MEQSEL®

Important note: Before prescribing, consult full prescribing information of MEQSEL® (trametinib). When used in combination with RAFINLAR® (dabrafenib), consult full prescribing information of both products.

Presentation: Film-coated tablets: contain trametinib dimethyl sulfoxide equivalent to 0.5 mg and 2 mg of trametinib.

Indications: ♦Trametinib is indicated, as a monotherapy and in combination with dabrafenib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation, as detected by an appropriate test. ♦Trametinib is indicated, in combination with dabrafenib, for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation. ♦Trametinib is indicated, in combination with dabrafenib, for the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations as detected by an appropriate test, and involvement of lymph node(s), following complete resection. ♦ Trametinib is indicated, in combination with dabrafenib, for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options. ♦ Trametinib is indicated, in combination with dabrafenib, for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. ♦ Limitations of Use: Trametinib is not indicated for treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition.

Dosage and administration: ♦Adults: Recommended dose either as monotherapy or in combination with dabrafenib is 2 mg once daily. *Pediatrics:* The recommended dosage for Trametinib in pediatric patients who weigh at least 26 kg, is based on body weight. A recommended dose of Trametinib for patients who weigh less than 26 kg has not been established. ♦ Trametinib in combination with dabrafenib should not be used in patients with colorectal cancer due to intrinsic resistance to BRAF inhibition. ♦Trametinib should be taken without food, with a full glass of water, at least 1 hour before or at least 2 hours after a meal.

When trametinib is taken in combination with dabrafenib, the once-daily dose of trametinib should be taken at the same time each day with either the morning or the evening dose of dabrafenib. **♦Missed dose:** A missed dose should be taken only if it is more than 12 hours until the next scheduled dose. **♦Dose modifications:** Management of adverse reactions may require treatment interruption, dose reduction or treatment discontinuation.

Special populations: ♦Children (< 6 years): Safety and efficacy not established. **♦Elderly (> 65 years):** No dose adjustment required. **♦Renal impairment:** Mild or moderate: No dose adjustment required. Severe: Should be used with caution. **♦Hepatic impairment:** Mild: No dose adjustment required. Moderate or severe: Should be used with caution.

Contraindications: None.

Warnings and precautions: ♦Left ventricular ejection fraction (LVEF) reduction/Left ventricular dysfunction: Cases of LVEF decrease reported. Should be used with caution when conditions could impair left ventricular function. All patients should be evaluated for LVEF prior to initiation of treatment with continued evaluation during treatment. Dose modification guidelines should be considered. **♦Hemorrhage:** Hemorrhagic events, including major and fatal hemorrhagic

events occurred in patients taking trametinib as monotherapy and in combination with dabrafenib. ♦**Visual impairment:** Visual disturbances, including chorioretinopathy or retinal pigment epithelial detachment (RPED) and retinal vein occlusion (RVO) observed. Not recommended for patients with history of RVO. Ophthalmological evaluation should be performed at baseline and during treatment. If retinal abnormalities observed, treatment should be interrupted immediately and referral to specialist should be considered. Permanent discontinuation of treatment if RVO occurs. ♦**Rash:** Observed in trametinib monotherapy and in combination with dabrafenib. ♦**Severe cutaneous adverse reactions (SCARs):** SCARs, including Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported with trametinib in combination with dabrafenib. 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, trametinib and dabrafenib should be withdrawn.

Venous thrombo-embolism (VTE): VTE including deep vein thrombosis (DVT) and pulmonary embolism (PE) can occur when used as monotherapy or in combination with dabrafenib. Patients should seek immediate medical care if they develop symptoms of VTE.

Pyrexia: Pyrexia including severe rigors, dehydration, and hypotension (including acute renal insufficiency) reported. Incidence and severity increased when Trametinib used in combination with dabrafenib. Monitoring serum creatinine and other evidence of renal function impairment during and following severe pyrexia events. Serious non-infectious febrile events observed. For management of pyrexia, therapy should be interrupted if the patient's temperature is ≥38°C (100.4°F). In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia.

Colitis and Gastrointestinal perforation: Colitis and gastrointestinal perforation, including fatal outcome, reported. Treatment with trametinib as monotherapy or in combination with dabrafenib should be used with caution in patients with risk factors for gastrointestinal perforation, including a history of diverticulitis, metastases to the gastrointestinal tract and concomitant use of medications with a recognized risk of gastrointestinal perforation. If patients develop symptoms of colitis and gastrointestinal perforation, they should immediately seek medical care. ♦**Hemophagocytic lymphohistiocytosis (HLH):** In post-marketing experience, HLH has been observed with Trametinib used in combination with dabrafenib. 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 Mekinist in combination with Tafinlar. Risk factors for TLS include rapidly growing tumors, a high tumor 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.

Pregnancy, lactation, females and males of reproductive potential:

Pregnancy: Trametinib can be harmful to the fetus. Pregnant women should be advised of the potential risk to the fetus.

Lactation: Nursing women should be advised of the potential risks to the child.

Females and males of reproductive potential: Sexually-active women should be advised to use effective contraception while on trametinib and for at least 16 weeks after stopping it. Efficacy of oral or any other systemic hormonal contraceptives may be decreased; an effective alternative method of contraception should be used. Male patients (including those that have had a

vasectomy) should be advised to use condoms while on trametinib and for at least 16 weeks after stopping it.

Infertility: May impair human fertility.

Adverse events with Trametinib monotherapy in metastatic melanoma:

Very common (≥10%): hypertension, haemorrhage, cough, dyspnoea, diarrhoea, nausea, vomiting, constipation, abdominal pain, dry mouth, rash, dermatitis acneiform, dry skin, pruritus, alopecia, fatigue, oedema peripheral, pyrexia.

Common (≥1 to <10%): hypersensitivity, folliculitis, paronychia, cellulitis, rash pustular, anaemia, dehydration, vision blurred, periorbital oedema, visual impairment, left ventricular dysfunction, ejection fraction decreased, bradycardia, lymphoedema, epistaxis, pneumonitis, stomatitis, skin chapped, erythema, palmar-plantar erythrodysaesthesia syndrome, skin fissures, blood creatine phosphokinase increased, face oedema, mucosal inflammation, asthenia, aspartate aminotransferase increased, alanine aminotransferase increased, blood alkaline phosphatase increased.

Uncommon (≥0.1 to <1%): chorioretinopathy, retinal vein occlusion, papilloedema, retinal detachment, cardiac failure, interstitial lung disease, gastrointestinal perforation, colitis, rhabdomyolysis.

Adverse events in combination with Dabrafenib in metastatic melanoma:

Very common (≥10%): urinary tract infection, nasopharyngitis, neutropenia, decreased appetite, headache, dizziness, hypertension, haemorrhage, cough, abdominal pain, constipation, diarrhoea, nausea, vomiting, dry skin, pruritus, rash, dermatitis acneiform, arthralgia, myalgia, pain in extremity, fatigue, oedema peripheral, pyrexia, chills, asthenia, alanine aminotransferase increased, aspartate aminotransferase increased.

Common (≥1 to <10%): cellulitis, folliculitis, paronychia, rash pustular, cutaneous squamous cell carcinoma (SCC) including SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma, papilloma including skin papilloma, seborrheic keratosis, acrochordon (skin tags), anaemia, thrombocytopenia, leukopenia, dehydration, hyperglycaemia, hyponatraemia, hypophosphataemia, vision blurred, visual impairment, ejection fraction decreased, bradycardia, hypotension, lymphoedema, dyspnoea, dry mouth, stomatitis, erythema, actinic keratosis, night sweats, hyperkeratosis, alopecia, palmar-plantar erythrodysesthesia syndrome, skin lesion, hyperhidrosis, skin fissures, panniculitis, photosensitivity, muscle spasms, blood creatine phosphokinase increased, renal failure, mucosal inflammation, influenza-like illness, face oedema, blood alkaline phosphatase increased, gamma-glutamyltransferase increased.

Uncommon (≥0.1 to <1%): new primary melanoma, hypersensitivity, chorioretinopathy, uveitis, retinal detachment, periorbital oedema, left ventricular dysfunction, cardiac failure, pneumonitis, interstitial lung disease, pancreatitis, gastrointestinal perforation, colitis, rhabdomyolysis, nephritis, renal failure acute.

Adverse drug reactions in combination with Dabrafenib in Stage III melanoma following complete resection:

Very common (≥10%): nasopharyngitis, neutropenia, decreased appetite, headache, dizziness, haemorrhage, hypertension, cough, nausea, diarrhoea, vomiting, abdominal pain, constipation, rash, dry skin, dermatitis acneiform, erythema, pruritus, arthralgia, myalgia, pain in extremity muscle spasms, pyrexia, fatigue, chills, oedema peripheral, influenza-like illness, alanine aminotransferase increased, aspartate aminotransferase increased.

Common (≥1 to <10%): uveitis, chorioretinopathy, retinal detachment, palmar-plantar erythrodysesthesia syndrome, alkaline phosphatase increased, ejection fraction decreased.

Uncommon (≥0.1 to <1%): rhabdomyolysis, renal failure.

Adverse drug reactions in combination with Dabrafenib in advanced non-small cell lung cancer:

Very common (≥10%): neutropenia, hyponatraemia, headache, dizziness, haemorrhage, hypotension, nausea, vomiting, diarrhoea, decreased appetite, constipation, erythema, dry skin, rash, pruritus, hyperkeratosis incl. hyperkeratosis, actinic and seborrheic keratosis and keratosis pilaris, muscle spasms, arthralgia, myalgia, pyrexia, asthenia incl. fatigue and malaise, oedema (generalized and peripheral), chills, blood alkaline phosphatase increased, aspartate aminotransferase increased, alanine aminotransferase increased.

Common (≥1 to <10%): cutaneous squamous cell carcinoma, leukopenia, dehydration, detachment of retina/retinal pigment epithelium, ejection fraction decreased, hypertension, pulmonary embolism, pancreatitis acute, renal failure, tubulointerstitial nephritis.

Adverse drug reactions in combination with Dabrafenib in locally advanced or metastatic anaplastic thyroid cancer (ATC):

Very common (≥10%): neutropenia, anaemia, leukopenia, hyperglycaemia, decreased appetite, headache, dizziness, haemorrhage, cough, nausea, vomiting, diarrhoea, constipation, dry mouth, rash, myalgia, arthralgia, fatigue, pyrexia, chills, oedema, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased.

Common (≥1 to <10%): hypophosphataemia, hyponatraemia, detachment of retinal pigment epithelium, hypertension, rhabdomyolysis, ejection fraction decreased.

Adverse drug reactions with Trametinib monotherapy from post-marketing experience and pooled clinical trials:

Common (≥1 to <10%): peripheral neuropathy

Uncommon (≥0.1 to <1%): atrioventricular block, bundle branch block

Adverse drug reactions with Trametinib monotherapy or in combination with Dabrafenib from post-marketing experience and pooled clinical trials:

Common (≥1 to <10%): VTE, peripheral neuropathy, atrioventricular block

Uncommon (≥0.1 to <1%): sarcoidosis, bundle branch bock

Not known: haemophagocytic lymphohistiocytosis, tumour lysis syndrome

For a complete list, consult full prescribing information.

Interactions: None.

Packs: 30 film-coated tablets

Before prescribing, please consult full prescribing information available from Novartis Healthcare Private Limited, Inspire BKC, 'G' Block, 7th floor, BKC Main Road, Bandra Kurla Complex, Bandra (East), Mumbai 400 051; Telephone +91 22 50243000

For the use of only Oncologist.

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