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

Indications and Usage (1)	01/2014
Dosage and Administration (2.2-2.3)	01/2014
Warnings and Precautions (5-5.10)	01/2014

INDICATIONS AND USAGE

MEKINIST is a kinase inhibitor indicated as a single agent and 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. The use in combination is based on the demonstration of durable response rate. Improvement in disease-related symptoms or overall survival has not been demonstrated for MEKINIST in combination with dabrafenib. (1, 14.1)

Limitation of use: MEKINIST as a single agent is not indicated for treatment of patients who have received prior BRAF-inhibitor therapy. (1)

DOSAGE AND ADMINISTRATION

- Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with MEKINIST. (2.1)
- The recommended dosage regimens of MEKINIST are 2 mg orally once daily as a single agent or in combination with dabrafenib 150 mg orally twice daily.Take MEKINIST at least 1 hour before or at least 2 hours after a meal. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 0.5 mg, 1 mg, and 2 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS and PRECAUTIONS

- New primary malignancies, cutaneous and non-cutaneous, can occur when MEKINIST is used in combination with dabrafenib. Monitor patients for new malignancies prior to initiation of therapy while on therapy, and following discontinuation of the combination treatment. (5.1, 2.3)
- Hemorrhage: Major hemorrhagic events can occur in patients receiving MEKINIST in combination with dabrafenib. Monitor for signs and symptoms of bleeding (5.2, 2.3)
- Venous Thromboembolism: Deep vein thrombosis and pulmonary embolism can occur in patients receiving MEKINIST in combination with dabrafenib. (5.3, 2.3).
- Cardiomyopathy: Assess LVEF before treatment, after one month of treatment, then every 2 to 3 months thereafter. (5.4, 2.3)
- Ocular Toxicities: Perform ophthalmologic evaluation for any visual disturbances. For Retinal Vein Occlusion (RVO), permanently discontinue MEKINIST. (5.5, 2.3).
- Interstitial Lung Disease (ILD): Withhold MEKINIST for new or progressive unexplained pulmonary symptoms. Permanently discontinue MEKINIST for treatment-related ILD or pneumonitis. (5.6, 2.3)
- Serious Febrile Reactions can occur when MEKINIST is used in combination with dabrafenib. (5.7, 2.3)
- Serious Skin Toxicity: Monitor for skin toxicities and for secondary infections. Discontinue for intolerable Grade 2, or Grade 3 or 4 rash not improving within 3 weeks despite interruption of MEKINIST. (5.8, 2.3)
- Hyperglycemia: Monitor serum glucose levels in patients with pre-existing diabetes or hyperglycemia. (5.9, 2.3)
- Embryofetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to the fetus. (5.10, 8.1, 8.6)

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 in combination with dabrafenib include pyrexia, chills, fatigue, rash, nausea, vomiting, diarrhea, abdominal pain, peripheral edema, cough, headache, arthralgia, night sweats, decreased appetite, constipation, and myalgia. (6.1**)**

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Avoid concurrent administration of strong inhibitors of CYP3A4 or CYP2C8 when MEKINIST is used in combination with dabrafenib. (7.1)
- Avoid concurrent administration of strong inducers of CYP3A4 or CYP2C8 when MEKINIST is used in combination with dabrafenib. (7.1)
- Concomitant use with agents that are sensitive substrates of CYP3A4, CYP2C8, CYP2C9, CYP2C19, or CYP2B6 may result in loss of efficacy of these agents when MEKINIST is used in combination with dabrafenib. (7.1)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Discontinue drug or nursing. (8.3)
- Females and Males of Reproductive Potential: Counsel female patients on pregnancy planning and prevention. May impair fertility. (8.6)

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

Revised: 01/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

MEKINIST™ as a single agent is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test *[see Clinical Studies (14.1)]*.

MEKINIST, in combination with dabrafenib, is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test. This indication is based on the demonstration of durable response rate *[see Clinical Studies (14.1)]*. Improvement in disease-related symptoms or overall survival has not been demonstrated for MEKINIST in combination with dabrafenib.

Limitation of use: MEKINIST as a single agent is not indicated for treatment of patients who have received prior BRAF-inhibitor therapy *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for treatment of unresectable or metastatic melanoma with MEKINIST based on presence of BRAF V600E or V600K mutation in tumor specimens *[see Clinical Studies (14.1)]*. Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosing

The recommended dosage regimens of MEKINIST are:

- 2 mg orally taken once daily as a single agent
- 2 mg orally taken once daily in combination with dabrafenib 150 mg orally taken twice daily

Continue treatment until disease progression or unacceptable toxicity occurs. Take MEKINIST as a single agent, or MEKINIST in combination with dabrafenib, 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. When administered in combination with dabrafenib, take the once daily dose of MEKINIST at the same time each day with either the morning dose or the evening dose of dabrafenib.

2.3 Dose Modifications

For New Primary Cutaneous Malignancies: No dose modifications are required.

For New Primary Non-Cutaneous Malignancies: No dose modifications are required for MEKINIST. If used in combination with dabrafenib, permanently discontinue dabrafenib in patients who develop RAS mutation-positive non-cutaneous malignancies.

Table 1. Recommended Dose Reductions

Dose Reductions for MEKINIST When Administered as a Single Agent or in Combination With Dabrafenib	
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
Dose Reductions for Dabrafenib When Administered in Combination With MEKINIST	
First Dose Reduction	100 mg orally twice daily
Second Dose Reduction	75 mg orally twice daily
Third Dose Reduction	50 mg orally twice daily
Subsequent Modification	Permanently discontinue dabrafenib if unable to tolerate 50 mg orally twice daily

Table 2. Recommended Dose Modifications for MEKINIST as a Single Agent and for MEKINIST and Dabrafenib Administered in Combination

Severity of Adverse Reaction[a]	MEKINIST[b]	Dabrafenib (When Used in Combination)[b,c]
Febrile drug reaction		
• Fever of 101.3°F to 104°F	Do not modify the dose of MEKINIST.	Withhold dabrafenib until fever resolves. Then resume at same or lower dose level.
• Fever higher than 104°F • Fever complicated by rigors, hypotension, dehydration, or renal failure	Withhold MEKINIST until fever resolves. Then resume MEKINIST at same or lower dose level.	• Withhold dabrafenib until fever resolves. Then resume at a lower dose level. Or • Permanently discontinue dabrafenib.
Cutaneous		
• Intolerable Grade 2 skin toxicity • Grade 3 or 4 skin toxicity	Withhold MEKINIST for up to 3 weeks. • If improved, resume at a lower dose level. • If not improved, permanently discontinue.	Withhold dabrafenib for up to 3 weeks. • If improved, resume at a lower dose level. • If not improved, permanently discontinue.
Cardiac		
• Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline and is below institutional lower limits of normal (LLN) from pretreatment value	Withhold MEKINIST for up to 4 weeks. • If improved to normal LVEF value, resume at a lower dose level. • If not improved to normal LVEF value, permanently discontinue.	Do not modify the dose of dabrafenib.
• Symptomatic congestive heart failure • Absolute decrease in LVEF of greater than 20% from baseline that is below LLN	Permanently discontinue MEKINIST.	Withhold dabrafenib, if improved, then resume at the same dose.

Severity of Adverse Reaction[a]	MEKINIST[b]	Dabrafenib (When Used in Combination)[b,c]
Venous Thromboembolism		
• Uncomplicated DVT or PE	Withhold MEKINIST for up to 3 weeks. • If improved to Grade 0-1, resume at a lower dose level. • If not improved, permanently discontinue.	Do not modify the dose of dabrafenib.
• Life Threatening PE	Permanently discontinue MEKINIST.	Permanently discontinue dabrafenib.
Ocular Toxicities		
• Grade 2-3 retinal pigment epithelial detachments (RPED)	Withhold MEKINIST for up to 3 weeks. • If improved to Grade 0-1, resume at a lower dose level. • If not improved, permanently discontinue.	Do not modify the dose of dabrafenib.
• Retinal vein occlusion	Permanently discontinue MEKINIST.	Do not modify the dose of dabrafenib.
• Uveitis and Iritis	Do not modify the dose of MEKINIST.	Withhold dabrafenib for up to 6 weeks. • If improved to Grade 0-1, then resume at the same dose. • If not improved, permanently discontinue.
Pulmonary		
• Interstitial lung disease/pneumonitis	Permanently discontinue MEKINIST.	Do not modify the dose of dabrafenib.

Severity of Adverse Reaction[a]	MEKINIST[b]	Dabrafenib (When Used in Combination)[b,c]
Other		
• Intolerable Grade 2 adverse reactions • Any Grade 3 adverse reactions	Withhold MEKINIST for up to 3 weeks. • If improved to Grade 0-1, resume at a lower dose level. • If not improved, permanently discontinue.	Withhold dabrafenib • If improved to Grade 0-1, resume at a lower dose level. • If not improved, permanently discontinue.
• First occurrence of any Grade 4 adverse reaction	• Withhold MEKINIST until adverse reaction improves to Grade 0-1. Then resume at a lower dose level. Or • Permanently discontinue.	• Withhold dabrafenib until adverse reaction improves to Grade 0-1. Then resume at a lower dose level. Or • Permanently discontinue.
• Recurrent Grade 4 adverse reaction	Permanently discontinue MEKINIST.	Permanently discontinue dabrafenib.

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

[b] See Table 1 for recommended dose reductions of MEKINIST and dabrafenib.

[c] Refer to the Full Prescribing Information for dabrafenib.

3 DOSAGE FORMS AND STRENGTHS

0.5-mg Tablets: Yellow, modified oval, biconvex, film-coated tablets with ‘GS’ debossed on one face and ‘TFC’ on the opposing face.

1-mg Tablets: White, round, biconvex, film-coated tablets with ‘GS’ debossed on one face and ‘LHE’ on the opposing face.

2-mg Tablets: Pink, round, biconvex, film-coated tablets with ‘GS’ debossed on one face and ‘HMJ’ on the opposing face.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

Review the Full Prescribing Information for dabrafenib prior to initiation of MEKINIST in combination with dabrafenib. The following serious adverse reactions of dabrafenib as a single agent, which may occur when MEKINIST is used in combination with dabrafenib, are not described in the Full Prescribing Information for MEKINIST:

- Tumor promotion in patients with BRAF wild-type melanoma
- Hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency

5.1 New Primary Malignancies

New primary malignancies, cutaneous and non-cutaneous, can occur when MEKINIST is used in combination with dabrafenib and with dabrafenib as a single agent *[refer to Full Prescribing Information for dabrafenib]*.

Cutaneous Malignancies:

In Trial 2, the incidence of basal cell carcinoma was increased in patients receiving MEKINIST in combination with dabrafenib, with an incidence of 9% (5/55) in patients receiving MEKINIST in combination with dabrafenib compared with 2% (1/53) in patients receiving dabrafenib as a single agent. The range of time to diagnosis of basal cell carcinoma was 28 to 249 days in patients receiving MEKINIST in combination with dabrafenib and was 197 days for the patient receiving dabrafenib as a single agent.

Cutaneous squamous cell carcinomas (SCC), including keratoacanthoma, occurred in 7% of patients receiving MEKINIST in combination with dabrafenib and 19% of patients receiving dabrafenib as a single agent. The range of time to diagnosis of cuSCC was 136 to197 days in the combination arm and was 9 to 197 days in the arm receiving dabrafenib as a single agent.

New primary melanoma occurred in 2% (1/53) of patients receiving dabrafenib and in none of the 55 patients receiving MEKINIST in combination with dabrafenib.

Perform dermatologic evaluations prior to initiation of MEKINIST in combination with dabrafenib, every 2 months while on therapy, and for up to 6 months following discontinuation of the combination. No dose modifications of MEKINIST or dabrafenib are recommended in patients who develop new primary cutaneous malignancies.

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 Full Prescribing Information for dabrafenib]*. In patients receiving MEKINIST in combination with dabrafenib, four cases of non-cutaneous malignancies were identified: KRAS mutation-positive pancreatic adenocarcinoma (n = 1), recurrent NRAS mutation-positive colorectal carcinoma (n = 1), head and neck carcinoma (n = 1), and glioblastoma (n = 1). Monitor patients receiving the combination closely for signs or symptoms of non-cutaneous malignancies. If used in

combination with dabrafenib, no dose modification is required for MEKINIST in patients who develop non-cutaneous malignancies. Permanently discontinue dabrafenib in patients who develop RAS mutation-positive non-cutaneous malignancies.

5.2 Hemorrhage

Hemorrhages, including major hemorrhages defined as symptomatic bleeding in a critical area or organ, can occur when MEKINIST is used in combination with dabrafenib.

In Trial 2, treatment with MEKINIST in combination with dabrafenib resulted in an increased incidence and severity of any hemorrhagic event: 16% (9/55) of patients treated with MEKINIST in combination with dabrafenib compared with 2% (1/53) of patients treated with dabrafenib as a single agent. The major hemorrhagic events of intracranial or gastric hemorrhage occurred in 5% (3/55) of patients treated with MEKINIST in combination with dabrafenib compared with none of the 53 patients treated with dabrafenib as a single agent. Intracranial hemorrhage was fatal in two (4%) patients receiving the combination of MEKINIST and dabrafenib.

Permanently discontinue MEKINIST, and also permanently discontinue dabrafenib if administered in combination, for all Grade 4 hemorrhagic events and for any Grade 3 hemorrhagic events that do not improve. Withhold MEKINIST for up to 3 weeks for Grade 3 hemorrhagic events; if improved resume at a lower dose level. Withhold dabrafenib for Grade 3 hemorrhagic events; if improved resume at a lower dose level.

5.3 Venous Thromboembolism

Venous thromboembolism can occur when MEKINIST is used in combination with dabrafenib.

In Trial 2, treatment with MEKINIST in combination with dabrafenib resulted in an increased incidence of deep venous thrombosis (DVT) and pulmonary embolism (PE): 7% (4/55) of patients treated with MEKINIST in combination with dabrafenib compared with none of the 53 patients treated with dabrafenib as a single agent. Pulmonary embolism was fatal in one (2%) patient receiving the combination of MEKINIST and dabrafenib.

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 and dabrafenib 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. Do not modify the dose of dabrafenib *[see Dosage and Administration (2.3)]*.

5.4 Cardiomyopathy

Cardiomyopathy can occur when MEKINIST is administered as a single agent or when used in combination with dabrafenib.

In Trial 1, cardiomyopathy (defined as cardiac failure, left ventricular dysfunction, or decreased left ventricular ejection fraction [LVEF]) occurred in 7% (14/211) of patients treated with MEKINIST; no chemotherapy-treated patients in Trial 1 developed cardiomyopathy. In Trial 2,

cardiomyopathy occurred in 9% (5/55) of patients treated with MEKINIST in combination with dabrafenib and in none of patients treated with dabrafenib as a single agent. The median time to onset of cardiomyopathy in patients treated with MEKINIST was 63 days (range: 16 to 156 days) for Trial 1 and 86 days (range: 27 to 253 days) for Trial 2.

Cardiomyopathy was identified within the first month of treatment with MEKINIST in 5 of 14 patients in Trial 1 and in 2 of 5 patients in Trial 2. Development of cardiomyopathy resulted in dose reduction (7/211) and/or discontinuation (4/211) of study drug in Trial 1, and resulted in dose reduction (4/55) and/or dose interruption (1/55) in Trial 2. Cardiomyopathy resolved in 10 of 14 (71%) patients in Trial 1 and in all 5 patients in Trial 2.

Across clinical trials of MEKINIST administered either as a single agent (N = 329), or in combination with dabrafenib (N = 202), 11% and 8% of patients, respectively, developed evidence of cardiomyopathy (decrease in LVEF below institutional lower limits of normal with an absolute decrease in LVEF ≥10% below baseline). Five percent and 2% in single-agent and in combination trials, respectively, demonstrated a decrease in LVEF below institutional lower limits of normal with an absolute decrease in LVEF of ≥20% below baseline.

Assess LVEF by echocardiogram or multigated acquisition (MUGA) scan before initiation of MEKINIST as a single agent and in combination with dabrafenib, one month after initiation, and then at 2- to 3-month intervals while on treatment. Withhold treatment with MEKINIST for up to 4 weeks if absolute LVEF value decreases by 10% from pretreatment values and is less than the lower limit of normal. For symptomatic cardiomyopathy or persistent, asymptomatic LV dysfunction that does not resolve within 4 weeks, permanently discontinue MEKINIST and withhold dabrafenib. Resume dabrafenib at the same dose upon recovery of cardiac function *[see Dosage and Administration (2.3)]*.

5.5 Ocular Toxicities

Retinal Vein Occlusion (RVO):

Across all clinical trials of MEKINIST, the incidence of RVO was 0.2% (4/1,749). 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. If MEKINIST is used in combination with dabrafenib, do not modify dabrafenib dose *[see Dosage and Administration (2.3)]*.

Retinal Pigment Epithelial Detachment (RPED):

Retinal pigment epithelial detachment (RPED) can occur when MEKINIST is administered as a single agent or when used in combination with dabrafenib.

In Trial 1 and Trial 2, ophthalmologic examinations including retinal evaluation were performed pretreatment and at regular intervals during treatment.

In Trial 1, one patient (0.5%) receiving MEKINIST developed RPED and no cases of RPED were identified in chemotherapy-treated patients. Across all clinical trials of MEKINIST, the incidence of RPED was 0.8% (14/1,749). Retinal detachments were often bilateral and multifocal, occurring in the macular region of the retina. RPED led to reduction in visual acuity that resolved after a median of 11.5 days (range: 3 to 71 days) following the interruption of dosing with MEKINIST, although Ocular Coherence Tomography (OCT) abnormalities persisted beyond a month in at least several cases.

In Trial 2, one patient (2%) receiving MEKINIST in combination with dabrafenib developed RPED.

Perform ophthalmological evaluation at any time a patient reports visual disturbances and compare with baseline, if available. Withhold MEKINIST if RPED is diagnosed. If resolution of the RPED is documented on repeat ophthalmological evaluation within 3 weeks, resume MEKINIST at a lower dose level. Discontinue MEKINIST if no improvement after 3 weeks. If MEKINIST is used in combination with dabrafenib, do not modify the dose of dabrafenib *[see Dosage and Administration (2.3)]*.

Uveitis and Iritis:

Uveitis and iritis can occur when MEKINIST is used in combination with dabrafenib and with dabrafenib as a single agent *[refer to Full Prescribing Information for dabrafenib]*.

Uveitis occurred in 1% (2/202) of patients treated with MEKINIST in combination with dabrafenib.

Symptomatic treatment employed in clinical trials included steroid and mydriatic ophthalmic drops. Monitor patients for visual signs and symptoms of uveitis (e.g., change in vision, photophobia, eye pain). If diagnosed, withhold dabrafenib for up to 6 weeks until uveitis/iritis resolves to Grade 0-1. If not improved, permanently discontinue dabrafenib. If MEKINIST is used in combination with dabrafenib, do not modify the dose of MEKINIST *[see Dosage and Administration (2.3)]*.

5.6 Interstitial Lung Disease

In clinical trials of MEKINIST (N = 329) as a single agent, ILD or pneumonitis occurred in 2% of patients. In Trial 1, 2% (5/211) of patients treated with MEKINIST developed ILD or pneumonitis; all five patients required hospitalization. The median time to first presentation of ILD or pneumonitis was 160 days (range: 60 to 172 days).

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. If MEKINIST is used in combination with dabrafenib, do not modify the dose of dabrafenib *[see Dosage and Administration (2.3)]*.

5.7 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 used in combination with dabrafenib and with dabrafenib as a single agent *[refer to Full Prescribing Information for dabrafenib]*.

The incidence and severity of pyrexia are increased when MEKINIST is used in combination with dabrafenib compared with dabrafenib as a single agent *[see Adverse Reactions (6.1)]*.

In Trial 2, the incidence of fever (serious and non-serious) was 71% (39/55) in patients treated with MEKINIST in combination with dabrafenib and 26% (14/53) in patients treated with dabrafenib as a single agent. Serious febrile reactions and fever of any severity accompanied by hypotension, rigors, or chills occurred in 25% (14/55) of patients treated with MEKINIST in combination with dabrafenib compared with 2% (1/53) of patients treated with dabrafenib as a single agent. Fever was complicated with chills/rigors in 51% (28/55), dehydration in 9% (5/55), renal failure in 4% (2/55), and syncope in 4% (2/55) of patients in Trial 2. In patients treated with MEKINIST in combination with dabrafenib, the median time to initial onset of fever was 30 days compared with 19 days in patients treated with dabrafenib as a single agent; the median duration of fever was 6 days with the combination compared with 4 days with dabrafenib as a single agent.

Across clinical trials of MEKINIST administered in combination with dabrafenib (N = 202), the incidence of pyrexia was 57% (116/202).

Withhold dabrafenib for fever of 101.3ºF or higher. Withhold MEKINIST for fever higher than 104ºF.Withhold dabrafenib and MEKINIST for any serious febrile reaction or fever accompanied by hypotension, rigors or chills, dehydration, or renal failure, and evaluate for signs and symptoms of infection. Refer to Table 2 for recommended dose modifications for adverse reactions *[see Dosage and Administration (2.3)]*. Prophylaxis with antipyretics may be required when resuming MEKINIST or dabrafenib.

5.8 Serious Skin Toxicity

Serious skin toxicity can occur when MEKINIST is administered as a single agent or when used in combination with dabrafenib. Serious skin toxicity can also occur with dabrafenib as a single agent *[refer to Full Prescribing Information for dabrafenib]*.

In Trial 1, the overall incidence of any skin toxicity, the most common of which were rash, dermatitis acneiform rash, palmar-plantar erythrodysesthesia syndrome, and erythema, was 87% in patients treated with MEKINIST and 13% in chemotherapy-treated patients. Severe skin toxicity occurred in 12% of patients treated with MEKINIST. Skin toxicity requiring hospitalization occurred in 6% of patients treated with MEKINIST, most commonly for secondary infections of the skin requiring intravenous antibiotics or severe skin toxicity without secondary infection. In comparison, no patients treated with chemotherapy required hospitalization for severe skin toxicity or infections of the skin. The median time to onset of skin

toxicity in patients treated with MEKINIST was 15 days (range: 1 to 221 days) and median time to resolution of skin toxicity was 48 days (range: 1 to 282 days). Reductions in the dose of MEKINIST were required in 12% and permanent discontinuation of MEKINIST was required in 1% of patients with skin toxicity.

In Trial 2, the incidence of any skin toxicity was similar for patients receiving MEKINIST in combination with dabrafenib (65% [36/55]) compared with patients receiving dabrafenib as a single agent (68% [36/53]). The median time to onset of skin toxicity in patients treated with MEKINIST in combination with dabrafenib was 37 days (range: 1 to 225 days) and median time to resolution of skin toxicity was 33 days (range: 3 to 421 days). No patient required dose reduction or permanent discontinuation of MEKINIST or dabrafenib for skin toxicity.

Across clinical trials of MEKINIST administered in combination with dabrafenib (n = 202), severe skin toxicity and secondary infection of the skin requiring hospitalization occurred in 2.5% (5/202) of patients treated with MEKINIST in combination with dabrafenib.

Withhold MEKINIST, and dabrafenib if used in combination, for intolerable or severe skin toxicity. MEKINIST and dabrafenib may be resumed at lower dose levels in patients with improvement or recovery from skin toxicity within 3 weeks *[see Dosage and Administration (2.3)]*.

5.9 Hyperglycemia

Hyperglycemia can occur when MEKINIST is used in combination with dabrafenib and with dabrafenib as a single agent. Hyperglycemia requiring an increase in the dose of, or initiation of insulin or oral hypoglycemic agent therapy occurred with dabrafenib as a single agent *[refer to Full Prescribing Information for dabrafenib]*.

In Trial 2, the incidence of Grade 3 hyperglycemia based on laboratory values was 5% (3/55) in patients treated with MEKINIST in combination with dabrafenib compared with 2% (1/53) in patients treated with dabrafenib as a single agent.

Monitor serum glucose levels as clinically appropriate during treatment with MEKINIST in combination with dabrafenib in patients with pre-existing diabetes or hyperglycemia. Advise patients to report symptoms of severe hyperglycemia.

5.10 Embryofetal Toxicity

Based on its mechanism of action, MEKINIST can cause fetal harm when administered to a pregnant woman. MEKINIST 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. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

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

effective non-hormonal method of contraception when MEKINIST is administered in combination with dabrafenib, since dabrafenib can render hormonal contraceptives ineffective. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking MEKINIST *[see Use in Specific Populations (8.1, 8.6)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in another section of the label:

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

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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in the Warnings and Precautions section and below reflect exposure to MEKINIST as a single agent and in combination with dabrafenib. MEKINIST as a single agent was evaluated in 329 patients including 107 (33%) exposed for greater than or equal to 6 months and 30 (9%) exposed for greater than or equal to one year. MEKINIST as a single agent was studied in open-label, single-arm trials (N = 118) or in an open-label, randomized, active-controlled trial (N = 211). The median age was 54 years, 60% were male, >99% were white, and all patients had metastatic melanoma. All patients received 2 mg once-daily doses of MEKINIST. The incidence of RPED and RVO are obtained from the 1,749 patients from all clinical trials with MEKINIST.

The safety of MEKINIST in combination with dabrafenib was evaluated in Trial 2 and other trials consisting of 202 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma who received MEKINIST 2 mg orally once daily in combination with dabrafenib 150 mg orally twice daily until disease progression or unacceptable toxicity. Among these 202 patients, 68 (34%) were exposed to MEKINIST and 66 (33%) were exposed to dabrafenib for greater than 6 to 12 months while 36 (18%) were exposed to MEKINIST and 40 (20%) were

exposed to dabrafenib for greater than one year. The median age was 54 years, 57% were male and >99% were white.

Table 3 presents adverse reactions identified from analyses of Trial 1, a randomized, open-label trial of patients with BRAF V600E or V600K mutation-positive melanoma receiving MEKINIST (N = 211) 2 mg orally once daily or chemotherapy (N = 99) (either dacarbazine 1,000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 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 from Trial 1. The median duration of treatment with MEKINIST was 4.3 months. In Trial 1, 9% of patients receiving MEKINIST experienced adverse reactions resulting in permanent discontinuation of trial medication. The most common adverse reactions resulting in permanent discontinuation of MEKINIST were decreased left ventricular ejection fraction (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 common reasons cited for dose reductions of MEKINIST.

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

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 disorders				
Rash	57	8	10	0
Dermatitis acneiform	19	<1	1	0
Dry skin	11	0	0	0
Pruritus	10	2	1	0
Paronychia	10	0	1	0
Gastrointestinal disorders				
Diarrhea	43	0	16	2
Stomatitis[c]	15	2	2	0
Abdominal pain[d]	13	1	5	1
Vascular disorders				
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 the following terms: stomatitis, aphthous stomatitis, mouth ulceration, and mucosal inflammation.

[d] Includes the following terms: abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness.

[e] Includes the following terms: lymphedema, edema, and peripheral edema.

[f] Includes the following terms: epistaxis, gingival bleeding, hematochezia, rectal hemorrhage, melena, vaginal hemorrhage, hemorrhoidal hemorrhage, hematuria, and conjunctival hemorrhage.

Other clinically important adverse reactions observed in ≤10% of patients (N = 329) treated with MEKINIST were:

Cardiac Disorders: Bradycardia.

Gastrointestinal Disorders: Xerostomia.

Infections and Infestations: Folliculitis, rash pustular, cellulitis.

Musculoskeletal and Connective Tissue Disorders: Rhabdomyolysis.

Nervous System Disorders: Dizziness, dysgeusia.

Ocular Disorders: Vision blurred, dry eye.

Table 4. Percent-Patient Incidence of Laboratory Abnormalities Occurring at a Higher Incidence in Patients Treated With MEKINIST in Trial 1 (Between-Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3 or 4][a])

Test	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
Increased alanine aminotransferase (ALT)	39	3	20	3
Hypoalbuminemia	42	2	23	1
Anemia	38	2	26	3
Increased alkaline phosphatase	24	2	18	3

[a] No Grade 4 events were reported in either treatment arm.

Table 5 presents adverse reactions from Trial 2, a multicenter, open-label, randomized trial of 162 patients with BRAF V600E or V600K mutation-positive melanoma receiving MEKINIST 2 mg once daily in combination with dabrafenib 150 mg twice daily (N = 55), MEKINIST 1 mg

once daily in combination with dabrafenib 150 mg twice daily (N = 54), and dabrafenib as a single agent 150 mg twice daily (N = 53) *[see Clinical Studies (14.1)]*. Patients with abnormal LVEF, history of acute coronary syndrome within 6 months, current evidence of Class II or greater congestive heart failure (New York Heart Association), history of RVO, or RPED, QTc interval ≥480 msec, treatment refractory hypertension, uncontrolled arrhythmias, history of pneumonitis or interstitial lung disease, or a known history of G6PD deficiency were excluded. The median duration of treatment was 10.9 months for both MEKINIST (2-mg once-daily treatment group) and dabrafenib when used in combination, 10.6 months for both MEKINIST (1-mg once-daily treatment group) and dabrafenib when used in combination, and 6.1 months for dabrafenib as a single agent.

In Trial 2, 13% of patients receiving MEKINIST in combination with dabrafenib at the recommended dose experienced adverse reactions resulting in permanent discontinuation of trial medication(s). The most common adverse reaction resulting in permanent discontinuation was pyrexia (4%). Adverse reactions led to dose reductions in 49% and dose interruptions in 67% of patients treated with MEKINIST in combination with dabrafenib. Pyrexia, chills, and nausea were the most common reasons cited for dose reductions, and pyrexia, chills, and decreased ejection fraction were the most common reasons cited for dose interruptions of MEKINIST and dabrafenib when used in combination.

Table 5. Common Adverse Drug Reactions Occurring in >10% (All Grades) or ≥5% (Grades 3 or 4) of Patients Treated With MEKINIST in Combination With Dabrafenib in Trial 2

Adverse Reactions	MEKINIST 2 mg plus Dabrafenib N = 55		MEKINIST 1 mg plus Dabrafenib N = 54		Dabrafenib N = 53	
	All Grades[a]	Grades 3 and 4	All Grades[a]	Grades 3 and 4	All Grades[a]	Grades 3 and 4
General disorders and administrative site conditions						
Pyrexia	71	5	69	9	26	0
Chills	58	2	50	2	17	0
Fatigue	53	4	57	2	40	6
Edema peripheral[b]	31	0	28	0	17	0
Skin and subcutaneous tissue disorders						
Rash[c]	45	0	43	2	53	0
Night Sweats	24	0	15	0	6	0
Dry skin	18	0	9	0	6	0
Dermatitis acneiform	16	0	11	0	4	0
Actinic keratosis	15	0	7	0	9	0
Erythema	15	0	6	0	2	0
Pruritus	11	0	11	0	13	0
Gastrointestinal disorders						
Nausea	44	2	46	6	21	0
Vomiting	40	2	43	4	15	0
Diarrhea	36	2	26	0	28	0
Abdominal pain[d]	33	2	24	2	21	2
Constipation	22	0	17	2	11	0
Dry mouth	11	0	11	0	6	0
Nervous system disorders						
Headache	29	0	37	2	28	0
Dizziness	16	0	13	0	9	0
Respiratory, thoracic, and mediastinal disorders						
Cough	29	0	11	0	21	0
Oropharyngeal pain	13	0	7	0	0	0
Musculoskeletal, connective tissue, and bone disorders						
Arthralgia	27	0	44	0	34	0
Myalgia	22	2	24	0	23	2
Back pain	18	5	11	0	11	2

Muscle spasms	16	0	2	0	4	0
Pain in extremity	16	0	11	2	19	0
Metabolism and nutritional disorders						
Decreased appetite	22	0	30	0	19	0
Dehydration	11	0	6	2	2	0
Psychiatric disorders						
Insomnia	18	0	11	0	8	2
Vascular disorders						
Hemorrhage[e]	16	5	11	0	2	0
Infections and infestations						
Urinary tract infection	13	2	6	0	9	2
Renal and urinary disorders						
Renal failure[f]	7	7	2	0	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.

[b] Includes the following terms: peripheral edema, edema, and lymphedema.

[c] Includes the following terms: rash, rash generalized, rash pruritic, rash erythematous, rash papular, rash vesicular, rash macular, and rash maculo-papular.

[d] Includes the following terms: abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.

[e] Includes the following terms: brain stem hemorrhage, cerebral hemorrhage, gastric hemorrhage, epistaxis, gingival hemorrhage, hematuria, vaginal hemorrhage, hemorrhage intracranial, eye hemorrhage, and vitreous hemorrhage.

[f] Includes the following terms: renal failure and renal failure acute.

Other clinically important adverse reactions (N = 202) observed in <10% of patients treated with MEKINIST in combination with dabrafenib were:

Eye Disorders: Vision blurred, transient blindness.

Gastrointestinal Disorders: Stomatitis, pancreatitis.

General Disorders and Administration Site Conditions: Asthenia.

Infections and Infestations: Cellulitis, folliculitis, paronychia, rash pustular.

Neoplasms Benign, Malignant, and Unspecified (including cysts and polyps): Skin papilloma.

Skin and Subcutaneous Tissue Disorders: Palmar-plantar erythrodysesthesia syndrome, hyperkeratosis, hyperhidrosis.

Vascular Disorders: Hypertension.

Table 6. Treatment-Emergent Laboratory Abnormalities Occurring at ≥10% (All Grades) or ≥2% (Grades 3 or 4)] of Patients Treated With MEKINIST in Combination With Dabrafenib in Trial 2

Test	MEKINIST 2 mg plus Dabrafenib N = 55		MEKINIST 1 mg plus Dabrafenib N = 54		Dabrafenib N = 53	
	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4[a]
Hematology						
Leukopenia	62	5	46	4	21	0
Lymphopenia	55	22	59	19	40	6
Neutropenia	55	13	37	2	9	2
Anemia	55	4	46	7	28	0
Thrombocytopenia	31	4	31	2	8	0
Liver Function Tests						
Increased AST	60	5	54	0	15	0
Increased alkaline phosphatase	60	2	67	6	26	2
Increased ALT	42	4	35	4	11	0
Hyperbilirubinemia	15	0	7	4	0	0
Chemistry						
Hyperglycemia	58	5	67	6	49	2
Increased GGT	56	11	54	17	38	2
Hyponatremia	55	11	48	15	36	2
Hypoalbuminemia	53	0	43	2	23	0
Hypophosphatemia	47	5	41	11	40	0
Hypokalemia	29	2	15	2	23	6
Increased creatinine	24	5	20	2	9	0
Hypomagnesemia	18	2	2	0	6	0
Hyperkalemia	18	0	22	0	15	4
Hypercalcemia	15	0	19	2	4	0
Hypocalcemia	13	0	20	0	9	0

[a] No Grade 4 events were reported in dabrafenib arm.

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; GGT = Gamma glutamyltransferase.

QT Prolongation: In Trial 2, QTcF prolongation to >500 msec occurred in 4% (2/55) of patients treated with MEKINIST in combination with dabrafenib and in 2% (1/53) of patients treated with dabrafenib as a single agent. The QTcF was increased more than 60 msec from baseline in

13% (7/55) of patients treated with MEKINIST in combination with dabrafenib and 2% (1/53) of patients treated with dabrafenib as a single agent.

7 DRUG INTERACTIONS

No formal clinical trials have been conducted to evaluate human cytochrome P450 (CYP) enzyme-mediated drug interactions with trametinib *[see Clinical Pharmacology (12.3)]*.

7.1 Dabrafenib

Coadministration of MEKINIST 2 mg once daily and dabrafenib 150 mg twice daily resulted in no clinically relevant pharmacokinetic drug interactions *[see Clinical Pharmacology (12.3)]*.

Refer to the Full Prescribing Information for dabrafenib for further details on the drug interaction potential of dabrafenib. Avoid concurrent administration of strong inhibitors or strong inducers of CYP3A4 or CYP2C8 with dabrafenib. If concomitant use of strong inhibitors or strong inducers of CYP3A4 or CYP2C8 is unavoidable, monitor patients closely for adverse reactions when taking strong inhibitors or loss of efficacy when taking strong inducers. Concomitant use of dabrafenib with agents that are sensitive substrates of CYP3A4, CYP2C8, CYP2C9, CYP2C19, or CYP2B6 may result in loss of efficacy of these agents. Substitute for these medications or monitor patients for loss of efficacy if use of these medications is unavoidable.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Risk Summary: 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. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus *[see Warnings and Precautions (5.7)]*.

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 based on AUC at the recommended dose). 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.

8.3 Nursing Mothers

It is not known whether this drug is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from MEKINIST, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

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.

Adequate juvenile animal studies using trametinib have not been completed. In a repeat-dose toxicity study in juvenile rats, an increased incidence of kidney cysts and tubular deposits were noted at doses as low as 0.2 times the human exposure at the recommended adult dose of dabrafenib based on AUC. Additionally, forestomach hyperplasia, decreased bone length, and early vaginal opening were noted at doses as low as 0.8 times the human exposure at the recommended adult dose based on AUC**.**

8.5 Geriatric Use

Clinical trials of MEKINIST as a single agent did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In Trial 1, 49 patients (23%) were 65 years of age and older, and 9 patients (4%) were 75 years of age and older.

Across all clinical trials of MEKINIST administered in combination with dabrafenib, there was an insufficient number of patients aged 65 years and over to determine whether they respond differently from younger patients. In Trial 2, 11 patients (20%) were 65 years of age and older, and 2 patients (4%) were 75 years of age and older.

8.6 Females and Males of Reproductive Potential

Contraception:

Females: MEKINIST can cause fetal harm when administered during pregnancy. Advise female patients of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose of MEKINIST. When MEKINIST is used in combination with dabrafenib, counsel patients to use a non-hormonal method of contraception since dabrafenib can render hormonal contraceptives ineffective. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking MEKINIST *[see Use in Specific Populations (8.1)]*.

Infertility:

Females: MEKINIST may impair fertility in female patients *[see Nonclinical Toxicology (13.1)]*.

Males: Effects on spermatogenesis have been observed in animals treated with dabrafenib. Advise male patients of the potential risk for impaired spermatogenesis, and to seek counseling on fertility and family planning options prior to starting treatment with MEKINIST in combination with dabrafenib.

8.7 Hepatic Impairment

No formal clinical trial has been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of trametinib. No dose adjustment is recommended in patients with mild hepatic impairment based on a population pharmacokinetic analysis *[see Clinical Pharmacology (12.3)]*.

The appropriate dose of MEKINIST has not been established in patients with moderate or severe hepatic impairment.

8.8 Renal Impairment

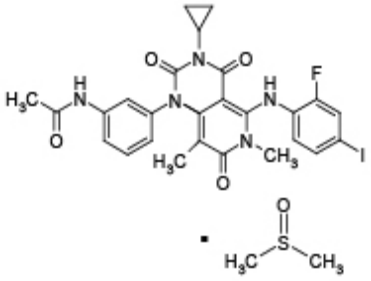
No formal clinical trial has been conducted to evaluate the effect of renal impairment on the pharmacokinetics of trametinib. No dose adjustment is recommended in patients with mild or moderate renal impairment based on a population pharmacokinetic analysis *[see Clinical Pharmacology (12.3)]*. The appropriate dose of MEKINIST has not been established in patients with severe renal impairment.

10 OVERDOSAGE

There were no reported cases of overdosage with MEKINIST. 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 retinal pigment epithelial detachments 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 $C_{26}H_{23}FIN_5O_4 \bullet C_2H_6OS$ with a molecular mass of 693.53. 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 are supplied as 0.5-mg, 1-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 1-mg tablet contains 1.127 mg trametinib dimethyl sulfoxide equivalent to 1 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, 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), 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 BRAF V600 mutation-positive melanoma cell growth in vitro and in vivo.

Trametinib and dabrafenib target two different tyrosine 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 melanoma cell lines in vitro and prolonged inhibition of tumor growth in BRAF V600 mutation positive melanoma xenografts compared with either drug alone.

12.2 Pharmacodynamics

Administration of 1 mg and 2 mg trametinib to patients with BRAF V600 mutation-positive melanoma resulted in dose-dependent changes in tumor biomarkers including inhibition of

phosphorylated ERK, inhibition of Ki67 (a marker of cell proliferation), and increases in p27 (a marker of apoptosis).

12.3 Pharmacokinetics

The pharmacokinetics (PK) of trametinib were characterized following single- and repeat-oral administration in patients with solid tumors and BRAF V600 mutation-positive metastatic melanoma.

Absorption: After oral administration, the median time to achieve peak plasma concentrations (T_{max}) is 1.5 hours post-dose. The mean absolute bioavailability of a single 2-mg oral dose of trametinib tablet is 72%. The increase in C_{max} was dose proportional after a single dose of 0.125 to 10 mg while the increase in AUC was greater than dose proportional. After repeat doses of 0.125 to 4 mg daily, both C_{max} and AUC increase proportionally with dose. Inter-subject variability in AUC and C_{max} at steady state is 22% and 28%, respectively.

Administration of a single dose of trametinib with a high-fat, high-calorie meal decreased AUC by 24%, C_{max} by 70%, and delayed T_{max} by approximately 4 hours as compared with fasted conditions *[see Dosage and Administration (2.2)]*.

Distribution: Trametinib is 97.4% bound to human plasma proteins. The apparent volume of distribution (V_c/F) is 214 L.

Metabolism: Trametinib is metabolized predominantly via deacetylation alone or with mono-oxygenation or in combination with glucuronidation biotransformation pathways in vitro. Deacetylation is likely mediated by hydrolytic enzymes, such as carboxyl-esterases or amidases.

Following a single dose of [^{14}C]-trametinib, approximately 50% of circulating radioactivity is represented as the parent compound. However, based on metabolite profiling after repeat dosing of trametinib, ≥75% of drug-related material in plasma is the parent compound.

Elimination: The estimated elimination half-life based on the population PK model is 3.9 to 4.8 days. The apparent clearance is 4.9 L/h.

Following oral administration of [^{14}C]-trametinib, >80% of excreted radioactivity was recovered in the feces while <20% of excreted radioactivity was recovered in the urine with <0.1% of the excreted dose as parent.

Specific Populations:

Based on a population pharmacokinetic analysis, age, gender, and body weight do not have a clinically important effect on the exposure of trametinib. There are insufficient data to evaluate potential differences in the exposure of trametinib by race or ethnicity.

Hepatic Impairment: Based on a population pharmacokinetic analysis in 64 patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin >1.0 to 1.5 x ULN and any AST), mild hepatic impairment has no clinically important effect on the systemic

exposure of trametinib. The pharmacokinetics of trametinib have not been studied in patients with moderate or severe hepatic impairment *[see Use in Specific Populations (8.7)]*.

Renal Impairment: As renal excretion of trametinib is low (<20%), renal impairment is unlikely to have a clinically important effect on the exposure of trametinib. Based on a population PK analysis in 223 patients with mild renal impairment (GFR 60 to 89 mL/min/1.73 m^2) and 35 patients with moderate renal impairment (GFR 30 to 59 mL/min/1.73 m^2), mild and moderate renal impairment have no clinically important effects on the systemic exposure of trametinib. The pharmacokinetics of trametinib have not been studied in patients with severe renal impairment *[see Use in Specific Populations (8.8)]*.

Pediatrics: No trials have been conducted to evaluate the pharmacokinetics of trametinib in pediatric patients.

Drug Interactions:

Trametinib is not a substrate of CYP enzymes or efflux transporters human P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) in vitro.

Based on in vitro studies, trametinib is not an inhibitor of CYP450 including CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, or of transporters including human organic anion transporting polypeptide (OATP1B1, OATP1B3), P-gp, and BCRP at a clinically relevant systemic concentration of 0.04 µM. Trametinib is an inhibitor of CYP2C8 in vitro.

Trametinib is an inducer of CYP3A4 in vitro. Based on cross-study comparisons, oral administration of trametinib 2 mg once daily with everolimus (sensitive CYP3A4 substrate) 5 mg once daily, had no clinically important effect on the AUC and C_{max} of everolimus.

Coadministration of trametinib 2 mg daily with dabrafenib 150 mg twice daily resulted in a 23% increase in AUC of dabrafenib, a 33% increase in AUC of desmethyl-dabrafenib, and no change in AUC of trametinib or hydroxy-dabrafenib as compared with administration of either drug alone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with trametinib have not been conducted. Trametinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells, and micronuclei in the bone marrow of rats.

Trametinib may impair fertility in humans. In female rats given trametinib for up to 13 weeks, increased follicular cysts and decreased corpora lutea were observed at doses ≥0.016 mg/kg/day (approximately 0.3 times the human exposure at the recommended dose based on AUC). In rat and dog toxicity studies up to 13 weeks in duration, there were no treatment effects observed on male reproductive tissues *[see Use in Specific Populations (8.6)]*.

14 CLINICAL STUDIES

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

The safety and efficacy of MEKINIST were evaluated in two clinical trials. Trial 1 was an international, multicenter, randomized (2:1), open-label, active-controlled trial in 322 patients with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma. Trial 2 was a multicenter, randomized (1:1:1), open-label, dose-ranging trial designed to evaluate the clinical activity and safety of MEKINIST (at two different doses) in combination with dabrafenib and to compare the safety with dabrafenib as a single agent in 162 patients with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma.

In Trial 1, patients were not permitted to have more than one prior chemotherapy regimen for advanced or metastatic disease; prior treatment with a BRAF inhibitor or MEK inhibitor was not permitted. The primary efficacy outcome measure was progression-free survival (PFS). Patients were randomized to receive MEKINIST 2 mg orally once daily (N = 214) or chemotherapy (N = 108) consisting of either dacarbazine 1,000 mg/m^2 intravenously every 3 weeks or paclitaxel 175 mg/m^2 intravenously every 3 weeks. Treatment continued until disease progression or unacceptable toxicity. Randomization was stratified according to prior use of chemotherapy for advanced or metastatic disease (yes versus no) and lactate dehydrogenase level (normal versus greater than upper limit of normal). Tumor tissue was evaluated for BRAF mutations at a central testing site using a clinical trial assay. Tumor samples from 289 patients (196 patients treated with MEKINIST and 93 chemotherapy-treated patients) were also tested retrospectively using an FDA-approved companion diagnostic test, THxID™-BRAF assay.

The median age for randomized patients was 54 years, 54% were male, >99% were white, and all patients had baseline ECOG performance status of 0 or 1. Most patients had metastatic disease (94%), were Stage M1c (64%), had elevated LDH (36%), no history of brain metastasis (97%), and received no prior chemotherapy for advanced or metastatic disease (66%). The distribution of BRAF V600 mutations was BRAF V600E (87%), V600K (12%), or both (<1%). The median durations of follow-up prior to initiation of alternative treatment were 4.9 months for patients treated with MEKINIST and 3.1 months for patients treated with chemotherapy. Fifty-one (47%) patients crossed over from the chemotherapy arm at the time of disease progression to receive MEKINIST.

Trial 1 demonstrated a statistically significant increase in progression-free survival in the patients treated with MEKINIST. Table 7 and Figure 1 summarize the PFS results.

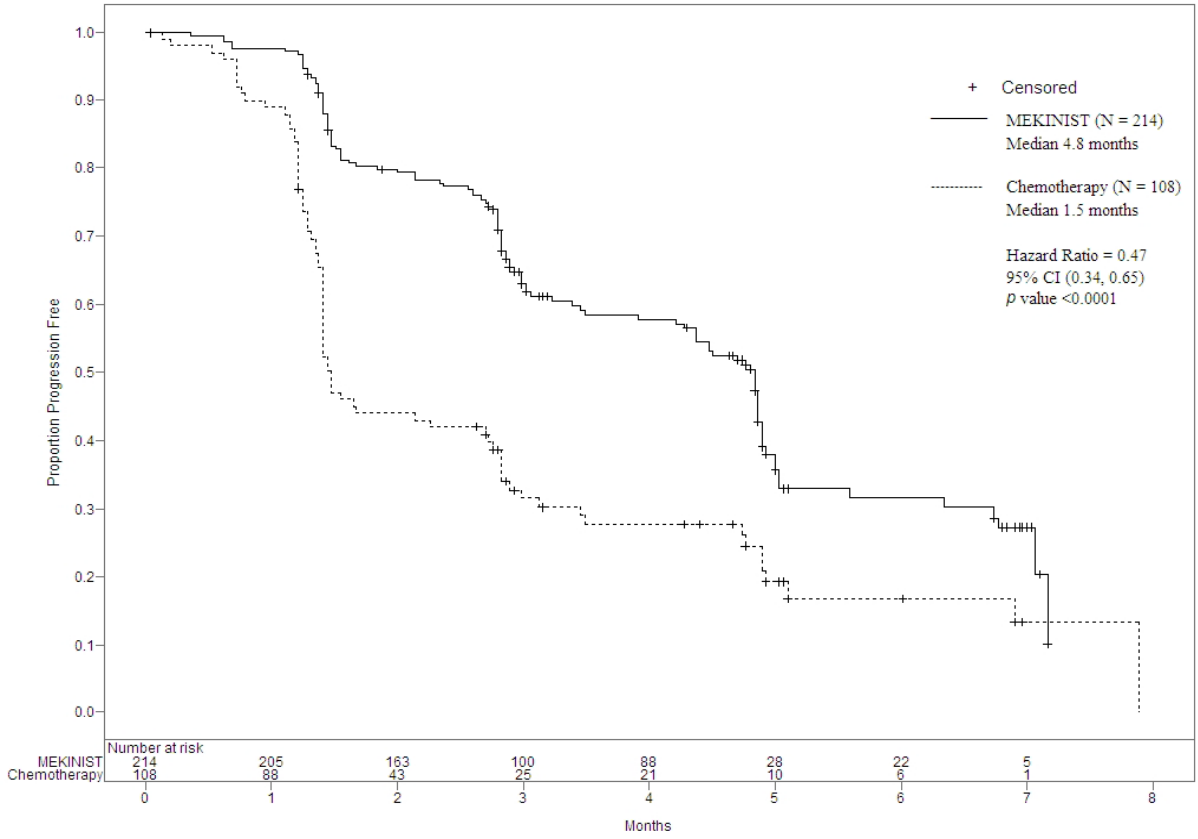
Table 7. Investigator-Assessed Progression-Free Survival and Confirmed Objective Response Results in Trial 1

	MEKINIST N = 214	**Chemotherapy N = 108**
PFS		
Number of Events (%)	117 (55%)	77 (71%)
Progressive Disease	107 (50%)	70 (65%)
Death	10 (5%)	7 (6%)
Median, months (95% CI)	4.8 (4.3, 4.9)	1.5 (1.4, 2.7)
HR[a] (95% CI)	0.47 (0.34, 0.65)	
P value (log-rank test)	*P*<0.0001	
Confirmed Tumor Responses		
Objective Response Rate	22%	8%
(95% CI)	(17, 28)	(4, 15)
CR, n (%)	4 (2%)	0
PR, n (%)	43 (20%)	9 (8%)
Duration of Response		
Median, months (95% CI)	5.5 (4.1, 5.9)	NR (3.5, NR)

[a] Pike estimator.

CI = Confidence interval; CR = Complete response; HR = Hazard ratio; NR = Not reached, PFS = Progression-free survival; PR = Partial response.

Figure 1. Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival (ITT population) in Trial 1



In supportive analyses based on independent radiologic review committee (IRRC) assessment, the PFS results were consistent with those of the primary efficacy analysis.

Trial 2 randomized (1:1:1) patients to MEKINIST (at two different doses) in combination with dabrafenib compared with dabrafenib as a single agent in 162 patients with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma. Patients were permitted to have had one prior chemotherapy regimen and prior aldesleukin; patients with prior exposure to BRAF or MEK inhibitors were ineligible. Patients were randomized to receive MEKINIST 2 mg orally once daily with dabrafenib 150 mg orally twice daily (n = 54), MEKINIST 1 mg orally once daily with dabrafenib 150 mg orally twice daily (n = 54), or dabrafenib 150 mg orally twice daily (n = 54). Treatment continued until disease progression or unacceptable toxicity. Patients randomized to receive dabrafenib as a single agent were offered MEKINIST 2 mg orally once daily with dabrafenib 150 mg orally twice daily at the time of investigator-assessed disease progression. The major efficacy outcome measure was investigator-assessed overall response rate (ORR). Additional efficacy outcome measures were investigator-assessed duration of response, independent radiology review committee (IRRC)-assessed ORR, and IRRC-assessed duration of response.

The median age of patients in Trial 2 was 53 years, 57% were male, >99% were white, 66% of patients had a pretreatment ECOG performance status of 0, 67% had M1c disease, 54% had a normal LDH at baseline, and 8% had a history of brain metastases. Most patients (81%) had not received prior anti-cancer therapy for unresectable or metastatic disease. All patients had tumor containing BRAF V600E or V600K mutations as determined by local laboratory or centralized testing, 85% with BRAF V600E mutations and 15% with BRAF V600K mutations.

The median duration of follow-up was 14 months. Efficacy outcomes for the arm receiving MEKINIST 2 mg daily in combination with dabrafenib and the arm receiving dabrafenib as a single agent are summarized in Table 8.

Table 8. Investigator-Assessed and Independent Review Committee-Assessed Response Rates and Response Durations in Trial 2

Endpoints	MEKINIST plus Dabrafenib N = 54	Dabrafenib N = 54
Investigator Assessment		
Responders (ORR%) (95% CI)	41 (76%) (62%, 87%)	29 (54%) (40%, 67%)
Complete response	9%	4%
Partial response	67%	50%
Duration of Response (months)		
Median (95% CI)	10.5 (7, 15)	5.6 (5, 7)
Independent Radiology Review Committee Assessment		
Responders (ORR%) (95% CI)	31 (57%) (43%, 71%)	25 (46%) (33%, 60%)
Complete response	9%	7%
Partial response	48%	39%
Duration of Response (months)		
Median (95% CI)	7.6 (7, NR)	7.6 (6, NR)

CI = Confidence interval; ORR = Confirmed overall response rate; NR = Not reported.

The ORR results were similar in subgroups defined by BRAF mutation subtype, i.e., in the 85% of patients with V600E mutation-positive melanoma and in the 15% of patients with V600K mutation-positive melanoma. In exploratory subgroup analyses of the patients with retrospectively confirmed BRAF V600E or V600K mutation-positive melanoma using the THxID™-BRAF assay, the ORR results were also similar to the intent-to-treat analysis.

14.2 Lack of Clinical Activity in Metastatic Melanoma Following BRAF-Inhibitor Therapy

The clinical activity of MEKINIST as a single agent was evaluated in a single-arm, multicenter, international trial (Trial 3) in 40 patients with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma who had received prior treatment with a BRAF inhibitor. All patients received MEKINIST at a dose of 2 mg orally once daily until disease progression or unacceptable toxicity.

The median age was 58 years, 63% were male, all were white, 98% had baseline ECOG PS of 0 or 1, and the distribution of BRAF V600 mutations was V600E (83%), V600K (10%), and the remaining patients had multiple V600 mutations (5%), or unknown mutational status (2%). No patient in Trial 3 achieved a confirmed partial or complete response as determined by the clinical investigators.

16 HOW SUPPLIED/STORAGE AND HANDLING

0.5-mg Tablets: Yellow, modified oval, biconvex, film-coated tablets with ‘GS’ debossed on one face and ‘TFC’ on the opposing face and are available in bottles of 30 (NDC 0173-0849-13).

1-mg Tablets: White, round, biconvex, film-coated tablets with ‘GS’ debossed on one face and ‘LHE’ on the opposing face and are available in bottles of 30 (NDC 0173-0858-13).

2-mg Tablets: Pink, round, biconvex, film-coated tablets with ‘GS’ debossed on one face and ‘HMJ’ on the opposing face and are available in bottles of 30 (NDC 0173-0848-13).

Store refrigerated at 2° to 8°C (36° to 46°F). Do not freeze. Dispense in original bottle. Do not remove desiccant. Protect from moisture and light. Do not place medication in pill boxes.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Inform patients of the following:

- Evidence of BRAF V600E or V600K mutation within the tumor specimen is necessary to identify patients for whom treatment with MEKINIST is indicated *[see Dosage and Administration (2.1)]*.
- MEKINIST administered in combination with dabrafenib can result in the development of new primary cutaneous and non-cutaneous malignancies. Advise patients to contact their doctor immediately for any new lesions, changes to existing lesions on their skin, or other signs and symptoms of malignancies *[see Warnings and Precautions (5.1)]*.
- MEKINIST administered in combination with dabrafenib increases the risk of intracranial and gastrointestinal hemorrhage. Advise patients to contact their healthcare provider to seek

immediate medical attention for signs or symptoms of unusual bleeding or hemorrhage *[see Warnings and Precautions (5.2)]*.

- MEKINIST administered in combination with dabrafenib increases the risks of pulmonary embolism and deep venous thrombosis. Advise patients to seek immediate medical attention for sudden onset of difficulty breathing, leg pain, or swelling *[see Warnings and Precautions (5.3)]*.
- MEKINIST can cause cardiomyopathy. Advise patients to immediately report any signs or symptoms of heart failure to their healthcare provider *[see Warnings and Precautions (5.4)]*.
- MEKINIST can cause severe visual disturbances that can lead to blindness. Advise patients to contact their healthcare provider if they experience any changes in their vision *[see Warnings and Precautions (5.5)]*.
- MEKINIST can cause interstitial lung disease (or pneumonitis). Advise patients to contact their healthcare provider as soon as possible if they experience signs such as cough or dyspnea *[see Warnings and Precautions (5.6)]*.
- MEKINIST can cause skin toxicities which may require hospitalization. Advise patients to contact their healthcare provider for progressive or intolerable rash *[see Warnings and Precautions (5.7)]*.
- MEKINIST used in combination with dabrafenib can cause serious febrile reactions. Instruct patients to contact their healthcare provider if they develop fever while taking MEKINIST with dabrafenib *[see Warnings and Precautions (5.8)]*.
- MEKINIST causes hypertension. Advise patients that they need to undergo blood pressure monitoring and to contact their healthcare provider if they develop symptoms of hypertension such as severe headache, blurry vision, or dizziness.
- MEKINIST often causes diarrhea which may be severe in some cases. Inform patients of the need to contact their healthcare provider if severe diarrhea occurs during treatment.
- MEKINIST should be taken at least 1 hour before or at least 2 hours after a meal.
- MEKINIST can cause fetal harm if taken during pregnancy. Instruct female patients to use highly effective contraception during treatment and for 4 months after treatment. Advise patients to use a highly effective non-hormonal method of contraception when MEKINIST is administered in combination with dabrafenib. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking MEKINIST *[see Use in Specific Populations (8.1, 8.6)]*.
- Nursing infants may experience serious adverse reactions if the mother is taking MEKINIST. Advise lactating mothers to discontinue nursing while taking MEKINIST *[see Use in Specific Populations (8.3)]*.

MEKINIST is a trademark of the GlaxoSmithKline group of companies.

THxID BRAF™ assay is a trademark of bioMerieux.

GlaxoSmithKline

Research Triangle Park, NC 27709

MKN:XPI

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

If your healthcare provider prescribes MEKINIST for you in combination with dabrafenib, also read the Medication Guide that comes with dabrafenib.

What is MEKINIST?

MEKINIST is a prescription medicine used by itself or in combination with dabrafenib to treat people with 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.

MEKINIST should not be used alone to treat people who already have received a BRAF inhibitor for treatment of their melanoma.

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

It is not known if MEKINIST is safe and effective in children.

What should I tell my healthcare provider before taking MEKINIST?

Before you take MEKINIST, tell your healthcare provider if you:

- have had bleeding problems or blood clots
- have heart problems
- have eye problems
- have lung or breathing problems
- have high blood pressure (hypertension)
- have liver or kidney problems
- have any other medical conditions
- 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 stopping treatment.
  - Birth control using hormones (such as birth control pills, injections, or patches) may not work as well while you are taking MEKINIST in combination

with dabrafenib. You should use another effective method of birth control while taking MEKINIST in combination with dabrafenib.
    - 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 during treatment with MEKINIST.
- are breastfeeding or plan to breastfeed. It is not known if MEKINIST passes into your breast milk. You and your healthcare provider should decide if you will take MEKINIST or breastfeed. You should not do both.

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.
- Take MEKINIST one time a day. If you are taking MEKINIST in combination with dabrafenib, you can take it at the same time as one of your doses of dabrafenib.
- 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 within 12 hours of your next scheduled dose, skip the missed dose. Just take the next dose at your regular time.
- If you take too much MEKINIST, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of MEKINIST?

MEKINIST may cause serious side effects, including

- **bleeding problems.** MEKINIST, when taken in combination with dabrafenib, can cause serious bleeding problems,especially in your brain or stomach, and can lead to death. Call your healthcare provider and get medical help right away if you have any unusual 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

- **blood clots.** MEKINIST, when taken in combination with dabrafenib, 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 or pale arm or leg
- **heart problems, including heart failure.** Your healthcare provider should check your heart function before you start taking MEKINIST by itself or in combination with dabrafenib, and during treatment. 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.** Tell your healthcare provider if you have any new or worsening symptoms of lung or breathing problems, including:
  - shortness of breath
  - cough
- **skin reactions.** 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, and may need to be treated in a hospital. Call your healthcare provider if you get any of the following symptoms:
  - skin rash that bothers you or does not go away
  - acne
  - redness, swelling, peeling, or tenderness of hands or feet
  - skin redness

- **fever.** MEKINIST in combination with dabrafenib can cause fever, which may be serious. 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 while taking MEKINIST.
- **increased blood sugar (hyperglycemia).** Some people may develop high blood sugar or worsening diabetes during treatment with MEKINIST in combination with dabrafenib. If you are diabetic, your healthcare provider should check your blood sugar levels closely during treatment with MEKINIST in combination with 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 used alone include:

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

Other common side effects of MEKINIST when used in combination with dabrafenib include:

- tiredness
- nausea or vomiting
- stomach-area (abdominal) pain
- diarrhea
- cough
- swelling of the face, arms, or legs
- headache
- night sweats
- decreased appetite
- constipation
- muscle or joint aches

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, 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.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of MEKINIST. For more information, ask your healthcare provider or pharmacist.

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

How should I store MEKINIST?

- Store MEKINIST in the refrigerator between 36°F to 46°F (2°C to 8°C). Do not freeze.
- 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 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.

For more information, go to www.MEKINIST.com or call 1-888-825-5249.

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.

This Patient Information has been approved by the U.S. Food and Drug Administration.

GlaxoSmithKline

Research Triangle Park, NC 27709

Revised: January 2014

MKN:XPIL