PRESCRIBING INFORMATION
TAFINLAR/ MEKINIST
Before prescribing TAFINLAR and MEKINIST, please refer to the Summaries of Product Characteristics (SPCs).

TAFINLAR® (dabrafenib) 50mg and 75mg capsules. Each capsule contains dabrafenib mesilate, equivalent to 50mg and 75mg of dabrafenib, respectively.
MEKINIST® (trametinib) 0.5mg and 2mg film-coated tablets. Each tablet contains trametinib dimethyl sulphoxide, equivalent to 0.5mg and 2mg of trametinib, respectively.
Indication: MELANOMA: *Dabrafenib*: As monotherapy and in combination with trametinib for adults with unresectable or metastatic melanoma with a BRAF V600 mutation. *Trametinib*: In combination with dabrafenib for adults with unresectable or metastatic melanoma with a BRAF V600 mutation. 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. **Posology and method of administration:** For oral use. Before taking dabrafenib or trametinib, patients must have confirmation of BRAF V600 mutation using a validated test. *Dabrafenib:* As monotherapy and in combination, 150mg twice daily (b.d.) with interval of ~12hrs between doses (max. total daily dose 300mg). *Trametinib*: In combination, 2mg once daily (o.d.), taken at same time each day with either morning or evening dose of dabrafenib. Treatment should continue until patient no longer derives benefit or develops unacceptable toxicity. In the adjuvant melanoma setting, patients should be treated for a period of 12 months unless there is disease recurrence or unacceptable toxicity. Take both medicines whole with water, ≥1 hour before or ≥2 hours after a meal, at similar times every day; do not crush or chew. If dose of dabrafenib is missed, do not take if <6 hours until next dose. If trametinib dose is missed, do not take if <12 hours until next dose. *Dose modification*: Management of ADRs may require treatment interruption, dose reduction or discontinuation; this should occur simultaneously when both medicines used in combination with some exceptions (see Special Warnings & Precautions). Dabrafenib dose reduction is the same in monotherapy and in combination. 1st reduction: dabrafenib 100mg b.d., trametinib 1.5mg o.d; 2nd reduction: dabrafenib 75 mg b.d., trametinib 1mg o.d (min. dose); 3rd reduction: dabrafenib 50mg b.d. (min. dose), trametinib 1mg o.d. Consider dose re-escalation following same dosing steps as de-escalation when ADR under effective management. *Renal impairment*: Both medicines: no dose adjustment required in mild or moderate impairment; caution advised in severe renal impairment. *Hepatic impairment:* Both medicines: no dose adjustment required in mild impairment. Caution advised in moderate and severe hepatic impairment. *Elderly*: Both medicines; no initial dose adjustment required in patients >65 yrs. *Paediatrics*: Both medicines: safety & efficacy not established in patients <18 yrs. **Contraindications:** Both medicines: hypersensitivity to active substance or excipients. **Special Warnings and Precautions:** Not evaluated in wild-type BRAF melanoma; limited data for combination in patients who have progressed on prior BRAF inhibitor. Evaluated in patients with BRAF mutant melanoma metastatic to brain; the safety profile observed in these patients appears to be consistent with the integrated safety profile of the combination. New malignancies, cutaneous and non-cutaneous, can occur when dabrafenib is used as monotherapy or in combination with trametinib. *Cutaneous squamous cell carcinoma (CuSCC) and new primary melanoma*: Examine skin prior to treatment, monthly during treatment and for 6 months after discontinuation. Patients should inform their HCP immediately if a new lesion develops. Manage by excision; continue dabrafenib and trametinib without dose adjustment. *Deep vein thrombosis (DVT)/pulmonary embolism (PE):* Patients should seek immediate medical care if they develop symptoms of DVT or PE. Permanently discontinue both medicines if life-threatening PE. *Haemorrhage*: Risk increased with concomitant antiplatelet/anticoagulant therapy. Treat as clinically indicated. *Hepatic events:* Monitor liver function every 4 weeks for 6 months after starting combination treatment, then as clinically indicated. *Hypertension:* Monitor BP at baseline and during combination use and control hypertension with standard therapy as appropriate. *Interstitial lung disease (ILD):* Withhold trametinib in patients with suspected ILD or pneumonitis; discontinue trametinib permanently if treatment-related ILD or pneumonitis diagnosed and continue dabrafenib at same dose. *LVEF reduction/LV dysfunction*: Use trametinib with caution in patients with impaired LV function. Evaluate LVEF prior to treatment, after one month, then at 3 monthly intervals while on treatment. Interrupt trametinib if asymptomatic decrease >10% in LVEF vs. baseline and ejection fraction below LLN; continue dabrafenib at same dose. If LVEF recovers, restart trametinib at reduced dose with careful monitoring. Persistent LVEF reduction or Grade 3/4 LV dysfunction requires permanent discontinuation of trametinib. *Non-cutaneous secondary/recurrent malignancy*: Consider benefits and risks before administering dabrafenib to patients with a prior/concurrent cancer associated with RAS mutations. Undertake head and neck examination and chest/abdominal CT scan prior to treatment. Monitor as clinically appropriate during treatment and for up to 6 months after discontinuation. No dose modification of trametinib required. *Pancreatitis*: Investigate unexplained abdominal pain promptly, including serum amylase & lipase measurements. Monitor closely when re-starting dabrafenib. *Pyrexia*: Interrupt dabrafenib if temperature ≥38.5ºC and investigate for infection; continue trametinib at same dose. Initiate anti-pyretics (consider oral steroids if insufficient). Once fever resolves, restart dabrafenib, either at same dose, or at reduced dose if fever accompanied by other severe symptoms, along with anti-pyretic prophylaxis.
Rash: Majority of cases in clinical studies have been Grade 1/2 and did not require dose interruptions/reductions. Follow dose modification schedule in SPCs if necessary. *Rhabdomyolysis:* Evaluate signs and symptoms and treat as indicated. Severe cases may require discontinuation of trametinib or both medicines. *Renal failure:* Monitor serum creatinine routinely, and interrupt dabrafenib as clinically appropriate if creatinine increases. *Visual impairment*: Monitor for signs/symptoms of ophthalmological reactions. *Uveitis:* If uveitis does not respond to local ocular therapy, nterrupt dabrafenib until ocular inflammation resolves and restart at reduced dose. No dose modification of trametinib required. *Retinal vein occlusion (RVO) and Retinal pigment epithelial detachment (RPED):* Trametinib not recommended in patients with history of RVO. Prompt ophthalmological examination recommended if patients report new visual disturbances. Permanently discontinue trametinib in patients diagnosed with RVO and follow trametinib dose modification schedule in SPC in patients diagnosed with RPED; continue dabrafenib at same dose. *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 dabrafenib/trametinib combination therapy. 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, dabrafenib and trametinib should be withdrawn. *Gastrointestinal disorders*: Treatment with trametinib monotherapy or in combination with dabrafenib should be used with caution in patients with risk factors for gastrointestinal perforation, including history of diverticulitis, metastases to the gastrointestinal tract and concomitant use of medications with a recognised risk of gastrointestinal perforation. **Interactions:** Dabrafenib (monotherapy/ combination with trametinib): Drug utilisation review essential. Avoid co-administration with strong inducers or inhibitors of CYP2C8 and CYP3A4. Exercise caution when co-administering with digoxin and with warfarin (consider additional INR monitoring). May reduce efficacy of hormonal contraceptives; use alternative effective contraception. Monitoring is recommended for adverse reactions if dabrafenib is co-administered with OATP1B1 or OATP1B3 substrates such as statins. Trametinib: Caution is advised when co-administering trametinib with medicinal products that are strong inhibitors of P-gp. **Other important information:** Women of childbearing potential must use effective methods of contraception during therapy and for 2 weeks following discontinuation of dabrafenib and 16 weeks following the last dose of trametinib when given in combination with dabrafenib. Dabrafenib may decrease the efficacy of oral or any systemic hormonal contraceptives and an effective alternative method of contraception should be used. Do not administer dabrafenib to pregnant women unless benefit to mother outweighs the risk to foetus. Trametinib should not be administered to pregnant women. A decision should be made whether to discontinue breast-feeding or discontinue trametinib and dabrafenib. Male patients taking dabrafenib as monotherapy or in combination with trametinib should be informed of the potential risk for impaired spermatogenesis, which may be irreversible. Dabrafenib and trametinib have minor influence on the ability to drive and use machines. **Undesirable effects:** Please refer to full SPCs before prescribing. *Dabrafenib monotherapy*: *Very common***:** Papilloma, decreased appetite, headache, cough, nausea, vomiting, diarrhoea, hyperkeratosis, alopecia, rash, palmar-plantar erythrodysaesthesia syndrome (PPE), arthralgia, myalgia, pain in extremity, pyrexia, fatigue, chills, asthenia. *Common*: Cutaneous squamous cell carcinoma (cuSCC), seborrhoeic keratosis, acrochordon (skin tags), basal cell carcinoma, hypophosphataemia, hyperglycaemia, constipation, dry skin, pruritus, actinic keratosis, skin lesion, erythema, photosensitivity, influenza-like illness. *Uncommon*: New primary melanoma, hypersensitivity, uveitis, pancreatitis, panniculitis, renal failure, acute renal failure, nephritis. *Dabrafenib and trametinib in combination*: *Very common*: Nasopharyngitis, decreased appetite, headache, dizziness, hypertension, haemorrhage, cough, abdominal pain, constipation, diarrhoea, nausea, vomiting, dry skin, pruritus, rash, erythema, arthralgia, myalgia, pain in extremity, muscle spasms, fatigue, chills, asthenia, oedema peripheral, pyrexia, influenza-like illness, alanine and aspartate aminotransferases increased. *Common*: Urinary tract infection (UTI), cellulitis, folliculitis, paronychia, rash pustular, cutaneous squamous cell carcinoma (cuSCC), papilloma, seborrhoeic keratosis, neutropenia, anaemia, thrombocytopenia, leukopenia, dehydration, hyponatraemia, hypophosphataemia, hyperglycaemia, vision blurred, visual impairment, uveitis, ejection fraction decreased, hypotension, lymphoedema, dyspnoea, dry mouth, stomatitis, dermatitis acneiform, actinic keratosis, night sweats, hyperkeratosis, alopecia, palmar-plantar erythrodysaesthesia syndrome (PPE), skin lesion, hyperhidrosis, panniculitis, skin fissures, photosensitivity, mucosal inflammation, face oedema, blood alkaline phosphate and gamma-glutamyltransferase (ALP/GGT) increased, blood creatine phosphokinase (CPK) increased. *Uncommon*: New primary melanoma, acrochordon (skin tags), hypersensitivity, chorioretinopathy, retinal detachment, pneumonitis, periorbital oedema, bradycardia, pancreatitis, colitis, renal failure, nephritis. *Rare:* Gastrointestinal perforation. *Not known:* Myocarditis, Stevens-Johnson syndrome, Drug reaction with eosinophilia and systemic symptoms, Dermatitis exfoliative generalised. **Legal category** POM. **Basic NHS Cost:** *Dabrafenib:* 50mg x 28-capsule pack £933.33; 75mg x 28-capsule pack £1,400.00. *Trametinib:* 0.5mg x 30-tablet pack £1,200.00; 2mg x 30-tablet pack £4,800.00. 0.5mg x 7-tablet pack £280.00; 2mg x 7-tablet pack £1,120.00. **Marketing authorisation (MA) nos:** *Dabrafenib:* EU/1/13/865/001; EU/1/13/865/003. *Trametinib:* EU/1/14/931/02; EU/1/14/931/06; EU/1/14/931/01; EU/1/14/931/05.
Further information available on request from Novartis Pharmaceuticals UK Ltd, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ, United Kingdom Phone: +44 (0)1276 698370.
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Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.UK/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the patient safety information (PSI) tool at https://psi.novartis.com.
If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com.