

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MEKINIST safely and effectively. See full prescribing information for MEKINIST.

MEKINIST® (trametinib) tablets, for oral use
Initial U.S. Approval: 2013

-----RECENT MAJOR CHANGES-----

Dosage and Administration (2.7) 12/2021
Warnings and Precautions (5.8) 12/2021

-----INDICATIONS AND USAGE-----

MEKINIST is a kinase inhibitor indicated as a single agent for the treatment of BRAF-inhibitor treatment-naïve patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. (1.1, 2.1)

MEKINIST is indicated, in combination with dabrafenib, for:

- the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. (1.1, 2.1)
- the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection. (1.2, 2.1)
- the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test. (1.3, 2.1)
- the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options. (1.4, 2.1)

-----DOSAGE AND ADMINISTRATION-----

- The recommended dosage of MEKINIST is 2 mg orally once daily. Take MEKINIST at least 1 hour before or at least 2 hours after a meal. (2)

-----DOSAGE FORMS AND STRENGTHS-----

Tablets: 0.5 mg, 2 mg (3)

-----CONTRAINDICATIONS-----

None. (4)

-----WARNINGS AND PRECAUTIONS-----

- New Primary Malignancies, Cutaneous, and Non-Cutaneous: can occur when MEKINIST is used with dabrafenib. Monitor patients for new malignancies prior to initiation of therapy, while on therapy, and following discontinuation of treatment. (5.1)
- Hemorrhage: Major hemorrhagic events can occur. Monitor for signs and symptoms of bleeding. (5.2)
- Colitis and Gastrointestinal Perforation: Colitis and gastrointestinal perforation can occur in patients receiving MEKINIST. (5.3)

- Venous Thromboembolism: Deep vein thrombosis (DVT) and pulmonary embolism (PE) can occur in patients receiving MEKINIST. (5.4, 2.7)
- Cardiomyopathy: Assess left ventricular ejection fraction (LVEF) before treatment, after one month of treatment, then every 2 to 3 months thereafter. (5.5, 2.7)
- Ocular Toxicities: Perform ophthalmologic evaluation for any visual disturbances. For Retinal Vein Occlusion (RVO), permanently discontinue MEKINIST. (5.6, 2.7)
- Interstitial Lung Disease (ILD): Withhold MEKINIST for new or progressive unexplained pulmonary symptoms. Permanently discontinue MEKINIST for treatment-related ILD or pneumonitis. (5.7, 2.7)
- Serious Febrile Reactions can occur when MEKINIST is used with dabrafenib. (5.8, 2.7)
- Serious Skin Toxicities: Monitor for skin toxicities and for secondary infections. Permanently discontinue MEKINIST for intolerable Grade 2, or Grade 3 or 4 rash not improving within 3 weeks despite interruption of MEKINIST. Permanently discontinue for severe cutaneous adverse reactions (SCARs). (5.9, 2.7)
- Hyperglycemia: Monitor serum glucose levels in patients with preexisting diabetes or hyperglycemia. (5.10)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus and to use effective contraception. (5.12, 8.1, 8.3)

-----ADVERSE REACTIONS-----

Most common adverse reactions (≥ 20%) for MEKINIST as a single agent include rash, diarrhea, and lymphedema. (6.1)

Most common adverse reactions (≥ 20%) for MEKINIST with dabrafenib include:

- Unresectable or metastatic melanoma: pyrexia, nausea, rash, chills, diarrhea, vomiting, hypertension, and peripheral edema. (6.1)
- Adjuvant treatment of melanoma: pyrexia, fatigue, nausea, headache, rash, chills, diarrhea, vomiting, arthralgia, and myalgia. (6.1)
- NSCLC: pyrexia, fatigue, nausea, vomiting, diarrhea, dry skin, decreased appetite, edema, rash, chills, hemorrhage, cough, and dyspnea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----USE IN SPECIFIC POPULATIONS-----

- Lactation: Do not breastfeed. (8.2)
- Females and Males of Reproductive Potential: May impair fertility. Counsel patients on pregnancy planning and prevention. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 01/2022

FULL PRESCRIBING INFORMATION: CONTENTS***1 INDICATIONS AND USAGE**

- 1.1 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma
- 1.2 Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma
- 1.3 BRAF V600E Mutation-Positive Metastatic NSCLC
- 1.4 BRAF V600E Mutation-Positive Locally Advanced or Metastatic Anaplastic Thyroid Cancer

2 DOSAGE AND ADMINISTRATION

- 2.1 Patient Selection
- 2.2 Recommended Dosage for Unresectable or Metastatic Melanoma
- 2.3 Recommended Dosage for the Adjuvant Treatment of Melanoma
- 2.4 Recommended Dosage for NSCLC
- 2.5 Recommended Dosage for ATC
- 2.6 Administration
- 2.7 Dosage Modifications for Adverse Reactions

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

- 5.1 New Primary Malignancies
- 5.2 Hemorrhage
- 5.3 Colitis and Gastrointestinal Perforation
- 5.4 Venous Thromboembolic Events
- 5.5 Cardiomyopathy
- 5.6 Ocular Toxicities
- 5.7 Interstitial Lung Disease/Pneumonitis
- 5.8 Serious Febrile Reactions
- 5.9 Serious Skin Toxicities
- 5.10 Hyperglycemia
- 5.11 Risks Associated With Combination Treatment
- 5.12 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment

10 OVERDOSAGE**11 DESCRIPTION****12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma
- 14.2 Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma
- 14.3 BRAF V600E Mutation-Positive Metastatic Non-Small Cell Lung Cancer
- 14.4 BRAF V600E Mutation-Positive Locally Advanced or Metastatic Anaplastic Thyroid Cancer
- 14.5 Lack of Clinical Activity in Metastatic Melanoma Following BRAF-Inhibitor Therapy

16 HOW SUPPLIED/STORAGE AND HANDLING**17 PATIENT COUNSELING INFORMATION**

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma

MEKINIST® is indicated, as a single agent in BRAF-inhibitor treatment-naïve patients or in combination with dabrafenib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test [see *Dosage and Administration (2.1)*].

1.2 Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma

MEKINIST is indicated, in combination with dabrafenib, for the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection [see *Dosage and Administration (2.1)*].

1.3 BRAF V600E Mutation-Positive Metastatic NSCLC

MEKINIST is indicated, in combination with dabrafenib, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test [see *Dosage and Administration (2.1)*].

1.4 BRAF V600E Mutation-Positive Locally Advanced or Metastatic Anaplastic Thyroid Cancer

MEKINIST 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 [see *Dosage and Administration (2.1)*].

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Melanoma

- Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with MEKINIST as a single agent or in combination with dabrafenib [see *Clinical Studies (14.1, 14.2)*].
- Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at: <http://www.fda.gov/CompanionDiagnostics>.

NSCLC

- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with MEKINIST and dabrafenib [see *Clinical Studies (14.3)*].
- Information on FDA-approved tests for the detection of BRAF V600E mutations in NSCLC is available at: <http://www.fda.gov/CompanionDiagnostics>.

ATC

- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with MEKINIST and dabrafenib [see *Clinical Studies (14.4)*]. An FDA-approved test for the detection of BRAF V600E mutation in ATC is not currently available.

2.2 Recommended Dosage for Unresectable or Metastatic Melanoma

The recommended dosage of MEKINIST is 2 mg orally taken once daily, as a single agent or in combination with dabrafenib, until disease progression or unacceptable toxicity. Refer to the dabrafenib prescribing information for recommended dabrafenib dosing information.

2.3 Recommended Dosage for the Adjuvant Treatment of Melanoma

The recommended dosage of MEKINIST is 2 mg orally taken once daily in combination with dabrafenib until disease recurrence or unacceptable toxicity for up to 1 year. Refer to the dabrafenib prescribing information for recommended dabrafenib dosing information.

2.4 Recommended Dosage for NSCLC

The recommended dosage of MEKINIST is 2 mg orally taken once daily in combination with dabrafenib until disease recurrence or unacceptable toxicity. Refer to the dabrafenib prescribing information for recommended dabrafenib dosing information.

2.5 Recommended Dosage for ATC

The recommended dosage of MEKINIST is 2 mg orally taken once daily in combination with dabrafenib until disease recurrence or unacceptable toxicity. Refer to the dabrafenib prescribing information for recommended dabrafenib dosing information.

2.6 Administration

- Take MEKINIST doses approximately 24 hours apart.
- Take MEKINIST at least 1 hour before or 2 hours after a meal [*see Clinical Pharmacology (12.3)*].
- Do not take a missed dose of MEKINIST within 12 hours of the next dose of MEKINIST.

2.7 Dosage Modifications for Adverse Reactions

Dose reductions for adverse reactions associated with MEKINIST are presented in Table 1.

Table 1. Recommended Dose Reductions for MEKINIST for Adverse Reactions

Action	Recommended Dose
First Dose Reduction	1.5 mg orally once daily
Second Dose Reduction	1 mg orally once daily
Subsequent Modification	Permanently discontinue if unable to tolerate MEKINIST 1 mg orally once daily

Dosage modifications for adverse reactions associated with MEKINIST are presented in Table 2.

Table 2. Recommended Dosage Modifications for MEKINIST for Adverse Reactions

Severity of Adverse Reaction ^a	Dosage Modification for MEKINIST ^b
<i>Hemorrhage [see Warnings and Precautions (5.2)]</i>	
<ul style="list-style-type: none"> Grade 3 	Withhold MEKINIST. <ul style="list-style-type: none"> If improved, resume MEKINIST at lower dose. If not improved, permanently discontinue MEKINIST.
<ul style="list-style-type: none"> Grade 4 	Permanently discontinue MEKINIST.
<i>Venous Thromboembolism [see Warnings and Precautions (5.4)]</i>	
<ul style="list-style-type: none"> Uncomplicated deep venous thrombosis (DVT) or pulmonary embolism (PE) 	Withhold MEKINIST for up to 3 weeks. <ul style="list-style-type: none"> If improved to Grade 0-1, resume MEKINIST at lower dose. If not improved, permanently discontinue MEKINIST.
<ul style="list-style-type: none"> Life threatening PE 	Permanently discontinue MEKINIST.
<i>Cardiomyopathy [see Warnings and Precautions (5.5)]</i>	
<ul style="list-style-type: none"> Asymptomatic, absolute decrease in left ventricular ejection fraction (LVEF) of 10% or greater from baseline and is below institutional lower limit of normal (LLN) from pretreatment value 	Withhold MEKINIST for up to 4 weeks. <ul style="list-style-type: none"> If improved to normal LVEF value, resume MEKINIST at lower dose. If not improved to normal LVEF value, permanently discontinue MEKINIST.
<ul style="list-style-type: none"> Symptomatic cardiomyopathy Absolute decrease in LVEF of greater than 20% from baseline that is below LLN 	Permanently discontinue MEKINIST.
<i>Ocular Toxicities [see Warnings and Precautions (5.6)]</i>	
<ul style="list-style-type: none"> Retinal pigment epithelial detachments (RPED) 	Withhold MEKINIST for up to 3 weeks. <ul style="list-style-type: none"> If improved, resume MEKINIST at same or lower dose. If not improved, permanently discontinue MEKINIST or resume MEKINIST at lower dose.
<ul style="list-style-type: none"> Retinal vein occlusion (RVO) 	Permanently discontinue MEKINIST.
<i>Pulmonary [see Warnings and Precautions (5.7)]</i>	
<ul style="list-style-type: none"> Interstitial lung disease (ILD)/pneumonitis 	Permanently discontinue MEKINIST.
<i>Febrile Reactions [see Warnings and Precautions (5.8)]</i>	
<ul style="list-style-type: none"> Fever of 100.4°F to 104°F (or first symptoms in case of recurrence) 	Withhold MEKINIST until fever resolves, then resume MEKINIST at same or lower dose.
<ul style="list-style-type: none"> Fever higher than 104°F Fever complicated by rigors, hypotension, dehydration, or renal failure 	<ul style="list-style-type: none"> Withhold MEKINIST until febrile reactions resolve for at least 24 hours, then resume MEKINIST at lower dose. Or <ul style="list-style-type: none"> Permanently discontinue MEKINIST.
<i>Skin Toxicities [see Warnings and Precautions (5.9)]</i>	
<ul style="list-style-type: none"> Intolerable Grade 2 Grade 3 or 4 	Withhold MEKINIST for up to 3 weeks. <ul style="list-style-type: none"> If improved, resume MEKINIST at lower dose. If not improved, permanently discontinue.
<ul style="list-style-type: none"> Severe cutaneous adverse reactions (SCARs) 	Permanently discontinue MEKINIST.
<i>Other Adverse Reactions^c</i>	
<ul style="list-style-type: none"> Intolerable Grade 2 Any Grade 3 	Withhold MEKINIST. <ul style="list-style-type: none"> If improved to Grade 0-1, resume at lower dose. If not improved, permanently discontinue.

<ul style="list-style-type: none"> • First occurrence of any Grade 4 	<ul style="list-style-type: none"> • Withhold MEKINIST until improves to Grade 0-1, then resume at lower dose. <p>Or</p> <ul style="list-style-type: none"> • Permanently discontinue MEKINIST.
<ul style="list-style-type: none"> • Recurrent Grade 4 	<ul style="list-style-type: none"> • Permanently discontinue MEKINIST.

^a National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

^b See Table 1 for recommended dose reductions of MEKINIST.

^c Dose modifications are not recommended for MEKINIST when administered with dabrafenib for the following adverse reactions of dabrafenib: non-cutaneous malignancies and uveitis. Dose modification of MEKINIST is not required for new primary cutaneous malignancies.

Refer to the dabrafenib prescribing information for dose modifications for adverse reactions associated with dabrafenib.

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 0.5 mg tablets: Yellow, modified oval, biconvex, film-coated tablets with ‘GS’ debossed on one face and ‘TFC’ on the opposing face.
- 0.5 mg tablets: Yellow, ovaloid, biconvex, unscored film-coated tablets with beveled edges and with the Novartis logo debossed on one side and ‘TT’ on the other side.
- 2 mg tablets: Pink, round, biconvex, film-coated tablets with ‘GS’ debossed on one face and ‘HMJ’ on the opposing face.
- 2 mg tablets: Pink, round, biconvex, unscored film-coated tablets with beveled edges and with the Novartis logo debossed on one side and ‘LL’ on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 New Primary Malignancies

Cutaneous Malignancies

Across clinical trials of MEKINIST administered with dabrafenib, cutaneous squamous cell carcinomas (cuSCCs) and keratoacanthomas occurred in 2% of patients. Basal cell carcinoma and new primary melanoma occurred in 3% and < 1% of patients, respectively.

Perform dermatologic evaluations prior to initiation of MEKINIST when used with dabrafenib, every 2 months while on therapy, and for up to 6 months following discontinuation of the combination.

Non-Cutaneous Malignancies

Based on its mechanism of action, dabrafenib may promote growth and development of malignancies with activation of RAS through mutation or other mechanisms; refer to the prescribing information for dabrafenib. Across clinical trials of MEKINIST administered with dabrafenib, non-cutaneous malignancies occurred in 1% of patients.

Monitor patients receiving MEKINIST and dabrafenib closely for signs or symptoms of non-cutaneous malignancies. No dose modification is required for MEKINIST in patients who develop non-cutaneous malignancies.

5.2 Hemorrhage

Hemorrhages, including major hemorrhages defined as symptomatic bleeding in a critical area or organ, can occur with MEKINIST. Fatal cases have been reported.

Across clinical trials of MEKINIST administered with dabrafenib, hemorrhagic events occurred in 17% of patients. Gastrointestinal hemorrhage occurred in 3% of patients who received MEKINIST administered with dabrafenib. Intracranial hemorrhage occurred in 0.6% of patients who received MEKINIST administered with dabrafenib. Fatal hemorrhage occurred in 0.5% of patients who received MEKINIST administered with dabrafenib. The fatal events were cerebral hemorrhage and brainstem hemorrhage.

Permanently discontinue MEKINIST for all Grade 4 hemorrhagic events and for any Grade 3 hemorrhagic events that do not improve. Withhold MEKINIST for Grade 3 hemorrhagic events; if improved, resume at the next lower dose level.

5.3 Colitis and Gastrointestinal Perforation

Colitis and gastrointestinal perforation, including fatal outcomes, have been reported in patients taking MEKINIST as a single agent and when administered with dabrafenib. Across clinical trials of MEKINIST, colitis occurred in < 1% of patients and gastrointestinal perforation occurred in < 1% of patients. Across clinical trials of MEKINIST administered with dabrafenib, colitis occurred in < 1% of patients and gastrointestinal perforation occurred in < 1% of patients.

Monitor patients closely for colitis and gastrointestinal perforations.

5.4 Venous Thromboembolic Events

Across clinical trials of MEKINIST administered with dabrafenib, deep vein thrombosis (DVT) and pulmonary embolism (PE) occurred in 2% of patients.

Advise patients to immediately seek medical care if they develop symptoms of DVT or PE, such as shortness of breath, chest pain, or arm or leg swelling. Permanently discontinue MEKINIST for life-threatening PE. Withhold MEKINIST for uncomplicated DVT and PE for up to 3 weeks; if improved, MEKINIST may be resumed at a lower dose level [*see Dosage and Administration (2.7)*].

5.5 Cardiomyopathy

Cardiomyopathy, including cardiac failure, can occur with MEKINIST.

Across clinical trials of MEKINIST administered with dabrafenib, cardiomyopathy, defined as a decrease in left ventricular ejection fraction (LVEF) $\geq 10\%$ from baseline and below the institutional lower limit of normal (LLN), occurred in 6% of patients. Development of cardiomyopathy resulted in dose interruption or discontinuation of MEKINIST in 3% and < 1% of patients, respectively. Cardiomyopathy resolved in 45 of 50 patients who received MEKINIST administered with dabrafenib.

Assess LVEF by echocardiogram or multi-gated acquisition (MUGA) scan before initiation of MEKINIST as a single agent or with dabrafenib, one month after initiation, and then at 2- to 3-month intervals while on treatment. For an asymptomatic absolute decrease in LVEF of 10% or greater from baseline that is below the LLN, withhold MEKINIST for up to 4 weeks. If improved to normal LVEF value, resume at a lower dose. If no improvement to normal LVEF value within 4 weeks, permanently discontinue MEKINIST. For symptomatic cardiomyopathy or an absolute decrease in LVEF of greater than 20% from baseline that is below LLN, permanently discontinue MEKINIST [*see Dosage and Administration (2.7)*].

5.6 Ocular Toxicities

Retinal Vein Occlusion

Across clinical trials with MEKINIST monotherapy, the incidence of retinal vein occlusion (RVO) was 0.6%. Across clinical trials of MEKINIST administered with dabrafenib, there were no cases of RVO. RVO may lead to macular edema, decreased visual function, neovascularization, and glaucoma.

Urgently (within 24 hours) perform ophthalmological evaluation for patient-reported loss of vision or other visual disturbances. Permanently discontinue MEKINIST in patients with documented RVO [*see Dosage and Administration (2.7)*].

Retinal Pigment Epithelial Detachment

Retinal pigment epithelial detachment (RPED) can occur with MEKINIST. Retinal detachments may be bilateral and multifocal, occurring in the central macular region of the retina or elsewhere in the retina. In melanoma and NSCLC trials, routine monitoring of patients to detect asymptomatic RPED was not conducted; therefore, the true incidence of this finding is unknown.

Perform ophthalmological evaluation periodically and at any time a patient reports visual disturbances. Withhold MEKINIST if RPED is diagnosed. If resolution of the RPED is documented on repeat ophthalmological evaluation within 3 weeks, resume MEKINIST at same or reduced dose. If no improvement after 3 weeks, resume at reduced dose or permanently discontinue MEKINIST [see *Dosage and Administration* (2.7)].

5.7 Interstitial Lung Disease/Pneumonitis

Across clinical trials of MEKINIST monotherapy, interstitial lung disease or pneumonitis occurred in 2% of patients. Across clinical trials of MEKINIST administered with dabrafenib, ILD or pneumonitis occurred in 1% of patients.

Withhold MEKINIST in patients presenting with new or progressive pulmonary symptoms and findings, including cough, dyspnea, hypoxia, pleural effusion, or infiltrates, pending clinical investigations. Permanently discontinue MEKINIST for patients diagnosed with treatment-related ILD or pneumonitis [see *Dosage and Administration* (2.7)].

5.8 Serious Febrile Reactions

Serious febrile reactions and fever of any severity accompanied by hypotension, rigors or chills, dehydration, or renal failure, can occur when MEKINIST is administered with dabrafenib.

Across clinical trials of MEKINIST administered with dabrafenib, fever occurred in 58% of patients. Serious febrile reactions and fever of any severity complicated by hypotension, rigors or chills, dehydration or renal failure occurred in 5% of patients. Fever was complicated by hypotension in 4%, dehydration in 3%, syncope in 2%, renal failure in 1%, and severe chills/rigors in < 1% of patients.

Withhold MEKINIST when used as monotherapy, and both MEKINIST and dabrafenib when used in combination, if the patient's temperature is $\geq 100.4^{\circ}\text{F}$. In case of recurrence, therapy can also be interrupted at the first symptom of pyrexia [see *Adverse Reactions* (6.1)]. Fever may be complicated by hypotension, rigors or chills, dehydration, or renal failure. Evaluate for signs and symptoms of infection, and monitor serum creatinine and other evidence of renal function during and following severe pyrexia. If appropriate, MEKINIST, or both MEKINIST and dabrafenib when used in combination, may be restarted if the patient has recovered from the febrile reaction for at least 24 hours, either at same or lower dose [see *Dosage and Administration* (2.7)]. Administer antipyretics as secondary prophylaxis when resuming MEKINIST if patient had a prior episode of severe febrile reaction or fever associated with complications. Administer corticosteroids (e.g., prednisone 10 mg daily) for at least 5 days for second or subsequent pyrexia if temperature does not return to baseline within 3 days of onset of pyrexia, or for pyrexia associated with complications, such as dehydration, hypotension, renal failure, or severe chills/rigors, and there is no evidence of active infection.

5.9 Serious Skin Toxicities

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported during treatment with MEKINIST administered with dabrafenib [see *Adverse Reactions* (6.2)].

Across clinical trials of MEKINIST administered with dabrafenib, other serious skin toxicity occurred in < 1% of patients.

Monitor for new or worsening serious skin reactions. Permanently discontinue MEKINIST for SCARs [see *Dosage and Administration* (2.7)]. For other skin toxicities, withhold MEKINIST for intolerable or severe skin

toxicity. Resume MEKINIST at a lower dose in patients with improvement or recovery from skin toxicity within 3 weeks. Permanently discontinue MEKINIST if skin toxicity has not improved in 3 weeks [see *Dosage and Administration* (2.7)].

5.10 Hyperglycemia

Across clinical trials of MEKINIST administered with dabrafenib, 15% of patients with a history of diabetes who had received MEKINIST with dabrafenib required more intensive hypoglycemic therapy. Grade 3 and Grade 4 hyperglycemia occurred in 2% of patients.

Monitor serum glucose levels upon initiation and as clinically appropriate when MEKINIST is administered with dabrafenib in patients with preexisting diabetes or hyperglycemia. Initiate or optimize anti-hyperglycemic medications as clinically indicated.

5.11 Risks Associated With Combination Treatment

MEKINIST is indicated for use in combination with dabrafenib. Review the prescribing information for dabrafenib for information on the serious risks of dabrafenib prior to initiation of MEKINIST with dabrafenib.

5.12 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, MEKINIST can cause fetal harm when administered to a pregnant woman. Trametinib was embryotoxic and abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 0.3 times the human exposure at the recommended clinical dose. Advise pregnant women of the potential risk to a fetus. Advise female patients of reproductive potential to use effective contraception during treatment with MEKINIST and for 4 months after treatment [see *Use in Specific Populations* (8.1, 8.3)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- New Primary Malignancies [see *Warnings and Precautions* (5.1)]
- Hemorrhage [see *Warnings and Precautions* (5.2)]
- Colitis and Gastrointestinal Perforation [see *Warnings and Precautions* (5.3)]
- Venous Thromboembolism [see *Warnings and Precautions* (5.4)]
- Cardiomyopathy [see *Warnings and Precautions* (5.5)]
- Ocular Toxicities [see *Warnings and Precautions* (5.6)]
- Interstitial Lung Disease/Pneumonitis [see *Warnings and Precautions* (5.7)]
- Serious Febrile Reactions [see *Warnings and Precautions* (5.8)]
- Serious Skin Toxicities [see *Warnings and Precautions* (5.9)]
- Hyperglycemia [see *Warnings and Precautions* (5.10)]

There are additional adverse reactions associated with dabrafenib. Refer to the dabrafenib prescribing information for additional information.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety populations described in the WARNINGS and PRECAUTIONS reflect exposure to MEKINIST as a single agent in 329 patients with various solid tumors enrolled in METRIC, MEK113583, and

MEK111054, and to MEKINIST administered with dabrafenib in 1087 patients enrolled in COMBI-d, COMBI-v, COMBI-AD, and BR113928 with unresectable or metastatic melanoma, adjuvant melanoma or NSCLC. Among the 329 patients who received MEKINIST as a single agent, 33% were exposed for 6 months or longer and 9% were exposed for at least one year. Among the 1087 patients who received MEKINIST administered with dabrafenib, 70% were exposed for 6 months or longer and 21% were exposed for greater than one year.

Unresectable or Metastatic BRAF V600E or V600K Mutation-Positive Melanoma

MEKINIST as a Single Agent

The safety of MEKINIST was evaluated in the METRIC study, a randomized, open-label trial of patients with BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma who received MEKINIST (N = 211) 2 mg orally once daily or chemotherapy (N = 99) (either dacarbazine 1000 mg/m² every 3 weeks or paclitaxel 175 mg/m² every 3 weeks) [see *Clinical Studies (14.1)*]. Patients with abnormal LVEF, history of acute coronary syndrome within 6 months, or current evidence of Class II or greater congestive heart failure (New York Heart Association) were excluded. The median duration of treatment with MEKINIST was 4.3 months.

In this study, 9% of patients who received MEKINIST experienced adverse reactions resulting in permanent discontinuation of trial medication. The most frequent adverse reactions resulting in permanent discontinuation of MEKINIST were decreased LVEF, pneumonitis, renal failure, diarrhea, and rash. Adverse reactions led to dose reductions in 27% of patients treated with MEKINIST. Rash and decreased LVEF were the most frequent reasons cited for dose reductions of MEKINIST. Tables 3 and 4 present adverse reactions and laboratory abnormalities, respectively, of MEKINIST as a single agent in the METRIC study.

Table 3. Select Adverse Reactions Occurring in ≥ 10% of Patients Who Received MEKINIST and at a Higher Incidence (≥ 5%) Than in the Chemotherapy Arm or ≥ 2% (Grades 3 or 4) Adverse Reactions in METRIC

Adverse Reactions	MEKINIST N = 211		Chemotherapy N = 99	
	All Grades ^a (%)	Grades 3 and 4 ^b (%)	All Grades ^a (%)	Grades 3 and 4 ^b (%)
Skin and subcutaneous tissue				
Rash	57	8	10	0
Acneiform dermatitis	19	< 1	1	0
Dry skin	11	0	0	0
Pruritus	10	2	1	0
Paronychia	10	0	1	0
Gastrointestinal				
Diarrhea	43	0	16	2
Stomatitis ^c	15	2	2	0
Abdominal pain ^d	13	1	5	1
Vascular				
Lymphedema ^e	32	1	4	0
Hypertension	15	12	7	3
Hemorrhage ^f	13	< 1	0	0

- ^a National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
- ^b Grade 4 adverse reactions limited to rash (n = 1) in trametinib arm and diarrhea (n = 1) in chemotherapy arm.
- ^c Includes stomatitis, aphthous stomatitis, mouth ulceration, and mucosal inflammation.
- ^d Includes abdominal pain, lower abdominal pain, upper abdominal pain, and abdominal tenderness.
- ^e Includes lymphedema, edema, and peripheral edema.
- ^f Includes epistaxis, gingival bleeding, hematochezia, rectal hemorrhage, melena, vaginal hemorrhage, hemorrhoidal hemorrhage, hematuria, and conjunctival hemorrhage.

Other clinically important adverse reactions observed in $\leq 10\%$ of patients (N = 329) who received MEKINIST were:

Cardiac: Bradycardia

Gastrointestinal: Dry mouth

Infections: Folliculitis, rash pustular, cellulitis

Musculoskeletal and Connective Tissue: Rhabdomyolysis

Nervous System: Dizziness, dysgeusia

Ocular: Blurred vision, dry eye

Table 4. Laboratory Abnormalities Occurring at a Higher Incidence in Patients Who Received MEKINIST in the METRIC Study [Between-Arm Difference of $\geq 5\%$ (All Grades) or $\geq 2\%$ (Grades 3 or 4)^a]

Laboratory Abnormality	MEKINIST N = 211		Chemotherapy N = 99	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Increased aspartate aminotransferase (AST)	60	2	16	1
Hypoalbuminemia	42	2	23	1
Increased alanine aminotransferase (ALT)	39	3	20	3
Anemia	38	2	26	3
Increased alkaline phosphatase	24	2	18	3

^a Only Grade 3 adverse reactions were reported in either treatment arm.

MEKINIST with Dabrafenib

The safety of MEKINIST, administered with dabrafenib, was evaluated in 559 patients with previously untreated, unresectable or metastatic, BRAF V600 mutation-positive melanoma who received MEKINIST in two trials, the COMBI-d study (n = 209), a multicenter, double-blind, randomized (1:1), active-controlled trial and the COMBI-v study (n = 350), a multicenter, open-label, randomized (1:1), active-controlled trial. In both trials, patients received MEKINIST 2 mg orally once daily and dabrafenib 150 mg orally twice daily until disease progression or unacceptable toxicity. The trials excluded patients with abnormal LVEF, history of acute coronary syndrome within 6 months, history of Class II or greater congestive heart failure (New York Heart Association), history of RVO or RPED, QTcB interval ≥ 480 msec, uncontrolled hypertension, uncontrolled arrhythmias, active brain metastases, or known history of glucose-6-phosphate dehydrogenase deficiency.

Among these 559 patients, 197 (35%) were exposed to MEKINIST for > 6 months to 12 months, while 185 (33%) were exposed to MEKINIST for > 1 year. The median age was 55 years (range: 18 to 91), 57% were male, and 98% were white, 72% had baseline ECOG performance status 0 and 28% had ECOG performance status 1, 64% had M1c stage disease, 35% had elevated lactate dehydrogenase (LDH) at baseline, and 0.5% had a history of brain metastases.

The most common adverse reactions ($\geq 20\%$) for MEKINIST in patients who received MEKINIST plus dabrafenib were: pyrexia, nausea, rash, chills, diarrhea, vomiting, hypertension, and peripheral edema.

The demographics and baseline tumor characteristics of patients enrolled in the COMBI-d study are summarized in Clinical Studies [see *Clinical Studies (14.1)*]. Patients who received MEKINIST plus dabrafenib had a median duration of exposure of 11 months (range: 3 days to 30 months) to MEKINIST. Among the 209 patients who received MEKINIST plus dabrafenib, 26% were exposed to MEKINIST for > 6 months to 12 months while 46% were exposed to MEKINIST for > 1 year.

In the COMBI-d study, adverse reactions leading to discontinuation of MEKINIST occurred in 11% of patients who received MEKINIST plus dabrafenib; the most frequent were pyrexia (1.4%) and decreased ejection fraction (1.4%). Adverse reactions leading to dose reductions of MEKINIST occurred in 18% of patients who received MEKINIST plus dabrafenib; the most frequent were pyrexia (2.9%), neutropenia (1.9%), decreased ejection fraction (1.9%), and rash (1.9%). Adverse reactions leading to dose interruptions of MEKINIST occurred in 46% of patients who received MEKINIST plus dabrafenib; the most frequent were pyrexia (18%), chills (7%), vomiting (6%), and decreased ejection fraction (4.8%).

Table 5 and Table 6 present selected adverse reactions and laboratory abnormalities, respectively, of MEKINIST observed in the COMBI-d study.

Table 5. Adverse Reactions Occurring in $\geq 10\%$ (All Grades) of Patients Who Received MEKINIST With Dabrafenib and at a Higher Incidence* Than in Patients Who Received Single-Agent Dabrafenib in COMBI-d^a

Adverse Reactions	Pooled MEKINIST plus Dabrafenib N = 559		COMBI-d Study			
			MEKINIST plus Dabrafenib N = 209		Dabrafenib N = 211	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
General						
Pyrexia	54	5	57	7	33	1.9
Chills	31	0.5	31	0	17	0.5
Peripheral edema ^b	21	0.7	25	1.4	11	0.5
Gastrointestinal						
Nausea	35	0.4	34	0.5	27	1.4
Diarrhea	31	1.3	30	1.4	16	0.9
Vomiting	27	1.1	25	1.0	14	0.5
Abdominal pain ^c	18	0.9	26	1.0	14	2.4
Skin						
Rash ^d	32	1.1	42	0	27	1.4
Vascular						
Hypertension	26	11	25	6	16	6
Hemorrhage ^e	18	2.0	19	1.9	15	1.9
Nervous system						
Dizziness	11	0.2	14	0	7	0

* $\geq 5\%$ for All Grades or $\geq 2\%$ for Grades 3–4 incidence in patients who received MEKINIST with dabrafenib compared with patients who received dabrafenib as a single agent.

^a National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

^b Includes peripheral edema, edema, lymphedema, localized edema, and generalized edema.

^c Includes abdominal pain, upper abdominal pain, lower abdominal pain, and abdominal discomfort.

^d Includes rash, generalized rash, pruritic rash, erythematous rash, papular rash, vesicular rash, macular rash, maculo-papular, and folliculitis rash.

^e Most common events ($\geq 1\%$) include epistaxis, hematochezia, decreased hemoglobin, purpura, and rectal hemorrhage. Grade 4 events were limited to hepatic hematoma and duodenal ulcer hemorrhage (each n = 1 in the pooled combination arm).

Other clinically important adverse reactions for MEKINIST observed in less than 10% of patients who received MEKINIST in combination with dabrafenib (N = 559) were:

Cardiac: Bradycardia

Immunologic: Sarcoidosis

Musculoskeletal: Rhabdomyolysis

Table 6. Laboratory Abnormalities Worsening From Baseline Occurring at $\geq 10\%$ (All Grades) of Patients Who Received MEKINIST With Dabrafenib and at a Higher Incidence* Than in Patients Who Received Single-Agent Dabrafenib in COMBI-d

Laboratory Abnormality	COMBI-d Study					
	Pooled MEKINIST plus Dabrafenib N = 559 ^a		MEKINIST plus Dabrafenib N = 209 ^b		Dabrafenib N = 211 ^b	
	All Grades (%)	Grades 3 and 4 ^c (%)	All Grades (%)	Grades 3 and 4 ^c (%)	All Grades (%)	Grades 3 and 4 ^c (%)
Chemistry						
Hyperglycemia	60	4.7	65	6	57	4.3
Hypoalbuminemia	48	1.1	53	1.4	27	0
Hyponatremia	25	8	24	6	14	2.9
Hepatic						
Increased AST	59	4.1	60	4.3	21	1.0
Increased blood alkaline phosphatase	49	2.7	50	1.0	25	0.5
Increased ALT	48	4.5	44	3.8	28	1.0
Hematology						
Neutropenia	46	7	50	6	16	1.9
Anemia	43	2.3	43	2.4	38	4.3
Lymphopenia	32	8	38	9	28	7
Thrombocytopenia	21	0.7	19	0.5	10	0.5

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

* $\geq 5\%$ for All Grades or $\geq 2\%$ for Grades 3–4 incidence in patients who received MEKINIST with dabrafenib compared with patients who received dabrafenib as a single agent.

^a For these laboratory tests the denominator is 556.

^b For these laboratory tests the denominator is 208 for the combination arm, 207–209 for the dabrafenib arm.

^c Grade 4 adverse reactions limited to lymphopenia and hyperglycemia (each n = 4), increased ALT and increased AST (each n = 3), neutropenia (n = 2), and hyponatremia (n = 1), in the pooled combination arm; neutropenia, lymphopenia, increased ALT, increased AST, hyperglycemia (each n = 1) in the COMBI-d study combination arm; neutropenia, thrombocytopenia, increased ALT, and increased AST (each n = 1) in the dabrafenib arm.

Adjuvant Treatment of BRAF V600E or V600K Mutation-Positive Melanoma

The safety of MEKINIST when administered with dabrafenib was evaluated in 435 patients with Stage III melanoma with BRAF V600E or V600K mutations following complete resection who received at least one dose of study therapy in the COMBI-AD study [see *Clinical Studies (14.2)*]. Patients received MEKINIST 2 mg orally once daily and dabrafenib 150 mg orally twice daily for 12 months. The trial excluded patients with abnormal LVEF; history of acute coronary syndromes, coronary angioplasty, or stenting within 6 months; Class II or greater congestive heart failure (New York Heart Association); QTc interval ≥ 480 msec; treatment refractory hypertension; uncontrolled arrhythmias; or history of RVO.

Patients who received MEKINIST in combination with dabrafenib had a median duration of exposure of 11 months (range: 0 to 12) to MEKINIST. Among the 435 patients who received MEKINIST in combination with dabrafenib, 72% were exposed to MEKINIST for > 6 months. The median age of patients who received MEKINIST in combination with dabrafenib was 50 years (range: 18 to 89), 56% were male, 99% were white, 92% had baseline ECOG performance status 0, and 8% had baseline ECOG performance status 1.

The most common adverse reactions ($\geq 20\%$) in patients who received MEKINIST in combination with dabrafenib were: pyrexia, fatigue, nausea, headache, rash, chills, diarrhea, vomiting, arthralgia, and myalgia.

Adverse reactions resulting in discontinuation and dose interruptions of MEKINIST occurred in 24% and 54% of patients, respectively; the most frequent for each were pyrexia and chills. Adverse reactions leading to dose reductions of MEKINIST occurred in 23% of patients; the most frequent were pyrexia and decreased ejection fraction.

Table 7 summarizes adverse reactions that occurred in at least 20% of the patients who received MEKINIST in combination with dabrafenib.

Table 7. Adverse Reactions Occurring in $\geq 20\%$ of Patients in COMBI-AD^a

Adverse Reactions	MEKINIST plus Dabrafenib N = 435		Placebo N = 432	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
General				
Pyrexia ^b	63	5	11	< 1
Fatigue ^c	59	5	37	< 1
Chills	37	1	4	0
Gastrointestinal				
Nausea	40	< 1	20	0
Diarrhea	33	< 1	15	< 1
Vomiting	28	< 1	10	0
Nervous system				
Headache ^d	39	1	24	0
Skin				
Rash ^e	37	< 1	16	< 1
Musculoskeletal				
Arthralgia	28	< 1	14	0
Myalgia ^f	20	< 1	14	0

^a NCI CTCAE version 4.0.

^b Includes pyrexia and hyperpyrexia.

^c Includes fatigue, asthenia, and malaise.

^d Includes headache and tension headache.

^e Includes rash, rash maculo-papular, rash macular, rash generalized, rash erythematous, rash papular, rash pruritic, nodular rash, rash vesicular, and rash pustular.

^f Includes myalgia, musculoskeletal pain, and musculoskeletal chest pain.

Other clinically important adverse reactions observed in less than 20% of patients in the COMBI-AD study who received MEKINIST in combination with dabrafenib were: blurred vision (6%), decreased ejection fraction (5%), rhabdomyolysis (< 1%), and sarcoidosis (< 1%).

The laboratory abnormalities are summarized in Table 8.

Table 8. Laboratory Abnormalities Worsening From Baseline Occurring in $\geq 20\%$ of Patients in COMBI-AD

Laboratory Abnormality	MEKINIST plus Dabrafenib ^a N = 435		Placebo ^a N = 432	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Chemistry				
Hyperglycemia	63	3	47	2
Hypophosphatemia	42	7	10	< 1
Hypoalbuminemia	25	< 1	< 1	0
Hepatic				
Increased AST	57	6	11	< 1
Increased ALT	48	5	18	< 1
Increased blood alkaline phosphatase	38	1	6	< 1
Hematology				
Neutropenia	47	6	12	< 1
Lymphopenia	26	5	6	< 1
Anemia	25	< 1	6	< 1

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

^a The incidence is based on the number of patients who had both a baseline and at least one on-study laboratory measurement: MEKINIST plus dabrafenib (range: 429 to 431) and placebo arm (range: 426 to 428).

Trial COMBI-APlus (Pyrexia Management Study)

COMBI-APlus evaluated the impact of pyrexia related outcomes of a revised pyrexia management algorithm in patients who received dabrafenib administered with trametinib in the adjuvant treatment of BRAF V600 mutation-positive melanoma after complete resection. The pyrexia management algorithm interrupted both dabrafenib and trametinib when patient's temperature is $\geq 100.4^\circ\text{F}$.

Grade 3-4 pyrexia occurred in 4.3% of patients, hospitalizations due to pyrexia occurred in 5.1% of patients, pyrexia with complications (dehydration, hypotension, renal dysfunction, syncope, severe chills) occurred in 2.2% of patients, and treatment discontinuation due to pyrexia occurred in 2.5% of patients.

Metastatic, BRAF V600E Mutation-Positive Non-Small Cell Lung Cancer

The safety of MEKINIST when administered with dabrafenib was evaluated in 93 patients with previously untreated (n = 36) and previously treated (n = 57) metastatic BRAF V600E mutation-positive NSCLC in a multicenter, multi-cohort, non-randomized, open-label trial (Study BR113928). Patients received MEKINIST 2 mg orally once daily and dabrafenib 150 mg orally twice daily until disease progression or unacceptable toxicity. The trial excluded patients with abnormal LVEF, history of acute coronary syndrome within 6 months, history of Class II or greater congestive heart failure (New York Heart Association), QTc interval ≥ 480 msec, treatment refractory hypertension, uncontrolled arrhythmias, active brain metastases, history of ILD or pneumonitis, or history or current RVO [see *Clinical Studies (14.3)*].

Among these 93 patients, 53 (57%) were exposed to MEKINIST and dabrafenib for > 6 months and 27 (29%) were exposed to MEKINIST and dabrafenib for ≥ 1 year. The median age was 65 years (range: 41 to 91), 46% were male, 85% were white; 32% had baseline ECOG performance status 0 and 61% had ECOG performance status 1; 98% had non-squamous histology; and 12% were current smokers, 60% were former smokers, and 28% had never smoked.

The most common adverse reactions ($\geq 20\%$) in these 93 patients were: pyrexia, fatigue, nausea, vomiting, diarrhea, dry skin, decreased appetite, edema, rash, chills, hemorrhage, cough, and dyspnea.

Adverse reactions resulting in discontinuation of MEKINIST occurred in 19% of patients; the most frequent were pyrexia (2.2%), decreased ejection fraction (2.2%), and respiratory distress (2.2%). Adverse reactions leading to dose reductions of MEKINIST occurred in 30% of patients who received MEKINIST plus dabrafenib; the most frequent were pyrexia (5%), nausea (4.3%), vomiting (4.3%), diarrhea (3.2%), and neutropenia (3.2%). Adverse reactions leading to dose interruptions of MEKINIST occurred in 57% of patients who received MEKINIST plus dabrafenib; the most frequent were pyrexia (16%), vomiting (10%), neutropenia (8%), nausea (5%), and decreased ejection fraction (5%).

Table 9 and Table 10 present adverse reactions and laboratory abnormalities, respectively, of MEKINIST in combination with dabrafenib in Study BR113928.

Table 9. Adverse Reactions Occurring in \geq 20% (All Grades) of Patients Treated With MEKINIST plus Dabrafenib in Study BR113928^a

Adverse Reactions	MEKINIST plus Dabrafenib N = 93	
	All Grades (%)	Grades 3 and 4 ^b (%)
General		
Pyrexia	55	5
Fatigue ^b	51	5
Edema ^c	28	0
Chills	23	1.1
Gastrointestinal		
Nausea	45	0
Vomiting	33	3.2
Diarrhea	32	2.2
Decreased appetite	29	0
Skin		
Dry skin	31	1.1
Rash ^d	28	3.2
Vascular		
Hemorrhage ^e	23	3.2
Respiratory system		
Cough	22	0
Dyspnea	20	5

^a NCI CTCAE version 4.0.

^b Includes fatigue, malaise, and asthenia.

^c Includes peripheral edema, edema, and generalized edema.

^d Includes rash, rash generalized, rash papular, rash macular, rash maculo-papular, and rash pustular.

^e Includes hemoptysis, hematoma, epistaxis, purpura, hematuria, subarachnoid hemorrhage, gastric hemorrhage, urinary bladder hemorrhage, contusion, hematochezia, injection site hemorrhage, pulmonary hemorrhage, and retroperitoneal hemorrhage.

Table 10. Treatment-Emergent Laboratory Abnormalities Occurring in $\geq 20\%$ (All Grades) of Patients Who Received MEKINIST Plus Dabrafenib in Study BRF113928

Laboratory Abnormality	MEKINIST plus Dabrafenib N = 93	
	All Grades (%)	Grades 3 and 4 (%)
Chemistry^a		
Hyperglycemia	71	9
Hyponatremia	57	17
Hypophosphatemia	36	7
Increased creatinine	21	1.1
Hepatic^a		
Increased blood alkaline phosphatase	64	0
Increased AST	61	4.4
Increased ALT	32	6
Hematology^b		
Leukopenia	48	8
Anemia	46	10
Neutropenia	44	8
Lymphopenia	42	14

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

^a For these laboratory tests the denominator is 90.

^b For these laboratory tests the denominator is 91.

Locally Advanced or Metastatic, BRAF V600E Mutation-Positive, Anaplastic Thyroid Cancer

The safety of MEKINIST when administered with dabrafenib was evaluated in a nine-cohort, multicenter, non-randomized, open-label study in patients with rare cancers with the BRAF V600E mutation, including locally advanced or metastatic ATC (Study BRF117019). At the time of the safety analysis, a total of 100 patients were enrolled in the trial, 16 of whom were enrolled in the ATC cohort. The primary safety population included all patients who received at least one dose of MEKINIST or dabrafenib. Patients received MEKINIST 2 mg orally once daily and dabrafenib 150 mg orally twice daily until disease progression or unacceptable toxicity.

Among these 100 patients, 46 (46%) were exposed to MEKINIST and dabrafenib for > 6 months and 23 (23%) were exposed to MEKINIST and dabrafenib for ≥ 1 year. The median age was 59.5 years (range: 18 to 85); 62% were male; 85% were white; and 31% had baseline ECOG performance status 0, and 59% had ECOG performance status 1.

The adverse reaction profile among all patients and among patients in the ATC cohort was similar to that observed in other approved indications.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of MEKINIST in combination with dabrafenib. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Dermatologic: SCAR (including DRESS and SJS)

7 DRUG INTERACTIONS

MEKINIST is indicated for use in combination with dabrafenib. Refer to the dabrafenib labeling for additional risk information that applies to combination use treatment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action [*see Clinical Pharmacology (12.1)*] and findings from animal reproduction studies, MEKINIST can cause fetal harm when administered to a pregnant woman. There is insufficient data in pregnant women exposed to MEKINIST to assess the risks. Trametinib was embryotoxic and abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 0.3 times the human exposure at the recommended clinical dose (*see Data*). Advise pregnant women of the potential risk to the fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In reproductive toxicity studies, administration of trametinib to rats during the period of organogenesis resulted in decreased fetal weights at doses greater than or equal to 0.031 mg/kg/day [approximately 0.3 times the human exposure at the recommended dose based on area under the curve (AUC)]. In rats, at a dose resulting in exposures 1.8-fold higher than the human exposure at the recommended dose, there was maternal toxicity and an increase in post-implantation loss.

In pregnant rabbits, administration of trametinib during the period of organogenesis resulted in decreased fetal body weight and increased incidence of variations in ossification at doses greater than or equal to 0.039 mg/kg/day (approximately 0.08 times the human exposure at the recommended dose based on AUC). In rabbits administered trametinib at 0.15 mg/kg/day (approximately 0.3 times the human exposure at the recommended dose based on AUC) there was an increase in post-implantation loss, including total loss of pregnancy, compared with control animals.

8.2 Lactation

Risk Summary

There are no data on the presence of trametinib in human milk, or the effects of trametinib on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in breastfed infants, advise women not to breastfeed during treatment with MEKINIST and for 4 months following the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating MEKINIST.

Contraception

Based on data from animal studies and its mechanism of action, MEKINIST can cause fetal harm when administered to pregnant women [*see Use in Specific Populations (8.1)*].

Females

Advise female patients of reproductive potential to use effective contraception during treatment with MEKINIST and for 4 months after the last dose.

Males

To avoid potential drug exposure to pregnant partners and female partners of reproductive potential, advise male patients (including those who have had vasectomies) with female partners of reproductive potential to use condoms during treatment with MEKINIST and for at least 4 months after the last dose.

Infertility

Females

Advise female patients of reproductive potential that MEKINIST may impair fertility. Increased follicular cysts and decreased corpora lutea were observed in female rats at dose exposures equivalent to 0.3 times the human exposure at the recommended dose [see *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and effectiveness of MEKINIST as a single agent or in combination with dabrafenib have not been established in pediatric patients.

Juvenile Animal Toxicity Data

In a repeat-dose toxicity study in juvenile rats, decreased bone length and corneal dystrophy were observed at doses resulting in exposures as low as 0.3 times the human exposure at the recommended adult dose based on AUC. Additionally, a delay in sexual maturation was noted at doses resulting in exposures as low as 1.6 times the human exposure at the recommended adult dose based on AUC.

8.5 Geriatric Use

Of the 214 patients with melanoma who received single agent MEKINIST in the METRIC study, 27% were aged 65 years and older and 4% were over 75 years old [see *Clinical Studies (14.1)*]. This study of single agent MEKINIST in melanoma did not include sufficient numbers of geriatric patients to determine whether they respond differently from younger adults.

Of the 994 patients with melanoma who received MEKINIST plus dabrafenib in the COMBI-d, COMBI-v, and COMBI-AD studies [see *Clinical Studies (14.1, 14.2)*], 21% were aged 65 years and older and 5% were aged 75 years and older. No overall differences in the effectiveness of MEKINIST plus dabrafenib were observed in geriatric patients as compared to younger adults across these melanoma studies. The incidences of peripheral edema (26% vs. 12%) and anorexia (21% vs. 9%) increased in geriatric patients as compared to younger adults in these studies.

Of the 93 patients with NSCLC who received MEKINIST in Study BR113928, there were insufficient numbers of geriatric patients aged 65 and older to determine whether they respond differently from younger adults [see *Clinical Studies (14.4)*].

Of the 26 patients with ATC who received MEKINIST in Study BR117019, 77% were aged 65 years and older and 31% were aged 75 years and older [see *Clinical Studies (14.4)*]. This study did not include sufficient numbers of younger adults to determine whether they respond differently compared to geriatric patients.

8.6 Hepatic Impairment

No dose adjustment is recommended in patients with mild (bilirubin \leq upper limit of normal (ULN) and aspartate aminotransferase (AST) $>$ ULN or bilirubin $>$ 1x to 1.5x ULN and any AST) hepatic impairment.

A recommended dosage of MEKINIST has not been established for patients with moderate (bilirubin $>$ 1.5x to 3x ULN and any AST) or severe (bilirubin $>$ 3x to 10x ULN and any AST) hepatic impairment. Consider the risk-benefit profile of MEKINIST related to dosing prior to determining whether to administer MEKINIST to patients with moderate or severe hepatic impairment.

In patients with moderate hepatic impairment, 3 patients who received a starting dose of 1.5 mg orally once daily and two patients who received a starting dose of 2 mg orally once daily did not experience dose limiting toxicities (DLTs) during the first cycle of therapy.

In patients with severe hepatic impairment, 3 patients who received a starting dose of 1 mg orally once daily did not experience DLTs during the first cycle; one patient who received a starting dose of 1.5 mg orally once daily experienced a DLT (grade 3 acneiform rash).

Compared to patients with normal hepatic function, there was no increase in exposure of trametinib in patients with moderate or severe hepatic impairment [see *Clinical Pharmacology* (12.3)].

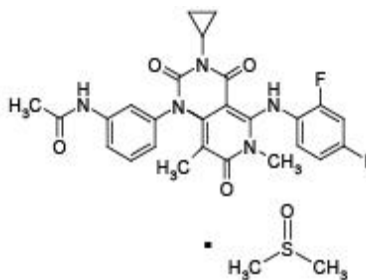
10 OVERDOSAGE

The highest doses of MEKINIST evaluated in clinical trials were 4 mg orally once daily and 10 mg administered orally once daily on 2 consecutive days followed by 3 mg once daily. In seven patients treated on one of these two schedules, there were two cases of RPEDs for an incidence of 28%.

Since trametinib is highly bound to plasma proteins, hemodialysis is likely to be ineffective in the treatment of overdose with MEKINIST.

11 DESCRIPTION

Trametinib dimethyl sulfoxide is a kinase inhibitor. The chemical name is acetamide, N-[3-[3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-3,4,6,7-tetrahydro-6,8-dimethyl-2,4,7-trioxopyrido[4,3-d]pyrimidin-1(2H)-yl]phenyl]-, compound with 1,1'-sulfinylbis[methane] (1:1). It has a molecular formula $C_{26}H_{23}FIN_5O_4 \cdot C_2H_6OS$ with a molecular mass of 693.53 g/mol. Trametinib dimethyl sulfoxide has the following chemical structure:



Trametinib dimethyl sulfoxide is a white to almost white powder. It is practically insoluble in the pH range of 2 to 8 in aqueous media.

MEKINIST (trametinib) tablets for oral use are supplied as 0.5 mg and 2 mg tablets for oral administration. Each 0.5 mg tablet contains 0.5635 mg trametinib dimethyl sulfoxide equivalent to 0.5 mg of trametinib non-solvated parent. Each 2 mg tablet contains 2.254 mg trametinib dimethyl sulfoxide equivalent to 2 mg of trametinib non-solvated parent.

The inactive ingredients of MEKINIST tablets are: **Tablet Core:** colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate (vegetable source), mannitol, microcrystalline cellulose, and sodium lauryl sulfate. **Coating:** hypromellose, iron oxide red (2 mg tablets), iron oxide yellow (0.5 mg tablets), polyethylene glycol, polysorbate 80 (2 mg tablets), and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Trametinib is a reversible inhibitor of mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2 activation and of MEK1 and MEK2 kinase activity. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. BRAF V600E mutations result in constitutive activation of the BRAF pathway which includes MEK1 and MEK2. Trametinib inhibits cell growth of various BRAF V600 mutation-positive tumors *in vitro* and *in vivo*.

Trametinib and dabrafenib target two different kinases in the RAS/RAF/MEK/ERK pathway. Use of trametinib and dabrafenib in combination resulted in greater growth inhibition of BRAF V600 mutation-positive tumor cell lines *in vitro* and prolonged inhibition of tumor growth in BRAF V600 mutation positive tumor xenografts compared with either drug alone.

Infertility

Advise females of reproductive potential of the potential risk for impaired fertility [*see Use in Specific Populations (8.3)*].

Administration

MEKINIST should be taken at least 1 hour before or at least 2 hours after a meal [*see Dosage and Administration (2.6)*].

THxID® BRAF assay is a trademark of bioMérieux.

Oncomine™ Dx Target Test is a trademark of Life Technologies Corporation, a part of Thermo Fisher Scientific Inc.

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Patient Information
MEKINIST® (MEK-in-ist)
(trametinib)
tablets

Important information: If your healthcare provider prescribes MEKINIST for you to be taken with dabrafenib, also read the Medication Guide that comes with dabrafenib.

What is the most important information I should know about MEKINIST?

MEKINIST may cause serious side effects, including:

Risk of new skin cancers. MEKINIST, when used with dabrafenib, may cause skin cancers, called cutaneous squamous cell carcinoma, keratoacanthoma, basal cell carcinoma, or melanoma.

Talk to your healthcare provider about your risk for these cancers.

Check your skin and tell your healthcare provider right away about any skin changes, including a:

- new wart
- skin sore or reddish bump that bleeds or does not heal
- change in size or color of a mole

Your healthcare provider should check your skin before treatment with MEKINIST and dabrafenib, every 2 months during treatment with MEKINIST and dabrafenib and for up to 6 months after you stop taking MEKINIST and dabrafenib to look for any new skin cancers.

Your healthcare provider should also check for cancers that may not occur on the skin. Tell your healthcare provider about any new symptoms that develop during treatment with MEKINIST with dabrafenib.

See "**What are the possible side effects of MEKINIST?**" for more information about side effects.

What is MEKINIST?

MEKINIST is a prescription medicine used:

- alone or in combination with a medicine called dabrafenib to treat a type of skin cancer called melanoma:
 - that has spread to other parts of the body or cannot be removed by surgery, **and**
 - that has a certain type of abnormal "BRAF" gene.
- in combination with dabrafenib, to help prevent melanoma that has a certain type of abnormal "BRAF" gene from coming back after the cancer has been removed by surgery.

MEKINIST should not be used to treat people who already have received a BRAF inhibitor for treatment of their melanoma, and it did not work or is no longer working.

- in combination with dabrafenib to treat a type of lung cancer called non-small cell lung cancer (NSCLC)
 - that has spread to other parts of the body, **and**
 - that has a certain type of abnormal "BRAF" gene.
- in combination with dabrafenib to treat a type of thyroid cancer called anaplastic thyroid cancer (ATC)
 - that has spread to other parts of the body and you have no satisfactory treatment options, **and**
 - that has a certain type of abnormal "BRAF" gene.

Your healthcare provider will perform a test to make sure that MEKINIST is right for you.

It is not known if MEKINIST alone or MEKINIST with dabrafenib is safe and effective in children.

Before you take MEKINIST, tell your healthcare provider about all of your medical conditions, including if you:

- have had bleeding problems or blood clots
- have stomach problems
- have inflammation of the colon
- have heart problems
- have eye problems
- have lung or breathing problems
- have high blood pressure (hypertension)
- have liver or kidney problems
- have diabetes

- are a male (including one who has had a vasectomy) with a female partner of reproductive potential.
 - Males (including those who have had a vasectomy) should use condoms during sexual intercourse during treatment with MEKINIST and for at least 4 months after your last dose of MEKINIST.
- are pregnant or plan to become pregnant. MEKINIST can harm your unborn baby.
 - Females who are able to become pregnant should use effective birth control (contraception) during treatment with MEKINIST and for 4 months after your last dose of MEKINIST.
 - Talk to your healthcare provider about birth control methods that may be right for you during this time.
 - Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with MEKINIST.
- are breastfeeding or plan to breastfeed. It is not known if MEKINIST passes into your breast milk.
 - Do not breastfeed during treatment and for 4 months after your last dose of MEKINIST. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take MEKINIST?

- Take MEKINIST exactly as your healthcare provider tells you to take it. Do not change your dose or stop MEKINIST unless your healthcare provider tells you.
- Your healthcare provider may change your dose of MEKINIST, temporarily stop, or completely stop your treatment with MEKINIST if you develop certain side effects.
- Take MEKINIST one time a day, about every 24 hours.
- Take MEKINIST at least 1 hour before or 2 hours after a meal.
- If you miss a dose, take it as soon as you remember. If it is less than 12 hours before your next scheduled dose, skip the missed dose. Just take the next dose at your regular time.

What are the possible side effects of MEKINIST?

MEKINIST may cause serious side effects, including:

- **See “What is the most important information I should know about MEKINIST?”**
- **bleeding problems.** MEKINIST can cause serious bleeding problems, especially in your brain or stomach, that can lead to death. Call your healthcare provider and get medical help right away if you have any signs of bleeding, including:
 - headaches, dizziness, or feeling weak
 - cough up blood or blood clots
 - vomit blood or your vomit looks like “coffee grounds”
 - red or black stools that look like tar
- **inflammation of the intestines, or tears (perforation) of the stomach or intestines.** MEKINIST can cause inflammation of your intestines, or tears in the stomach or intestines that can lead to death. Tell your healthcare provider immediately if you have any of the following symptoms:
 - bleeding. See “**bleeding problems**” above.
 - diarrhea (loose stools) or more bowel movements than usual
 - stomach-area (abdomen) pain or tenderness
 - fever
 - nausea
- **blood clots.** MEKINIST can cause blood clots in your arms or legs, which can travel to your lungs and can lead to death. Get medical help right away if you have the following symptoms:
 - chest pain
 - sudden shortness of breath or trouble breathing
 - pain in your legs with or without swelling
 - swelling in your arms or legs
 - a cool pale arm or leg

- **heart problems**, including heart failure. Your healthcare provider should check your heart function before and during treatment with MEKINIST. Call your healthcare provider right away if you have any of the following signs and symptoms of a heart problem:
 - feeling like your heart is pounding or racing
 - shortness of breath
 - swelling of your ankles and feet
 - feeling lightheaded
- **eye problems**. MEKINIST can cause severe eye problems that might lead to blindness. Call your healthcare provider right away if you get these symptoms of eye problems:
 - blurred vision, loss of vision, or other vision changes
 - see color dots
 - halo (seeing blurred outline around objects)
 - eye pain, swelling, or redness
- **lung or breathing problems**. MEKINIST can cause lung or breathing problems. Tell your healthcare provider if you have any new or worsening symptoms of lung or breathing problems, including:
 - shortness of breath
 - cough
- **fever**. Fever is common during treatment with MEKINIST and dabrafenib, but it may also be serious. When taking MEKINIST with dabrafenib, fever may happen more often or may be more severe. In some cases, chills or shaking chills, too much fluid loss (dehydration), low blood pressure, dizziness, or kidney problems may happen with the fever.

Call your healthcare provider right away if you get a fever during treatment with MEKINIST.

Your healthcare provider may temporarily or permanently stop your treatment, or change your dose of MEKINIST with dabrafenib if you have fevers. Your healthcare provider will treat you as needed for your fever and any signs and symptoms of infection, and should check your kidney function during and after you have had severe fever.

- **serious skin reactions**. Skin rash is a common side effect of MEKINIST. MEKINIST can also cause other skin reactions. In some cases these rashes and other skin reactions can be severe or serious, and may need to be treated in a hospital or lead to death.

Tell your healthcare provider if you get a skin rash or acne that bothers you or worsens.

Tell your healthcare provider right away if you develop any of the following signs or symptoms of a severe skin reaction, including:

- blisters or peeling of your skin
- mouth sores
- blisters on your lips, or around your mouth or eyes
- high fever or flu-like symptoms
- enlarged lymph nodes
- **increased blood sugar (hyperglycemia)**. Some people may develop high blood sugar or worsening diabetes during treatment with MEKINIST and dabrafenib. If you are diabetic, your healthcare provider should check your blood sugar levels closely during treatment with MEKINIST and dabrafenib. Your diabetes medicine may need to be changed. Tell your healthcare provider if you have any of the following symptoms of severe high blood sugar:
 - increased thirst
 - urinating more often than normal or urinating an increased amount of urine

The most common side effects of MEKINIST when taken alone include:

- rash
- diarrhea. Call your healthcare provider if you get severe diarrhea.
- swelling of the face, arms, or legs

The most common side effects of MEKINIST when taken with dabrafenib in people with melanoma that has spread to other parts of the body or cannot be removed by surgery include:

- fever
- rash
- nausea
- chills
- diarrhea
- vomiting
- high blood pressure (hypertension)
- swelling of the face, arms, or legs

The most common side effects of MEKINIST when taken with dabrafenib to help prevent melanoma from coming back after the cancer has been removed by surgery include:

- fever
- fatigue
- nausea
- headache
- rash
- chills
- diarrhea
- vomiting
- joint aches
- muscle aches

The most common side effects of MEKINIST when taken with dabrafenib in people with NSCLC include:

- fever
- fatigue
- nausea
- vomiting
- diarrhea
- dry skin
- decreased appetite
- rash
- swelling of face, arms, and legs
- chills
- bleeding
- cough
- shortness of breath

MEKINIST can cause new or worsening high blood pressure (hypertension). Your healthcare provider should check your blood pressure during treatment with MEKINIST. Call your healthcare provider right away if you develop high blood pressure, your blood pressure worsens, or you have severe headache, lightheadedness, blurry vision, or dizziness.

MEKINIST may cause fertility problems in females. This could affect your ability to become pregnant. Talk to your healthcare provider if this is a concern for you.

These are not all the possible side effects of MEKINIST.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Novartis Pharmaceuticals Corporation at 1-888-669-6682.

How should I store MEKINIST?

- Store MEKINIST in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Keep MEKINIST dry and away from moisture and light.
- The bottle of MEKINIST contains a desiccant packet to help keep your medicine dry. Do not throw away the desiccant packet.
- Keep MEKINIST in its original bottle. Do not place tablets in a pill box.
- Safely throw away MEKINIST that is out of date or no longer needed.

Keep MEKINIST and all medicine out of the reach of children.

General information about the safe and effective use of MEKINIST.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use MEKINIST for a condition for which it was not prescribed. Do not give MEKINIST to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about MEKINIST that is written for health professionals.

What are the ingredients in MEKINIST?

Active ingredient: trametinib

Inactive ingredients:

Tablet Core: colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate (vegetable source), mannitol, microcrystalline cellulose, sodium lauryl sulfate.

Tablet Coating: hypromellose, iron oxide red (2 mg tablets), iron oxide yellow (0.5 mg tablets), polyethylene glycol, polysorbate 80 (2 mg tablets), titanium dioxide.

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For more information, go to www.MEKINIST.com or call 1-888-669-6682.

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