Name: Tafinlar 50 mg / 75 mg hard capsules. **Composition:** Each hard capsule contains dabrafenib mesilate equivalent to 50 mg / 75 mg of dabrafenib. For the full list of excipients, see full leaflet. **Pharmaceutical form:** Hard capsule (capsule). Tafinlar 50 mg hard capsules: Opaque dark red capsules, approximately 18 mm long, with capsule shell imprinted with "GS TEW" and "50 mg". Tafinlar 75 mg hard capsules: Opaque dark pink capsules, approximately 19 mm long, with capsule shell imprinted with "GS LHF" and "75 mg". **Therapeutic indications:** Melanoma: Dabrafenib as monotherapy or in combination with trametinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see full leaflet). Adjuvant treatment of melanoma.Dabrafenib in combination with trametinib is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection. Non-small cell lung cancer (NSCLC): Dabrafenib in combination with trametinib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation. **Posology:** Treatment with dabrafenib should be initiated and supervised by a qualified physician experienced in the use of anticancer medicinal products. Before taking dabrafenib, patients must have confirmation of tumour BRAF V600 mutation using a validated test. The efficacy and safety of dabrafenib have not been established in patients with wild-type BRAF melanoma or wild-type BRAF NSCLC therefore dabrafenib should not be used in patients with wild-type BRAF melanoma or wild-type BRAF NSCLC (see full leaflet). The recommended dose of dabrafenib, either used as monotherapy or in combination with trametinib, is 150 mg (two 75 mg capsules) twice daily (corresponding to a total daily dose of 300 mg). The recommended dose of trametinib, when used in combination with dabrafenib, is 2 mg once daily. *Duration of treatment:* Treatment should continue until the patient no longer derives benefit or the development of unacceptable toxicity (see full leaflet, Table 2). In the adjuvant melanoma setting, patients should be treated for a period of 12 months unless there is disease recurrence or unacceptable toxicity.. *Missed doses:* If a dose of dabrafenib is missed, it should not be taken if it is less than 6 hours until the next scheduled dose. If a dose of trametinib is missed, when dabrafenib is given in combination with trametinib, the dose of trametinib should only be taken if it is more than 12 hours until the next scheduled dose. *Dose modification:* Two dabrafenib capsule strengths, 50 mg and 75 mg, are available to effectively manage dose modification requirements. The management of adverse reactions may require treatment interruption, dose reduction, or treatment discontinuation (see full leaflet, Tables 1 and 2). Dose modifications or interruptions are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma (see full leaflet). No dose modifications are required for uveitis as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, withhold dabrafenib until resolution of ocular inflammation and then restart dabrafenib reduced by one dose level. Recommended dose level reductions and recommendations for dose modifications are provided in Tables 1 and 2, respectively

Table 1 Recommended dose level reductions

Dose level	**Dabrafenib dose** Used as monotherapy or in combination with trametinib	**Trametinib dose*** Only when used in combination with dabrafenib
Starting dose	150 mg twice daily	2 mg once daily
1st dose reduction	100 mg twice daily	1.5 mg once daily
2nd dose reduction	75 mg twice daily	1 mg once daily
3rd dose reduction	50 mg twice daily	1 mg once daily
Dose adjustment for dabrafenib below 50 mg twice daily is not recommended, whether used as monotherapy or in combination with trametinib. Dose adjustment for trametinib below 1 mg once daily is not recommended, when used in combination with dabrafenib.		
*Please refer to the trametinib SmPC, Posology and method of administration, for dosing instructions for treatment with trametinib monotherapy.		

Table 2 Dose modification schedule based on the grade of any Adverse Events (AE) (excluding pyrexia)

Grade (CTC-AE)*	**Recommended dabrafenib dose modifications** Used as monotherapy or in combination with trametinib
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 to 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 (CTC-AE) v4.0	

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 dabrafenib dose should not exceed 150 mg twice daily. *Pyrexia.* If a patient's temperature is ≥38ºC therapy should be interrupted (dabrafenib when used as monotherapy, and both dabrafenib and trametinib when used in combination). In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Treatment with anti-pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Patients should be evaluated for signs and symptoms of infection and if necessary treated in line with local practice (see section 4.4). Dabrafenib, or both dabrafenib and trametinib when used in combination, should be restarted if the patient is symptom free for at least 24 hours, either 1) at the same dose level, or 2) reduced by one dose level if the pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure. If treatment-related toxicities occur when dabrafenib is used in combination with trametinib, then both treatments should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose modifications are necessary for only one of the two treatments are detailed below for uveitis, RAS mutation positive non-cutaneous malignancies (primarily related to dabrafenib), left ventricular ejection fraction (LVEF) reduction, retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED) and interstitial lung disease (ILD)/pneumonitis (primarily related to trametinib). *Dose modification exceptions (where only one of the two therapies is dose reduced) for selected adverse reactions: see full leaflet. Non-Caucasian patients:* Limited safety and efficacy data have been collected on dabrafenib in non-Caucasian patients. The population pharmacokinetic analysis showed no significant differences in the pharmacokinetics of dabrafenib between Asian and Caucasian patients. No dabrafenib dose adjustment is needed in Asian patients. *Elderly:* No adjustment of the initial dose is required in patients >65 years of age. *Paediatric population:* The safety and efficacy of dabrafenib have not yet been established in children and adolescents (<18 years). No clinical data are available. Studies in juvenile animals have shown adverse effects of dabrafenib which had not been observed in adult animals. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Undesirable effects:** Summary of the safety profile: see full leaflet. *Tabulated summary of adverse reactions:* ADRs which were reported are listed below by MedDRA body system organ class and by frequency. The following convention has been utilised for the classification of frequency: 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), Not known (cannot be estimated from the available data). *Table 3: Adverse reactions reported in the integrated safety population of dabrafenib* monotherapy in the studies BRF113683 (BREAK-3), BRF113929 (BREAK-MB), BRF113710 (BREAK-2), BRF113220, and BRF112680 (n=578).System Organ Class: Frequency (all grades): Adverse Reactions.Neoplasms benign, malignant and unspecified (including cysts and polyps): Very common: Papilloma. - Common: Cutaneous squamous cell carcinoma, Seborrhoeic keratosis, Acrochordon (skin tags), Basal cell carcinoma. - Uncommon: New primary melanoma. / Immune system disorders: Uncommon: Hypersensitivity. / Metabolism and nutrition disorders: Very common: Decreased appetite. - Common: Hypophosphataemia, Hyperglycaemia. / Nervous system disorders: Very common: Headache. / Eye disorders: Uncommon: Uveitis. / Respiratory, thoracic and mediastinal disorders: Very common: Cough. / Gastrointestinal disorders: Very common: Nausea, Vomiting, Diarrhoea. - Common: Constipation. - Uncommon: Pancreatitis. / Skin and subcutaneous tissue disorders: Very common:

Hyperkeratosis, Alopecia, Rash, Palmar-plantar erythrodysaesthesia syndrome. - Common: Dry skin, Pruritus, Actinic keratosis, Skin lesion, Erythema, Panniculitis, Skin fissures, Photosensitivity – Not known: Stevens-Johnson syndrome, Drug reaction with eosinophilia and systemic symptoms, Dermatitis exfoliative generalised. / Musculoskeletal and connective tissue disorders: Very common: Arthralgia, Myalgia, Pain in extremity. / Renal and urinary disorders: Uncommon: Renal failure, acute renal failure, Nephritis. / General disorders and administration site conditions: Very common: Pyrexia, Fatigue, Chills, Asthenia - Common: Influenza-like illness. *Table 4: Adverse reactions reported in the integrated safety population of dabrafenib in combination with trametinib in the studies MEK115306, MEK116513a, BRF113928, and BRF115532(n=1076).* System organ class: Frequency (all grades): Adverse reactions. Infections and infestations: Very common: Nasopharyngitis. - Common: Urinary tract infection, Cellulitis, Folliculitis, Paronychia, Rash pustular. / Neoplasms benign, malignant and unspecified (incl cysts and polyps): Common: Cutaneous squamous cell carcinomab, Papillomac, Seborrhoeic keratosis. - Uncommon: New primary melanomad, Acrochordon (skin tags). / Blood and lymphatic system disorders: Common: Neutropenia, Anaemia, Thrombocytopenia, Leukopenia. / Immune system disorders: Uncommon: Hypersensitivity[e], Sarcoidosis / Metabolism and nutrition disorders: Very common: Decreased appetite. - Common: Dehydration, Hyponatraemia, Hypophosphataemia, Hyperglycaemia. / Nervous system disorders: Very common: Headache, Dizziness. / Eye disorders: Common: Vision blurred, Visual impairment, Uveitis. - Uncommon: Chorioretinopathy, Retinal detachment, Periorbital oedema. / Cardiac disorders: Common: Ejection fraction decreased. - Uncommon: Bradycardia. - Not known: Myocarditis. / Vascular disorders: Very common: Hypertension, Haemorrhagef. - Common: Hypotension, Lymphoedema. / Respiratory, thoracic and mediastinal disorders: Very common: Cough. - Common: Dyspnoea. - Uncommon: Pneumonitis. / Gastrointestinal disorders: Very common: Abdominal paing, Constipation, Diarrhoea, Nausea, Vomiting. - Common: Dry mouth, Stomatitis. - Uncommon: Pancreatitis, Colitis. - Rare: Gastrointestinal perforation. / Skin and subcutaneous disorders: Very common: Dry skin, Pruritus, Rash, Erythema[h]. - Common: Dermatitis acneiform, Actinic keratosis, Night sweats, Hyperkeratosis, Alopecia, Palmar-plantar erythrodysaesthesia syndrome, Skin lesion, Hyperhidrosis, Panniculitis, Skin fissures, Photosensitivity reaction. / Musculoskeletal and connective tissue disorders: Very common: Arthralgia, Myalgia, Pain in extremity, Muscle spasmsi. / Renal and urinary disorders: Uncommon: Renal failure, Nephritis. / General disorders and administration site conditions: Very common: Fatigue, Chills, Asthenia, Oedema peripheral, Pyrexia, Influenza-like illness. - Common: Mucosal inflammation, Face oedema. / Investigations: Very common: Alanine aminotransferase increased, Aspartate aminotransferase increased. - Common: Blood alkaline phosphatase increased, Gamma-glutamyltransferase increased, Blood creatine phosphokinase increased. [a] The safety profile from MEK116513 is generally similar to that of MEK115306 with the following exceptions: 1) The following adverse reactions have a higher frequency category as compared to MEK115306: muscle spasm (very common); renal failure and lymphoedema (common); acute renal failure (uncommon); 2) The following adverse reactions have occurred in MEK116513 but not in MEK115306: cardiac failure, left ventricular dysfunction, interstitial lung disease (uncommon). 3) The following adverse reaction has occurred in MEK116513 and BRF115532 but not in MEK115306 and BRF113928: rhabdomyolysis (uncommon). - [b] Cutaneous squamous cell carcinoma (cu SCC): SCC, SCC of the skin, SCC *in situ* (Bowen's disease) and keratoacanthoma. - [c] Papilloma, skin papilloma. - [d] Malignant melanoma, metastatic malignant melanoma, and superficial spreading melanoma stage III. - [e] Includes drug hypersensitivity. - [f] Bleeding from various sites, including intracranial bleeding and fatal bleeding. - [g] Abdominal pain upper and abdominal pain lower. - [h] Erythema, generalised erythema. - [i] Muscle spasms, musculoskeletal stiffness.
Reporting of suspected adverse reactions: Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system. Description of selected adverse reactions: *Cutaneous squamous cell carcinoma, New primary melanoma, Non-cutaneous malignancy, Haemorrhage, LVEF reduction/Left ventricular dysfunction, Pyrexia, Hepatic events, Hypertension, Arthralgia, Hypophosphataemia, Pancreatitis, Renal failure.* Special populations: *Elderly:* Of the total number of patients in the integrated safety population of dabrafenib monotherapy (n=578), 22% were 65 years of age and older, and 6% were 75 years of age and older. Compared with younger subjects (<65), more subjects ≥65 years old had adverse reactions that led to study drug dose reductions (22% versus 12%) or interruptions (39% versus 27%). In addition, older patients experienced more serious adverse reactions compared to younger patients (41% versus 22%). No overall differences in efficacy were observed between these subjects and younger subjects. In the integrated safety population of dabrafenib in combination with trametinib (n=641), 180 patients (28%) were ≥65 years of age, 50 patients (8%) were ≥75 years of age. The proportion of patients experiencing AEs was similar in those aged <65 years and those aged ≥65 years in all studies. Patients ≥65 years were more likely to experience SAEs and AEs leading to permanent discontinuation of medicinal product, dose reduction and dose interruption than those <65 years. *Dabrafenib in combination with trametinib in patients with brain metastases.* The safety and efficacy of the combination of dabrafenib and trametinib have been evaluated in a multi-cohort, open-label, Phase II study in patients with BRAF V600 mutant melanoma with brain metastases. The safety profile observed in these patients appears to be consistent with the integrated safety profile of the combination. Reporting of suspected adverse reactions. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system. **Marketing authorisation holder and numbers:** Novartis Europharm Limited, Elm Park, Merrion Road, Dublin 4, Ireland. EU/1/13/865/001-004. **Mode of delivery**: Medicinal prduct subject to medical prescription. **Date of revision of the text:** 11.11.2021. Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

NAME OF THE MEDICINAL PRODUCT. Mekinist 0.5 mg film-coated tablets. Mekinist 2.0 mg film-coated tablets. **QUALITATIVE AND QUANTITATIVE COMPOSITION.** Each film-coated tablet contains trametinib dimethyl sulfoxide equivalent to 0.5 mg, respectively 2.0 mg of trametinib
PHARMACEUTICAL FORM. Film-coated tablet (tablet). 0.5 mg: Yellow, modified oval, biconvex, film- coated tablets, approximately 4.8 x 8.9 mm, with 'GS' debossed on one face and 'TFC' on the opposing face. 2.0 mg: Pink, round, biconvex, film-coated tablets, approximately 7.5 mm, with 'GS' debossed on one face and 'HMJ' on the opposing face. **THERAPEUTIC INDICATIONS**. Melanoma. Trametinib as monotherapy or in combination with dabrafenib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.Trametinib monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy. Adjuvant treatment of melanoma. Trametinib in combination with dabrafenib is indicated for the adjuvant treatment of adult patients with Stage III melanoma with a BRAF V600 mutation, following complete resection. Non-small cell lung cancer (NSCLC). Trametinib in combination with dabrafenib is indicated for the treatment of adult patients with advanced non-small cell lung cancer with a BRAF V600 mutation.
POSOLOGY AND MODE OF ADMINISTRATION. Treatment with trametinib should only be initiated and supervised by a physician experienced in the administration of anti-cancer medicinal products. Before taking trametinib, patients must have confirmation of BRAF V600 mutation using a validated test. Posology. The recommended dose of trametinib, either used as monotherapy or in combination with dabrafenib, is 2 mg once daily. The recommended dose of dabrafenib, when used in combination with trametinib, is 150 mg twice daily. *Duration of treatment.* It is recommended that patients continue treatment with trametinib until patients no longer derive benefit or the development of unacceptable toxicity (see Table 2). In the adjuvant melanoma setting, patients should be treated for a period of 12 months unless there is disease recurrence or unacceptable toxicity. *Missed doses.* If a dose of trametinib is missed, it should only be taken if it is more than 12 hours until the next scheduled dose. If a dose of dabrafenib is missed, when trametinib is given in combination with dabrafenib, the dose of dabrafenib should only be taken if it is more than 6 hours until the next scheduled dose. *Dose modification.* The management of adverse reactions may require dose reduction, treatment interruption or treatment discontinuation (see Tables 1 and 2). Dose modifications are not recommended for adverse reactions of cutaneous squamous cell carcinoma (cuSCC) or new primary melanoma (see dabrafenib SmPC for further details).

Table 1 Recommended dose level reductions

Dose level	**Trametinib dose** Used as monotherapy or in combination with dabrafenib	**Dabrafenib dose*** Only when used in combination with trametinib
Starting dose	2 mg once daily	150 mg twice daily
1st dose reduction	1.5 mg once daily	100 mg twice daily
2nd dose reduction	1 mg once daily	75 mg twice daily
3rd dose reduction (combination only)	1 mg once daily	50 mg twice daily
Dose adjustment for trametinib below 1 mg once daily is not recommended, whether used as monotherapy or in combination with dabrafenib. Dose adjustment for dabrafenib below 50 mg twice daily is not recommended when used in combination with trametinib.		
*Please refer to the dabrafenib SmPC, Posology and method of administration, for dosing instructions for treatment with dabrafenib monotherapy.		

Table 2 Dose modification schedule based on the grade of any adverse reactions (excluding pyrexia)

Grade (CTC-AE)*	**Recommended trametinib dose modifications** Used as monotherapy or in combination with dabrafenib
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 to 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 reactions graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE)	

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 trametinib dose should not exceed 2 mg once daily. *Pyrexia.* If a patient's temperature is ≥38ºC, therapy should be interrupted (trametinib when used as monotherapy, and both trametinib and dabrafenib when used in combination). In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia. Treatment with anti-pyretics such as ibuprofen or acetaminophen/paracetamol should be initiated. The use of oral corticosteroids should be considered in those instances in which anti-pyretics are insufficient. Patients should be evaluated for signs and symptoms of infection and if necessary treated in line with local practice (see section 4.4). Trametinib, or both trametinib and dabrafenib when used in combination, should be restarted if the patient is symptom free for at least 24 hours either (1) at the same dose level, or (2) reduced by one dose level, if pyrexia is recurrent and/or was accompanied by other severe symptoms including dehydration, hypotension or renal failure.If treatment-related toxicities occur when trametinib is used in combination with dabrafenib, then both treatments should be simultaneously dose reduced, interrupted or discontinued. Exceptions where dose modifications are necessary for only one of the two treatments are detailed below for uveitis, RAS mutation positive non-cutaneous malignancies (primarily related to dabrafenib), left ventricular ejection fraction (LVEF) reduction, retinal vein occlusion (RVO), retinal pigment epithelial detachment (RPED) and interstitial lung

disease (ILD)/pneumonitis (primarily related to trametinib). *Dose modification exceptions (where only one of the two therapies is dose reduced) for selected adverse reactions. Uveitis.* No dose modifications are required for uveitis as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, dabrafenib should be withheld until resolution of ocular inflammation and then dabrafenib should be restarted reduced by one dose level. No dose modification of trametinib is required when taken in combination with dabrafenib. *RAS-mutation-positive non-cutaneous malignancies.* The benefits and risks must be considered before continuing treatment with dabrafenib in patients with a non-cutaneous malignancy that has a RAS mutation. No dose modification of trametinib is required when taken in combination with dabrafenib. *Left ventricular ejection fraction (LVEF) reduction/Left ventricular dysfunction.* Trametinib should be interrupted in patients who have an asymptomatic, absolute decrease of >10% in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal (LLN) (see section 4.4). No dose modification of dabrafenib is required when trametinib is taken in combination with dabrafenib. If the LVEF recovers, treatment with trametinib may be restarted, but the dose should be reduced by one dose level with careful monitoring. Trametinib should be permanently discontinued in patients with Grade 3 or 4 left ventricular cardiac dysfunction or clinically significant LVEF reduction which does not recover within 4 weeks. *Retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED).* If patients report new visual disturbances such as diminished central vision, blurred vision, or loss of vision at any time while on trametinib therapy, a prompt ophthalmological assessment is recommended. In patients who are diagnosed with RVO, treatment with trametinib, whether given as monotherapy or in combination with dabrafenib, should be permanently discontinued. No dose modification of dabrafenib is required when trametinib is taken in combination with dabrafenib. If RPED is diagnosed, follow the dose modification schedule in Table 3 below for trametinib.**Table 3 Recommended dose modifications for trametinib for RPED.**

Grade 1 RPED	Continue treatment with retinal evaluation monthly until resolution. If RPED worsens follow instructions below and withhold trametinib for up to 3 weeks.
Grade 2-3 RPED	Withhold trametinib for up to 3 weeks.
Grade 2-3 RPED that improves to Grade 0-1 within 3 weeks	Resume trametinib at a lower dose (reduced by 0.5 mg) or discontinue trametinib in patients taking trametinib 1 mg daily.
Grade 2-3 RPED that does not improve to at least Grade 1 within 3 weeks	Permanently discontinue trametinib.

Interstitial lung disease (ILD)/Pneumonitis. Trametinib must be withheld in patients with suspected ILD or pneumonitis, including patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnoea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. Trametinib must be permanently discontinued in patients diagnosed with treatment-related ILD or pneumonitis. No dose modification of dabrafenib is required when trametinib is taken in combination with dabrafenib for cases of ILD or pneumonitis. *Renal impairment.* No dosage adjustment is required in patients with mild or moderate renal impairment (see section 5.2). There are no data with trametinib in patients with severe renal impairment; therefore, the potential need for starting dose adjustment cannot be determined. Trametinib should be used with caution in patients with severe renal impairment when administered as monotherapy or in combination with dabrafenib. *Hepatic impairment*. No dosage adjustment is required in patients with mild hepatic impairment. Available data from a clinical pharmacology study indicate a limited impact of moderate to severe hepatic impairment on trametinib exposure (see full leaflet). Trametinib should be used with caution in patients with moderate or severe hepatic impairment when administered as monotherapy or in combination with dabrafenib. *Non-Caucasian patients.* The safety and efficacy of trametinib in non-Caucasian patients have not been established. No data are available. *Elderly.* No initial dose adjustment is required in patients >65 years of age. More frequent dose adjustments (see Tables 1 and 2 above) may be required in patients >65 years of age. *Paediatric population.* The safety and efficacy of trametinib have not been established in children and adolescents (<18 years). No data are available. Studies in juvenile animals have shown adverse effects of trametinib which were not observed in adult animals. Method of administration. Trametinib should be taken orally with a full glass of water. The tablets should not be chewed or crushed and they should be taken without food, at least 1 hour before or 2 hours after a meal.

It is recommended that the dose of trametinib is taken at a similar time every day. When trametinib and dabrafenib are taken in combination, the once-daily dose of trametinib should be taken at the same time each day with either the morning dose or the evening dose of dabrafenib. If a patient vomits after taking trametinib, the patient should not retake the dose and should take the next scheduled dose. Please refer to dabrafenib SmPC for information on method of administration when given in combination with trametinib. **CONTRA-INDICATIONS**. Hypersensitivity to the active substance or to any of the excipients. **UNDESIRABLE EFFECTS**. Summary of the safety profile. The safety of trametinib monotherapy has been evaluated in the integrated safety population of 329 patients with BRAF V600 mutant unresectable or metastatic melanoma treated with trametinib 2 mg once daily in studies MEK114267, MEK113583, and MEK111054. Of these patients, 211 were treated with trametinib for BRAF V600 mutant melanoma in the randomised open label Phase III study MEK114267 (METRIC) (see section 5.1). The most common adverse reactions (incidence ≥20%) for trametinib were rash, diarrhoea, fatigue, oedema peripheral, nausea, and dermatitis acneiform. The safety of trametinib in combination with dabrafenib has been evaluated in the integrated safety population of 1076 patients with BRAF V600 mutant unresectable or metastatic melanoma, Stage III BRAF V600 mutant melanoma following complete resection (adjuvant treatment) and advanced NSCLC treated with trametinib 2 mg once daily and dabrafenib 150 mg twice daily. Of these patients, 559 were treated with the combination for BRAF V600 mutant melanoma in two randomised Phase III studies, MEK115306 (COMBI-d) and MEK116513 (COMBI-v), 435 were treated with the combination in the adjuvant treatment of Stage III BRAF V600 mutant melanoma after complete resection in a randomised Phase III study BRF115532 (COMBI-AD) and 82 were treated with the combination for BRAF V600 mutant NSCLC in a multicohort, non-randomised Phase II study BRF113928. The most common adverse reactions (incidence 320%) for trametinib in combination with dabrafenib were: pyrexia, fatigue, nausea, chills, headache, diarrhoea, vomiting, arthralgia and rash. *Tabulated summary of adverse reactions*. Adverse reactions are listed below by MedDRA body system organ class. The following convention has been utilised for the classification of frequency: Very common: ≥1/10 - Common: ≥1/100 to<1/10. - Uncommon: ≥1/1,000 to<1/100. - Rare: 31/10,000 to<1/1,000. - Notknown: (cannot be estimated from the availabledata). Categories have been assigned based on absolute frequencies in the clinical trial data. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. *Table 4: Adverse reactions reported in the integrated safety population of trametinib monotherapy (n=329).* System Organ Class: Frequency (all grades): Adverse Reactions.Infections and infestation: Common: Folliculitis, Paronychia, Cellulitis, Rash pustular. Blood and lymphatic system disorders: Common: Anaemia. Immune system disorders: Common: Hypersensitivitya. Metabolism and nutrition disorders: Common: Dehydration. Eye disorders: Common: Vision blurred, Periorbital oedema, Visual impairment. - Uncommon: Chorioretinopathy, Papilloedema, Retinal detachment, Retinal vein occlusion. Cardiac disorders: Common: Left ventricular dysfunction, Ejection fraction decreased, Bradycardia. - Uncommon: Cardiac failure. Vascular disorders: Very common: Hypertension, Haemorrhageb. - Common: Lymphoedema. Respiratory, thoracic and mediastinal disorders: Very common: Cough, Dyspnoea. - Common: Pneumonitis. - Uncommon: Interstitial lung disease. Gastrointestinal disorders: Very common: Diarrhoea, Nausea, Vomiting, Constipation, Abdominal pain, Dry mouth. - Common: Stomatitis. - Uncommon: Gastrointestinal perforation, Colitis. Skin and subcutaneous disorders: Very common: Rash, Dermatitis acneiform, Dry skin, Pruritus, Alopecia. - Common: Erythema, Palmar-plantar erythrodysaesthesia syndrome, Skin fissures, Skin chapped. Musculoskeletal and connective tissue disorders: Uncommon: Rhabdomyolysis. General disorders and administration site conditions: Very common: Fatigue, Oedema peripheral, Pyrexia. - Common: Face oedema, Mucosal inflammation, Asthenia. Investigations: Very common: Aspartate aminotransferase increased. - Common: Alanine aminotransferase increased, Blood alkaline phosphatase increased, Blood creatine phosphokinase increased. a May present with symptoms such as fever, rash, increased liver transaminases, and visual disturbances. b Events include but are not limited to: epistaxis, haematochezia, gingival bleeding, haematuria, and rectal, haemorrhoidal, gastric, vaginal, conjunctival, intracranial and post procedural haemorrhage.*Table 5: Adverse reactions reported in the integrated safety population of trametinib in combination with dabrafenib in the studies MEK115306, MEK116513a, BRF113928, and BRF115532(n=1076).* System Organ Class: Frequency (all grades): Adverse Reactions. Infections and infestations: Very common: Nasopharyngitis. - Common: Urinary tract infection, Cellulitis, Folliculitis, Paronychia, Rash pustular. Neoplasms benign, malignant and unspecified (incl cysts and polyps): Common: Cutaneous squamous cell carcinomab, Papillomac, Seborrhoeic keratosis. - Uncommon: New primary melanomad, Acrochordon (skin tags). Blood and lymphatic system disorders: Common: Neutropenia, Anaemia, Thrombocytopenia, Leukopenia. Immune system disorders: Uncommon: HypersensitivitySarcoidosis. Metabolism and nutrition disorders: Very common: Decreased appetite. - Common: Dehydration, Hyponatraemia, Hypophosphataemia, Hyperglycaemia. Nervous system disorders: [e], Very common: Headache, Dizziness. Eye disorders: Common: Vision blurred, Visual impairment, Uveitis. - Uncommon: Chorioretinopathy, Retinal

detachment, Periorbital oedema. Cardiac disorders: Common: Ejection fraction decreased. - Uncommon: Bradycardia. - Not known: Myocarditis. Vascular disorders: Very common: Hypertension, Haemorrhage[f]. - Common: Hypotension, Lymphoedema. Respiratory, thoracic and mediastinal disorders: Very common: Cough. - Common: Dyspnoea. - Uncommon: Pneumonitis. Gastrointestinal disorders: Very common: Abdominal paing, Constipation, Diarrhoea, Nausea, Vomiting. - Common: Dry mouth, Stomatitis. - Uncommon: Pancreatitis, Colitis. - Rare: Gastrointestinal perforation. Skin and subcutaneous disorders: Very common: Dry skin, Pruritus, Rash, Erythema[h]. - Common: Dermatitis acneiform, Actinic keratosis, Night sweats, Hyperkeratosis, Alopecia, Palmar-plantar erythrodysaesthesia, syndrome, Skin lesion, Hyperhidrosis, Panniculitis, Skin fissures, Photosensitivity. – Not known: Stevens-Johnson syndrome, Drug reaction with eosinophilia and systemic symptoms, Dermatitis exfoliative generalised. Musculoskeletal and connective tissue disorders: Very common: Arthralgia, Myalgia, Pain in extremity, Muscle spasms[i]. Renal and urinary disorders: Uncommon: Renal failure, Nephritis. General disorders and administration site conditions: Very common: Fatigue, Chills, Asthenia, Oedema peripheral, Pyrexia, Influenza-like illness. - Common: Mucosal inflammation, Face oedema. Investigations: Very common: Alanine aminotransferase increased, Aspartate aminotransferase increased. - Common: Blood alkaline phosphatase increased, Gamma-glutamyltransferase increased, Blood creatine phosphokinase increased. [a] The safety profile from MEK116513 is generally similar to that of MEK115306 with the following exceptions: 1) The following adverse reactions have a higher frequency category as compared to MEK115306: muscle spasm (very common); renal failure and lymphoedema (common); acute renal failure (uncommon); 2) The following adverse reactions have occurred in MEK116513 but not in MEK115306: cardiac failure, left ventricular dysfunction, interstitial lung disease (uncommon). 3) The following adverse reaction has occurred in MEK116513 and BRF115532 but not in MEK115306 and BRF113928: rhabdomyolysis (uncommon). [b] Cutaneous squamous cell carcinoma (cu SCC): SCC, SCC of the skin, SCC *in situ* (Bowen's disease) and keratoacanthoma. [c] Papilloma, skin papilloma. [d] Malignant melanoma, metastatic malignant melanoma, and superficial spreading melanoma stage III. [e] Includes drug hypersensitivity. [f] Bleeding from various sites, including intracranial bleeding and fatal bleeding. [g] Abdominal pain upper and abdominal pain lower. [h] Erythema, generalised erythema. [i] Muscle spasms, musculoskeletal stiffness. Reporting of suspected adverse reactions. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system. Description of selected adverse reactions. *New malignancies*. New malignancies, cutaneous and non-cutaneous, can occur when trametinib is used in combination with dabrafenib. Please refer to the dabrafenib SmPC.*Haemorrhage*. Haemorrhagic events, including major haemorrhagic events and fatal haemorrhages occurred in patients taking trametinib as monotherapy and in combination with dabrafenib. The majority of bleeding events were mild. Fatal intracranial haemorrhages occurred in the integrated safety population of trametinib in combination with dabrafenib in <1% (8/1076) of patients. The median time to onset of the first occurrence of haemorrhagic events for the combination of trametinib and dabrafenib was 94 days in the melanoma Phase III studies and 75 days in the NSCLC study for the patients who had received prior anti-cancer therapy. The risk of haemorrhage may be increased with concomitant use of antiplatelet or anticoagulant therapy. If haemorrhage occurs, treat as clinically indicated. *LVEFreduction/Left ventricular dysfunction*. Trametinib has been reported to decrease LVEF when used as monotherapy or in combination with dabrafenib. In clinical trials, the median time to first occurrence of left ventricular dysfunction, cardiac failure and LVEF decrease was between 2 to 5 months. In the integrated safety population of trametinib in combination with dabrafenib, decreased LVEF has been reported in 6% (65/1076) of patients with most cases being asymptomatic andreversible. Patients with LVEF lower than the institutional lower limit of normal were not included in clinical trials with trametinib. Trametinib should be used with caution in patients with conditions that could impair left ventricular function *Pyrexia.* Pyrexia has been reported in clinical trials with trametinib as monotherapy and in combination with dabrafenib; however, the incidence and severity of pyrexia are increased with the combination therapy. Please refer to full leaflet of the dabrafenib SmPC. *Hepatic events*. Hepatic adverse events have been reported in clinical trials with trametinib as monotherapy and in combination with dabrafenib. Of the hepatic AEs, increased ALT and AST were the most common events and the majority were either Grade 1 or 2. For trametinib monotherapy, more than 90% of these liver events occurred within the first 6 months of treatment. Liver events were detected in clinical trials with monitoring every four weeks. It is recommended that patients receiving treatment with trametinib monotherapy or in combination with dabrafenib have liver function monitored every four weeks for 6

months. Liver monitoring may be continued thereafter as clinically indicated.*Hypertension.*Elevations in blood pressure have been reported in association with trametinib as monotherapy and in combination with dabrafenib, in patients with or without pre-existing hypertension. Blood pressure should be measured at baseline and monitored during treatment, with control of hypertension by standard therapy as appropriate.*Interstitial lung disease (ILD)/Pneumonitis.* Patients treated with trametinib or combination with dabrafenib may develop ILD or pneumonitis. Trametinib should be withheld in patients with suspected ILD or pneumonitis, including patients presenting with new or progressive pulmonary symptoms and findings including cough, dyspnoea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. For patients diagnosed with treatment-related ILD or pneumonitis trametinib should be permanently discontinued .*Visual impairment*. Disorders associated with visual disturbances, including RPED and RVO, have been observed with trametinib. Symptoms such as blurred vision, decreased acuity, and other visual disturbances have been reported in the clinical trials with trametinib. *Rash*. Rash has been observed in about 60% of patients when given as monotherapy and in about 24% of patients in trametinib and dabrafenib combination studies in the integrated safety population. The majority of these cases were Grade 1 or 2 and did not require any dose interruptions or dose reductions. *Rhabdomyolysis.* Rhabdomyolysis has been reported in patients taking trametinib alone or in combination with dabrafenib. Signs or symptoms of rhabdomyolysis should warrant an appropriate clinical evaluation and treatment as indicated. *Pancreatitis*. Pancreatitis has been reported with dabrafenib in combination with trametinib. Please see the dabrafenib SmPC. *Renal failure.* Renal failure has been reported with dabrafenib in combination with trametinib. Please see the dabrafenib SmPC.Special populations. *Elderly*. In the Phase III study with trametinib in patients with unresectable or metastatic melanoma (n=211), 49 patients (23%) were ≥65 years of age, and 9 patients (4%) were ≥75 years of age. The proportion of subjects experiencing adverse events (AE) and serious adverse events (SAE) was similar in the subjects aged <65 years and those aged ≥65 years. Patients ≥65 years were more likely to experience AEs leading to permanent discontinuation of medicinal product, dose reduction and dose interruption than those <65 years. In the integrated safety population of trametinib in combination with dabrafenib (n=1076) 265 patients (25%) were ≥65 years of age; 62 patients (6%) were ≥75 years of age. The proportion of patients experiencing AEs was similar in those aged <65 years and those aged ≥65 years in all studies. Patients ≥65 years were more likely to experience SAEs and AEs leading to permanent discontinuation of medicinal product, dose reduction and dose interruption than those <65 years. *Renal impairment*. No dosage adjustment is required in patients with mild or moderate renal impairment. Trametinib should be used with caution in patients with severe renal impairment. *Hepaticimpairment.* No dosage adjustment is required in patients with mild hepatic impairment. Trametinib should be used with caution in patients with moderate or severe hepatic impairment. *Trametinib in combination with dabrafenib in patients with brain metastases.* The safety and efficacy of the combination of trametinib and dabrafenib have been evaluated in a multi-cohort, open-label, Phase II study in patients with BRAF V600 mutant melanoma with brain metastases. The safety profile observed in these patients appears to be consistent with the integrated safety profile of the combination. Reporting of suspected adverse reactions. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system. **MARKETING AUTHORISATION HOLDER.** Novartis Europharm Limited, Vista Building, Elm Park, Merrion Road, Dublin 4, Ireland. **MARKETING AUTHORISATION NUMBER(S).** EU/1/14/931/001-002; EU/1/14/931/005-006. **MODE OF DELIVERY**. Medicinal product subject to medical prescription. **DATE OF REVISION OF THE TEXT.** 29.04.2022. Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu