levels prior to initiating treatment) and treated as clinically indicated.

**4.5 Interaction with other medicines and other forms of interactions**

*Effect of other medicine on RAFINLAR*

Based on *in vitro* studies, RAFINLAR was shown to be primarily metabolised by cytochrome P450 (CYP) 2C8 and CYP3A4. Pharmacokinetic data showed an increase in repeat dose RAFINLAR Cmax (33 %) and AUC (71 %) upon co-administration with ketoconazole (CYP3A4 inhibitor) and increases of 82 % and 68 % of hydroxy- and desmethyl-dabrafenib AUC, respectively. A decrease in AUC was noted for carboxy-dabrafenib (decrease of 16 %). Co-administration of RAFINLAR and gemfibrozil (a CYP2C8 inhibitor) resulted in an increase in repeat-dose RAFINLAR AUC (47 %) and no relevant change in the concentrations of the metabolites. Medicines that are strong inhibitors or inducers of CYP2C8 or CYP3A4 are likely to increase or decrease, respectively, RAFINLAR concentrations. Alternative medicines should be considered during administration with RAFINLAR when possible. Use caution if strong inhibitors (e.g. ketoconazole, nefazodone, clarithromycin, ritonavir, gemfibrozil) or inducers (e.g. rifampin, phenytoin, carbamazepine, phenobarbitone, St John’s wort) of CYP2C8 or CYP3A4 are co-administered with RAFINLAR.

*Medicine that affect gastric pH*

Medicines that alter the pH of the upper gastrointestinal (GI) tract (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) may alter the solubility of RAFINLAR and reduce its bioavailability. However, no formal clinical trial has been conducted to evaluate the effect of gastric pH-altering medicines on the systemic exposure

of RAFINLAR. When RAFINLAR is co-administered with a proton pump inhibitor, H2-receptor antagonist, or antacid, systemic exposure of RAFINLAR may be decreased and the effect on efficacy of RAFINLAR is unknown.

*Effect of RAFINLAR on other medicines*

RAFINLAR induces CYP3A4- and CYP2C9-mediated metabolism and may induce other enzymes including CYP2B6, CYP2C8, CYP2C19 and UDP glucuronosyltransferases (UGT). RAFINLAR may also induce transporters (e.g. P-glycoprotein (Pgp)). In a clinical study in 12 patients using a single-dose of midazolam, a CYP3A4 substrate, Cmax and AUC were decreased by 61 % and 74 %, respectively, with co-administration of repeat dose RAFINLAR 150 mg twice daily. In a separate trial in 14 patients, repeat-dose RAFINLAR decreased the single-dose AUC of S-warfarin (a substrate of CYP2C9) and of R-warfarin (a substrate of CYP3A4/CYP1A2) by 37 % and 33 %, respectively, with a small increase in Cmax (18 and 19 % respectively). Co-administration of RAFINLAR and medicines which are affected by the induction of CYP3A4 or CYP2C9 such as hormonal contraceptives, warfarin or dexamethasone may result in decreased concentrations and loss of efficacy. If co-administration of these medications is necessary, monitor patients for loss of efficacy or consider substitutions of these.

*Combination therapy and non-fixed dose combination therapy*

*Combination with trametinib:*

Co-administration of repeat dosing RAFINLAR 150 mg twice daily and trametinib 2 mg once daily resulted in a 16 % increase in RAFINLAR Cmax and a 23 % increase in RAFINLAR AUC. A small decrease in trametinib bioavailability, corresponding to a decrease in AUC of 12 %, was estimated when RAFINLAR is administered in combination with trametinib using a population pharmacokinetic analysis. These changes in RAFINLAR or trametinib Cmax and AUC are considered not clinically relevant.

**4.6 Fertility, pregnancy and lactation**

*Pregnancy*

RAFINLAR is contraindicated during pregnancy or in a woman who may become pregnant (see section 4.3).

RAFINLAR can cause fatal harm when administered to a pregnant woman. Reproductive studies in animals (rats) have demonstrated dabrafenib induced embryotoxicity and teratogenicity. Following prenatal exposure to RAFINLAR at concentrations 0.5 times the exposure in humans.

*Breastfeeding*

Women should not breastfeed their infants whilst on treatment with RAFINLAR (see section 4.3).

*Contraception*

Sexually active females of reproductive potential should use effective contraception (methods that result in less than 1 % pregnancy rates) when using RAFINLAR during treatment and for four weeks after stopping treatment with RAFINLAR**.**

RAFINLAR may decrease the efficacy of hormonal contraceptives and an alternate method of contraception, such as barrier methods, should be used.

Male patients must use a condom during intercourse and not to father a child during therapy and for 4 months following discontinuation of dabrafenib to avoid unnecessary exposure of dabrafenib to the foetus.

*Infertility*

Adverse effects on male reproductive organs have been seen in animals. Male patients should be informed of the potential risk for impaired spermatogenesis, which may be irreversible**.**

**4.7 Effects on ability to drive and use machines**

The clinical status of the patient and the adverse event profile of RAFINLAR should be borne in mind when considering the patient's ability to perform tasks that require judgment, motor and cognitive skills. Driving ability may be impaired by such adverse events.

**4.8 Undesirable effects**

**Summary of the safety profile**

**Unresectable or metastatic melanoma**

Safety data for RAFINLAR monotherapy was integrated from five clinical monotherapy studies and included 578 patients with BRAF V600 mutant unresectable or metastatic melanoma. Approximately 30 % of patients received treatment with RAFINLAR for more than six months. In the integrated RAFINLAR safety population, the most common (≥ 15 %) adverse events were hyperkeratosis, headache, pyrexia, arthralgia, fatigue, nausea, skin papilloma, alopecia, rash and vomiting**.**

*Tabulated summary of adverse events from clinical trials in metastatic melanoma:*

Adverse events from clinical trials in patients with metastatic melanoma are listed in Table 6 for RAFINLAR monotherapy. Adverse drug reactions are ranked by frequency with the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

**Table 6 Melanoma - adverse events for RAFINLAR monotherapy**

| **Adverse events** | **Frequency category** |
|---|---|
| **Infections and infestations** | |
| Nasopharyngitis | Common |
| **Neoplasms benign and malignant (including cysts and polyps)** | |
| Papilloma | Very common |
| Acrochordon (skin tags), cutaneous squamous cell carcinoma (SCC) including SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma, seborrhoeic keratosis | Common |
| New primary melanoma | Uncommon |
| **Immune System Disorders** | |
| Hypersensitivity | Uncommon |
| **Metabolism and nutrition disorders** | |

| | |
|---|---|
| Decreased appetite | Very common |
| Hypophosphataemia<br><br>Hyperglycaemia | Common |
| **Nervous system disorders** | |
| Headache | Very common |
| **Eye disorders** | |
| Uveitis | Uncommon |
| **Respiratory, thoracic and mediastinal disorders** | |
| Cough | Very common |
| **Gastrointestinal disorders** | |
| Nausea, vomiting, diarrhoea | Very common |
| Constipation | Common |
| Pancreatitis | Uncommon |
| **Skin and subcutaneous tissue disorders** | |
| Skin effects (rash, hyperkeratosis), alopecia, palmar- | Very common |
| Skin effects (actinic keratosis, skin lesion, dry skin,<br><br>erythema, pruritus | Common |
| Panniculitis | Uncommon |
| Photosensitivity reaction[1] | Common |
| **Musculoskeletal and connective tissue disorders** | |
| Arthralgia, myalgia, pain in extremity | Very common |
| **Renal disorders** | |
| Renal failure, acute renal failure | Uncommon |
| Tubulointerstitial nephritis | Uncommon |

[1] Photosensitivity cases were also observed in post-marketing experience. All cases reported in clinical trials were Grade 1 and no dose modification was required.

Table 7 lists adverse events when RAFINLAR was used in combination with trametinib from the randomised double-blind Phase III study MEK115306 (N=209), and integrated safety data from MEK115306 (N=209) and from the randomised open-label Phase III study MEK116513 (N=350).

**Table 7 Unresectable or metastatic melanoma - adverse events for RAFINLAR in combination with trametinib**

| **Adverse events** | **Frequency category** | |
|---|---|---|
| | Double blind study n=209 | Open label studies Integrated Safety Data n=559 |
| **Infections and Infestations** | | |
| Urinary tract infection | Very common | Common |
| Nasopharyngitis | Very common | Very common |
| Cellulitis | Common | Common |
| Folliculitis | Common | Common |
| Paronychia | Common | Common |
| Rash pustular | Common | Common |
| **Neoplasms benign, malignant and unspecified (including cysts and polyps)** | | |
| Cutaneous squamous cell carcinoma (SCC) including SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma | Common | Common |
| Papilloma including skin papilloma | Common | Common |
| Seborrhoeic keratosis | Common | Common |
| Acrochordon (skin tags) | Common | Uncommon |
| New primary melanoma | Uncommon | Uncommon |
| **Blood and lymphatic system disorders** | | |
| Neutropenia | Very Common | Common |
| Anaemia | Common | Common |
| Thrombocytopenia | Common | Common |

| | | |
|---|---|---|
| Leukopenia | Common | Common |
| **Immune system disorders** | | |
| Hypersensitivity | Uncommon | Uncommon |
| **Metabolic and nutrition disorders** | | |
| Decreased appetite | Very common | Very common |
| Dehydration | Common | Common |
| Hyperglycaemia | Common | Common |
| Hyponatraemia | Common | Common |
| Hypophosphataemia | Common | Common |
| **Nervous system disorders** | | |
| Headache | Very common | Very common |
| Dizziness | Very common | Very common |
| **Eye disorders** | | |
| Vision blurred | Common | Common |
| Visual impairment | Common | Common |
| Chorioretinopathy | Uncommon | Uncommon |
| Uveitis | Uncommon | Uncommon |
| Retinal detachment | Uncommon | Uncommon |
| Periorbital oedema | Uncommon | Uncommon |
| **Cardiac disorders** | | |
| Ejection fraction decreased | Common | Common |
| Left ventricular dysfunction | Not reported | Uncommon |
| Cardiac failure | Not reported | Uncommon |
| Bradycardia | Common | Common |
| **Vascular disorders** | | |
| Hypertension | Very common | Very common |

| | | |
|---|---|---|
| Haemorrhage[1)] | Very common | Very common |
| Hypotension | Common | Common |
| Lymphoedema | Uncommon | Common |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Cough | Very common | Very common |
| Dyspnoea | Common | Common |
| Pneumonitis | Uncommon | Uncommon |
| Interstitial lung disease | Not reported | Uncommon |
| **Gastrointestinal disorders** | | |
| Gastrointestinal perforation | Not reported | Uncommon |
| Colitis | Uncommon | Uncommon |
| Abdominal pain | Very common | Very common |
| Constipation | Very common | Very common |
| Diarrhoea | Very common | Very common |
| Nausea | Very common | Very common |
| Vomiting | Very common | Very common |
| Dry mouth | Common | Common |
| Stomatitis | Common | Common |
| Pancreatitis | Uncommon | Uncommon |
| **Skin and subcutaneous tissue disorders** | | |
| Dry skin | Very common | Very common |
| Pruritus | Very common | Very common |
| Rash | Very common | Very common |
| Dermatitis acneiform | Very common | Common |
| Erythema | Common | Common |
| Actinic keratosis | Common | Common |

| | | |
|---|---|---|
| Night sweats | Common | Common |
| Hyperkeratosis | Common | Common |
| Alopecia | Common | Common |
| Palmar-plantar erythrodysaesthesia syndrome | Common | Common |
| Skin lesion | Common | Common |
| Hyperhidrosis | Common | Common |
| Skin fissures | Common | Common |
| Panniculitis | Common | Common |
| Photosensitivity reaction[2)] | Common | Common |
| **Musculoskeletal and connective tissue disorders** | | |
| Arthralgia | Very common | Very common |
| Myalgia | Very common | Very common |
| Pain in extremity | Very common | Very common |
| Muscle spasms | Common | Common |
| Blood creatine phosphokinase increased | Common | Common |
| Rhabdomyolysis | Not reported | Uncommon |
| **Renal disorders** | | |
| Renal failure | Uncommon | Common |
| Nephritis | Uncommon | Uncommon |
| Renal failure acute | Not reported | Uncommon |
| **General disorders and administration site disorders** | | |
| Fatigue | Very common | Very common |
| Oedema peripheral | Very common | Very common |
| Pyrexia | Very common | Very common |

| | | |
|---|---|---|
| Chills | Very common | Very common |
| Asthenia | Very common | Very common |
| Mucosal inflammation | Common | Common |
| Influenza-like illness | Common | Common |
| Face oedema | Common | Common |
| **Investigations** | | |
| Alanine aminotransferase increased | Very common | Very common |
| Aspartate aminotransferase increased | Very common | Very common |
| Blood alkaline phosphatase increased | Common | Common |
| Gamma-glutamyltransferase increased | Common | Common |

*[1)] The majority of bleeding events were mild. Major events, defined as symptomatic bleeding in a critical area or organ, and fatal intracranial haemorrhages have been reported.*

*[2)] Photosensitivity cases were also observed in post-marketing experience. All cases reported in clinical trials were Grade 1 and no dose modification was required.*

**Adjuvant treatment of melanoma**

*RAFINLAR in combination with trametinib*

The safety of RAFINLAR in combination with trametinib was evaluated in a Phase III, randomised, double-blind study of RAFINLAR in combination with trametinib versus two placebos in the adjuvant treatment of Stage III BRAF V600 mutation-positive melanoma after surgical resection.

In the RAFINLAR 150 mg twice daily and trametinib 2 mg once daily arm, the most common adverse reactions (≥ 20 %) were pyrexia, fatigue, nausea, headache, rash, chills, diarrhoea, vomiting, arthralgia, and myalgia.

Table 8 lists the adverse drug reactions in study BRF115532 (COMBI-AD) occurring at an incidence ≥ 10 % for all grade adverse reactions or at an incidence ≥ 2 % for Grade 3 and Grade 4 adverse drugs reactions or adverse events that are medically significant in the RAFINLAR in combination with trametinib arm.

Adverse drug reactions are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent adverse drug reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

**Table 8: Adjuvant treatment of melanoma – adverse drug reactions for RAFINLAR in combination with trametinib vs. placebo**

| Adverse drug reactions | RAFINLAR in combination with Trametinib N=435 % | | Placebo N=432 % | | Frequency category (combination arm, all grades) |
|---|---|---|---|---|---|
| | All Grades % | Grade 3/4 % | All Grades % | Grade 3/4 % | |
| **Infections and infestations** | | | | | |
| Nasopharyngitis[1)] | 12 | <1 | 12 | NR | Very common |
| **Blood and lymphatic system disorders** | | | | | |
| Neutropenia[2)] | 10 | 5 | <1 | NR | Very common |
| **Metabolism and nutrition disorders** | | | | | |
| Decreased appetite | 11 | <1 | 6 | NR | Very common |
| **Nervous system disorders** | | | | | |
| Headache[3)] | 39 | 1 | 24 | NR | Very common |
| Dizziness[4)] | 11 | <1 | 10 | NR | Very common |
| **Eye disorders** | | | | | |
| Uveitis | 1 | <1 | <1 | NR | Common |
| Chorioretinopathy[5)] | 1 | <1 | <1 | NR | Common |
| Retinal detachment[6)] | 1 | <1 | <1 | NR | Common |
| **Vascular disorders** | | | | | |
| Haemorrhage[7)] | 15 | <1 | 4 | <1 | Very common |

| | | | | | |
|---|---|---|---|---|---|
| Hypertension[8)] | 11 | 6 | 8 | 2 | Very common |
| **Respiratory, thoracic, and mediastinal disorders** | | | | | |
| Cough[9)] | 17 | NR | 8 | NR | Very common |
| **Gastrointestinal disorders** | | | | | |
| Nausea | 40 | <1 | 20 | NR | Very common |
| Diarrhoea | 33 | <1 | 15 | <1 | Very common |
| Vomiting | 28 | <1 | 10 | NR | Very common |
| Abdominal pain[10)] | 16 | <1 | 11 | <1 | Very common |
| Constipation | 12 | NR | 6 | NR | Very common |
| **Skin and subcutaneous tissue disorders** | | | | | |
| Rash[11)] | 37 | <1 | 16 | <1 | Very common |
| Dry skin[12)] | 14 | NR | 9 | NR | Very common |
| Dermatitis acneiform | 12 | <1 | 2 | NR | Very common |
| Erythema[13)] | 12 | NR | 3 | NR | Very common |
| Pruritus[14)] | 11 | <1 | 10 | NR | Very common |
| Palmar-plantar erythrodysaesthesia syndrome | 6 | <1 | 1 | <1 | Common |
| **Musculoskeletal and connective tissue disorders** | | | | | |
| Arthralgia | 28 | <1 | 14 | NR | Very common |
| Myalgia[15)] | 20 | <1 | 14 | NR | Very common |
| Pain in extremity | 14 | <1 | 9 | NR | Very common |
| Muscle spasms[16)] | 11 | NR | 4 | NR | Very common |
| Rhabdomyolysis | <1 | <1 | NR | NR | Uncommon |
| **Renal and urinary disorders** | | | | | |
| Renal failure | <1 | NR | NR | NR | Uncommon |
| **General disorders and administration site conditions** | | | | | |
| Pyrexia[17)] | 63 | 5 | 11 | <1 | Very common |
| Fatigue[18)] | 59 | 5 | 37 | <1 | Very common |
| Chills | 37 | 1 | 4 | NR | Very common |
| Oedema peripheral[19)] | 16 | <1 | 6 | NR | Very common |
| Influenza-like illness | 15 | <1 | 7 | NR | Very common |
| **Investigations** | | | | | |
| Alanine aminotransferase increased[20)] | 17 | 4 | 2 | <1 | Very common |
| Aspartate aminotransferase increased[21)] | 16 | 4 | 2 | <1 | Very common |
| Alkaline phosphatase increased | 7 | <1 | <1 | <1 | Common |
| Ejection fraction decreased | 5 | NR | 2 | <1 | Common |

[1] *Nasopharyngitis also includes pharyngitis.*
[2] *Neutropenia also includes febrile neutropenia and cases of neutrophil count decreased that met the criteria for neutropenia.*
[3] *Headache also includes tension headache.*
[4] *Dizziness also includes vertigo.*
[5] *Chorioretinopathy also includes chorioretinal disorder.*
[6] *Retinal detachment also includes detachment of macular retinal pigment epithelium and detachment of retinal pigment epithelium.*
[7] *Haemorrhage includes a comprehensive list of hundreds of event terms that capture bleeding events.*
[8] *Hypertension also includes hypertensive crisis.*
[9] *Cough also includes productive cough.*
[10] *Abdominal pain also includes abdominal pain upper and abdominal pain lower.*
[11] *Rash also includes rash maculo-papular, rash macular, rash generalized, rash erythematous, rash papular, rash pruritic, nodular rash, rash vesicular, and rash pustular.*
[12] *Dry skin also includes xerosis and xeroderma.*
[13] *Erythema also includes generalized erythema.*
[14] *Pruritus also includes pruritus generalised and pruritus genital.*
[15] *Myalgia also includes musculoskeletal pain and musculoskeletal chest pain.*
[16] *Muscle spasms also includes musculoskeletal stiffness.*
[17] *Pyrexia also includes hyperpyrexia.*
[18] *Fatigue also includes asthenia and malaise.*
[19] *Oedema peripheral also includes peripheral swelling.*
[20] *Alanine aminotransferase increased also includes hepatic enzyme increased, liver function test increased, liver function test abnormal, and hypertransaminasaemia.*
[21] *Aspartate aminotransferase increased also includes hepatic enzyme increased, liver function test increased, liver function test abnormal, and hypertransaminasaemia.*
*NR: not reported*

**Advanced non-small cell cancer**

*RAFINLAR monotherapy:*

The safety of RAFINLAR monotherapy has been evaluated in a Phase II, multicentre, multi-cohort, non-randomised, open label study of patients with BRAF V600E mutation metastatic NSCLC.

In the RAFINLAR 150 mg twice daily (N=84) monotherapy arm (Cohort A) the most common adverse drug reactions (≥ 20 %) were pyrexia, asthenia, fatigue, hyperkeratosis, cough, skin papilloma, dry skin, palmar-plantar erythrodysaesthesia syndrome, alopecia, nausea, and dyspnoea.

*RAFINLAR in combination with trametinib:*

The safety of RAFINLAR in combination with trametinib has been evaluated in a Phase II, multicentre, multi- cohort, non-randomised, open label study of patients with BRAF V600E mutation metastatic NSCLC.

In the trametinib 2 mg orally once daily and RAFINLAR 150 mg orally twice daily arms (Cohorts B and C), the most common adverse drug reactions (≥ 20 %) for trametinib and dabrafenib combination therapy were pyrexia, nausea, vomiting, diarrhoea, decreased appetite, asthenia, dry skin, chills, cough, fatigue, rash, dyspnoea and peripheral oedema.

Table 9 lists the adverse drug reactions for RAFINLAR in combination with trametinib occurring at an incidence ≥ 10 % for all grade adverse drug reactions or at an incidence ≥ 2 % for Grade 3 and Grade 4 adverse drug reactions in Cohorts B and C of study BRF113928.

**Table 9 Advanced NSCLC - Adverse drug reactions for RAFINLAR in combination with trametinib**

| **Adverse drug reaction** | **Trametinib in combination with RAFINLAR** | | **Frequency category** |
|---|---|---|---|
| | All grades n = 93 % | Grades 3/4 n = 93 % (%) | |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | | | |
| Cutaneous squamous cell carcinoma of skin | 3 | 2 | Common |
| **Blood and lymphatic system disorders** | | | |
| Neutropenia [1] | 15 | 8 | Very common |
| Leukopenia | 6 | 2 | Common |
| **Metabolism and nutrition disorders** | | | |
| Hyponatraemia | 14 | 9 | Very Common |
| Dehydration | 8 | 3 | Common |
| **Eye disorders** | | | |
| Detachment of retina/retinal pigment | 2 | NR | Common |
| **Nervous system disorders** | | | |
| Headache | 16 | NR | Very common |
| Dizziness | 14 | NR | Very common |
| Cardiac disorders | | | |
| Ejection fraction decreased | 9 | 4 | Common |
| **Vascular disorders** | | | |

| | | | |
|---|---|---|---|
| Haemorrhage[2] | 26 | 3 | Very common |
| Hypotension | 15 | NR | Very common |
| Pulmonary embolism | 4 | 2 | Common |
| Hypertension | 8 | 6 | Common |
| **Gastrointestinal disorders** | | | |
| Nausea | 46 | NR | Very common |
| Vomiting | 37 | 3 | Very common |
| Diarrhoea | 33 | 2 | Very common |
| Decreased appetite | 28 | NR | Very common |
| Constipation | 16 | NR | Very common |
| Pancreatitis acute | 13 | 1 | Very common |
| **Skin and subcutaneous tissue disorders** | | | |
| Erythema | 10 | NR | Very common |
| Dry skin | 32 | 1 | Very common |
| Rash [3] | 31 | 3 | Very common |
| Pruritus [4] | 15 | 2 | Very common |
| Hyperkeratosis [5] | 13 | 1 | Very common |
| **Musculoskeletal and connective tissue disorders** | | | |
| Muscle spasms | 10 | NR | Very common |
| Arthralgia | 16 | NR | Very common |
| Myalgia | 13 | NR | Very common |
| **Renal and urinary disorders** | | | |
| Renal failure | 3 | 1 | Common |
| Tubulointerstitial nephritis | 2 | 2 | Common |
| **General disorders and administration site disorders** | | | |
| Pyrexia | 55 | 5 | Very common |
| Asthenia [6] | 47 | 6 | Very common |
| Oedema [7] | 35 | NR | Very common |
| Chills | 24 | 1 | Very common |
| **Investigations** | | | |
| Blood alkaline phosphatase increased | 12 | NR | Very common |
| Gamma-glutamyltransferase increased | 2 | 2 | Common |
| Aspartate aminotransferase increased | 11 | 2 | Very Common |
| Alanine aminotransferase increased | 10 | 4 | Very Common |

*[1] Neutropenia includes neutropenia and neutrophil count decreased. Neutrophil count decreased qualified as a neutropenia event.*
*[2.] Haemorrhage includes cases of haemoptysis, haematoma, epistaxis, purpura, haematuria, subarachnoid haemorrhage, gastric haemorrhage, urinary bladder haemorrhage, contusion, haematochezia, injection site haemorrhage, melaena, pulmonary and retroperitoneal haemorrhage.*
*[3] Rash includes rash, rash generalized, rash papular, rash macular, rash maculo-papular, and rash pustular.*
*[4] Pruritus includes pruritus, pruritus generalized, and eye pruritus.*
*[5] Hyperkeratosis includes hyperkeratosis, actinic keratosis, seborrhoeic keratosis, and keratosis pilaris.*
*[6] Asthenia also includes fatigue and malaise.*
*[7] Oedema includes generalized oedema and peripheral oedema.*
*NR: Not Reported*

**Unresectable or metastatic solid tumours**

*RAFINLAR in combination with trametinib*

Further safety of RAFINLAR in combination with trametinib was evaluated in a multi-cohort, multi-centre, non-randomised, open-label study in adult patients with cancers with the BRAF V600E mutation (Study BRF117019). A total of 206 patients were enrolled in the trial, 36 of whom were enrolled in the ATC cohort, 105 were enrolled in specific solid tumour cohorts, and 65 in other malignancies. Patients received RAFINLAR 150 mg orally twice daily and trametinib 2 mg orally once daily until disease progression or unacceptable toxicity.

Among these 206 patients, 103 (50 %) were exposed to RAFINLAR for ≥ 1 year and 101 (49 %) were exposed to trametinib for ≥ 1 year. The median age was 60 years (range: 18 to 89); 56 % were male; 79 % were white; and 34 % had baseline ECOG performance status 0 and 60 % had ECOG performance status 1.

The adverse reaction profile among all patients in Study BRF117019 was similar to that observed in other approved indications.

**Special populations**

**Paediatric patients**

*RAFINLAR in combination with trametinib*

The safety of RAFINLAR in combination with trametinib was studied in 171 paediatric patients across two studies (G2201 and X2101) with BRAF V600E mutation-positive advanced solid tumours, of which 4 (2.3 %) patients were 1 to < 2 years of age, 39 (22.8 %) patients were 2 to < 6 years of age, 54 (31,6 %) patients were 6 to < 12 years of age, and 74 (43.3 %) patients were 12 to < 18 years of age.

The overall safety profile in the paediatric population was similar to the safety profile observed in adults. The most frequently reported adverse drug reactions (≥ 20 %) were pyrexia, rash, headache, vomiting, dry skin, fatigue, diarrhoea, haemorrhage, neutropenia, nausea, dermatitis acneiform, abdominal pain, and cough.

An adverse drug reaction of weight increased was identified in the paediatric safety pool with a frequency of 15.2 % (very common). Fifty-one out of 171 patients (29.8 %) had an increase from baseline of ≥ 2 BMI-for-age- percentile categories.

Adverse drug reactions occurring at a higher frequency category in paediatric patients compared to adult patients were neutropenia, dermatitis acneiform, paronychia, anaemia, leukopenia (very common); bradycardia, dermatitis exfoliative generalised, hypersensitivity and pancreatitis (common).

**Table 10 Most frequent Grade 3/4 Adverse drug reactions (≥ 2 %) for RAFINLAR in combination with trametinib in paediatric patients**

| **Adverse drug reactions** | **RAFINLAR in combination with trametinib N=171** |
|---|---|
| | **Grade 3/4 n (%)** |
| Neutropenia[1] | 25 (15) |
| Pyrexia | 15 (9) |
| Alanine aminotransferase increased[2] | 10 (6) |
| Aspartate aminotransferase increased[3] | 6 (4) |
| Weight Increased | 7 (4) |
| Headache | 5 (3) |
| Vomiting | 5 (3) |
| Hypotension | 4 (2) |
| Rash[4] | 4 (2) |
| Blood alkaline phosphatase increased | 4 (2) |

1. *Neutropenia includes neutropenia, neutrophil count decreased, and febrile neutropenia.*
2. *ALT includes Alanine aminotransferase increased and transaminases increased.*
3. *AST includes Aspartate aminotransferase increased and transaminases increased.*
4. *Rash includes rash, rash maculo-papular, rash pustular, rash erythematous, rash papular, and rash macular.*

**Adverse drug reactions (ADRs) from post-marketing experience and pooled clinical trials**

The following ADRs have been derived from post-marketing experience including spontaneous case reports with RAFINLAR in combination with trametinib. Because post-marketing ADRs are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency. Where applicable, these ADR frequencies have been calculated from the pooled clinical trials across indications. ADRs are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

**Table 11 ADRs from post-marketing experience and pooled clinical trials across indications**

| **Adverse drug reaction** | **RAFINLAR in combination with trametinib Frequency category** | **RAFINLAR monotherapy Frequency category** |
|---|---|---|
| **Cardiac disorders** | | |
| Atrioventricular block[1] | Uncommon | - |
| Bundle branch block[2] | Rare | - |
| **Immune system disorders** | | |
| Sarcoidosis | Uncommon | - |
| Haemophagocytic lymphohistiocytosis | Not known | - |
| **Vascular disorders** | | |
| Venous thrombo-embolism[3] | Common | - |

| | | |
|---|---|---|
| **Metabolism and nutrition disorders** | | |
| Tumour lysis syndrome | Not known | - |
| **Nervous system disorders** | | |
| Peripheral neuropathy | Common | Common |

*1) Atrioventricular block includes atrioventricular block, atrioventricular block first degree, atrioventricular block second degree and atrioventricular block complete.*
*2) Bundle branch block includes bundle branch block, bundle branch block right and bundle branch block left.*
*3) VTE includes, pulmonary embolism, deep vein thrombosis, embolism and venous thrombosis.*

*Reporting of suspected adverse reactions*

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

**4.9 Overdose**

There is currently very limited experience with overdosage with RAFINLAR. The maximum dose of RAFINLAR administered during clinical trials was 600 mg (300 mg twice daily)**.**

*Treatment*

There is no specific antidote for overdosage of RAFINLAR. Patients who develop adverse reactions should receive appropriate symptomatic treatment. In case of suspected overdose, RAFINLAR should be withheld and supportive care instituted.

**5. PHARMACOLOGICAL PROPERTIES**

**Pharmacotherapeutic group, ATC**

B-Raf serine-threonine kinase (BRAF) inhibitors, ATC code: L01EC02.

**5.1 Pharmacodynamic properties**

Dabrafenib is a potent, selective, ATP-competitive inhibitor of RAF kinases with IC50 values of 0.65, 0.5 and 1.84 nM for BRAFV600E, BRAFV600K and BRAFV600D enzymes, respectively. Oncogenic mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway and stimulation of tumour cell growth. BRAF mutations have been identified. Dabrafenib also inhibits wildtype BRAF and CRAF enzymes with IC50 values of 3.2 and 5.0 nM, respectively. Dabrafenib inhibits BRAF V600 mutant melanoma cell growth *in vitro* and *in vivo*.

In patients with BRAF V600 mutant melanoma, administration of dabrafenib resulted in inhibition of tumour phosphorylated ERK relative to baseline.

*Cardiac electrophysiology*

The potential effect of dabrafenib on QT prolongation was assessed in a dedicated multiple dose QT study. A supratherapeutic dose of 300 mg RAFINLAR twice daily was administered in 32 patients with BRAF V600 mutation-positive tumours. No clinically relevant effect of dabrafenib or its metabolites on the QTc interval was observed.

**Other Studies**

*Pyrexia Management Analysis*

Pyrexia is observed in patients treated with dabrafenib and trametinib combination therapy. The initial registration studies for the combination therapy in the unresectable or metastatic melanoma setting (COMBI-d and COMBI-v; total N=559) and in the adjuvant melanoma setting (COMBI-AD, N=435) recommended to interrupt only dabrafenib in case of pyrexia. In two subsequent studies in unresectable or metastatic melanoma (COMBI-i control arm, N=264) and in the adjuvant melanoma setting (COMBI-A plus, N=552), interruption of both dabrafenib and trametinib when patient's temperature was ≥ 38 ºC (COMBI-A plus) or at the first symptom of pyrexia (COMBI-i; COMBI-A plus for recurrent pyrexia), resulted in improved pyrexia-related outcomes without impacting efficacy:

Unresectable or metastatic melanoma setting (COMBI-d/v vs COMBI-i):

- grade 3/4 pyrexia reduced from 6.6 % to 3.4 %
- hospitalisation due to pyrexia reduced from 12.3 % to 6.1 %
- pyrexia with complications (dehydration, hypotension, renal dysfunction, syncope, severe chills) reduced from 6.4 % to 1.9 %
- treatment discontinuation rates due to pyrexia were comparable, 1.1 % vs 1.9 %

Adjuvant melanoma setting (COMBI-AD vs COMBI- Aplus):

- grade 3/4 pyrexia reduced from 5.7 % to 4.3 %
- hospitalisation due to pyrexia reduced from 11.0 % to 5.1 %
- pyrexia with complications (dehydration, hypotension, renal dysfunction, syncope, severe chills) reduced from 6.0 % to 22 %
- treatment discontinuation due to pyrexia reduced from 6.2 % to 2.5 %

**5.2 Pharmacokinetic properties**

**Absorption**

Dabrafenib is absorbed orally with median time to achieve peak plasma concentration of 2 hours post-dose. Mean absolute bioavailability of oral dabrafenib is 95 % (90 % CI: 81, 110). Dabrafenib exposure ($C_{max}$ and AUC) increased in a dose proportional manner between 12 and 300 mg following single-dose administration, but the increase was less than dose-proportional after repeat twice daily dosing. There was a decrease in exposure observed with repeat dosing, likely due to induction of its own metabolism. Mean accumulation AUC Day 18/Day 1 ratios was 0.73. Following administration of 150 mg twice daily, geometric mean Cmax, AUC0- $\tau$ and predose concentration ($C\tau$) were 1.478 ng/mL, 4.341 ng*hr/mL and 26 ng/mL, respectively. Administration of dabrafenib with food reduced the bioavailability ($C_{max}$ and AUC decreased by 51 % and 31 % respectively) and delayed absorption of dabrafenib when compared to the fasted state**.** Dabrafenib capsules are immediate-release formulations that are expected to have similar food effects on PK.

**Distribution**

Dabrafenib binds to human plasma protein and is 99.7 % bound. The steady-state volume of distribution following intravenous microdose administration is 46 L**.**

**Biotransformation/metabolism**

The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4 to form hydroxy-dabrafenib, which is further oxidised via CYP3A4 to form carboxy-dabrafenib. Carboxy-dabrafenib can be decarboxylated via a non-enzymatic process to form desmethyl-dabrafenib. Carboxy-dabrafenib is excreted in bile and urine. Desmethyl-dabrafenib may also be formed in the gut and reabsorbed. Desmethyl-dabrafenib is metabolised by CYP3A4 to oxidative metabolites. Hydroxy-dabrafenib terminal half-life parallels that of parent with a half- life of 10 hrs while the carboxy- and desmethyl-metabolites exhibited longer half-lives (21 to 22 hours). Mean metabolite to parent AUC ratios following repeat-dose administration were 0.9, 11 and 0.7 for hydroxy-, carboxy-, and desmethyl-dabrafenib, respectively. Based on exposure, relative potency, and pharmacokinetic properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib; while the activity of carboxy-dabrafenib is not likely to be significant.

**Elimination**

Terminal half-life following IV microdose is 2.6 hours. Dabrafenib terminal half-life is 8 hours due to a prolonged terminal phase after oral administration. IV plasma clearance is 12 L/hour. Faecal excretion is the major route of elimination after oral dosing, accounting for 71 % of a radioactive dose while urinary excretion accounted for 23 % of radioactivity**.**

*In vitro evaluation of medicines interaction potential effect of other medicines on dabrafenib:*

*In vitro* results indicate that CYP2C8 and CYP3A4 are the primary CYP enzymes involved in the oxidative metabolism of dabrafenib while hydroxy-dabrafenib and desmethyl-dabrafenib are CYP3A4 substrates. Therefore, inhibitors or inducers of these enzymes have the potential to affect the PK of dabrafenib or its metabolites (see section 4.5). Dabrafenib is a substrate of human Pgp and breast cancer resistance protein

(BCRP) in vitro. However, these transporters have minimal impact on dabrafenib oral bioavailability and elimination, and the risk of a interaction is minimal**.**

*Effect of dabrafinib on other medicine:*

In human hepatocytes, dabrafenib produced concentration-dependent increases in CYP2B6 and CYP3A4 mRNA levels up to 32 times the control levels. Although dabrafenib and its metabolites, hydroxy-dabrafenib, carboxy-dabrafenib and desmethyl-dabrafenib, were inhibitors of human organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic anion transporter (OAT) 1 and OAT3, and dabrafenib and its desmethyl metabolite were found to be inhibitors of organic cation transporter 2 (OCT2) *in vitro*, the risk of an interaction is minimal based on clinical exposure. Dabrafenib and desmethyl-dabrafenib were shown to be moderate inhibitors of human BCRP; however, based on clinical exposure, the risk of a interaction is minimal. Neither dabrafenib nor its 3 metabolites were demonstrated to be inhibitors of Pgp *in vitro***.**

**SPECIAL POPULATIONS:**

*Paediatric population (below 18 years)*

The pharmacokinetics of dabrafenib in glioma and other solid tumours were evaluated in 243 paediatric patients (1 to < 18 years old) following single or repeat weight-adjusted dosing. Pharmacokinetic characteristics (drug absorption rate, metabolite ratios, drug clearance) of dabrafenib in paediatric patients are comparable to those of adults. Weight was found to influence dabrafenib oral clearance. The pharmacokinetic exposures of dabrafenib at the recommended weight-adjusted dosage in paediatric patients were within range of those observed in adults**.**

*Elderly population (65 years of age or older)*

Based on the population pharmacokinetic analysis, age had no significant effect on dabrafenib pharmacokinetics. Age greater than 75 years was a significant predictor of carboxy- and desmethyl- dabrafenib plasma concentrations with a 40 % greater exposure in patients ≥ 75 years of age, relative to patients < 75 years old**.**

*Gender/Weight*

Based on the adult population pharmacokinetic analysis, gender and weight were found to influence dabrafenib oral clearance; weight also impacted oral volume of distribution and distributional clearance. These pharmacokinetic differences were not considered clinically relevant**.**

*Renal impairment*

The pharmacokinetics of dabrafenib were characterised in 233 patients with mild renal impairment (GFR 60 to 89 mL/min/1.73 $m^2$) and 30 patients with moderate renal impairment (GFR 30 to 59 mL/min/1.73 $m^2$) enrolled in clinical trials using a population analysis. The effect of mild or moderate renal impairment on dabrafenib oral clearance was small (< 6 % for both categories) and not clinically relevant. In addition, mild and moderate renal impairment did not have a significant effect on hydroxy-, carboxy-, and desmethyl- dabrafenib plasma concentrations. No data are available in patients with severe renal impairment (see section 4.2).

*Hepatic impairment*

The pharmacokinetics of dabrafenib has been characterised in 65 patients with mild hepatic impairment (based on National Cancer Institute [NCI] classification) enrolled in clinical trials using a population analysis. Dabrafenib oral clearance was not significantly different between these patients and patients with normal hepatic function (4 % difference). In addition, mild hepatic impairment did not have a significant effect on dabrafenib metabolite plasma concentrations. No data are available in patients with moderate to severe hepatic impairment (see section 4.2).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Hypromellose capsule: microcrystalline cellulose, magnesium stearate (vegetable source), colloidal silicon dioxide.
Shell composition: red iron oxide, titanium dioxide, hypromellose.
Monogramming: black iron oxide, shellac ammonium hydroxide.

RAFINLAR does not contain sugar.

**6.3 Shelf-life**

36 months

**6.4 Special precautions for storage**

Store at or below 30 ˚C. Store in the original container. Do not remove the desiccant.

**6.5 Nature and contents of container**

**RAFINLAR 50 and 75 mg capsules** are packed in white HDPE bottles with white child resistant polypropylene closures inside an outer carton. This product is packaged with a silica desiccant.

Pack sizes: 28, 56 or 120 capsules per bottle.

**7. HOLDER OF CERTIFICATE OF REGISTRATION**

Novartis South Africa (Pty) Ltd.

Magwa Crescent West

Waterfall City, Jukskei View

Johannesburg

2090

+27 11 347 6600

**8. REGISTRATION NUMBERS**

**RAFINLAR 50 mg:** 51/32.2/0817

**RAFINLAR 75 mg:** 51/32.2/0818

**9. DATE OF FIRST AUTHORISATION**

20 March 2019

## 10. DATE OF REVISION OF THE TEXT

20 August 2026