PRODUCT MONOGRAPH

Pr MEKINIST®

Trametinib Tablets

0.5 mg, 1.0 mg and 2.0 mg

Protein Kinase Inhibitor

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Date of Revision:
July 31, 2015

Submission Control No: 185240

TABLE OF CONTENTS

PAGE

Pr MEKINIST®

Trametinib Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet/ 0.5 mg, 1.0 mg and 2.0 mg	No clinically relevant nonmedicinal ingredients. *For a complete listing see the DOSAGE FORMS, COMPOSITION, AND PACKAGING section.*

INDICATIONS AND CLINICAL USE

MEKINIST (trametinib) is indicated as a monotherapy for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation. A validated test is required to identify BRAF V600 mutation status.

Clinical data supporting the effectiveness of MEKINIST in patients with BRAF V600K mutation are limited and fewer responses were reported in BRAF V600K patients compared to BRAF V600E patients (see PART II, CLINICAL TRIALS). There are no clinical data for other less common BRAF V600 mutations.

MEKINIST should not be used in patients who have progressed on a prior BRAF inhibitor therapy (see WARNINGS AND PRECAUTIONS, General and PART II, CLINICAL TRIALS).

MEKINIST has not been compared with a BRAF inhibitor in a clinical study in patients with unresectable or metastatic melanoma (see WARNINGS AND PRECAUTIONS, General).

Geriatrics (≥65 years of age)

No overall differences in effectiveness of MEKINIST were observed between elderly patients (≥65 years) and younger patients. However, permanent discontinuation and dose reductions/interruptions of MEKINIST were reported more frequently in elderly patients than in younger patients (see WARNINGS AND PRECAUTIONS, Special Populations and ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions).

Pediatrics (<18 years of age)

The safety and efficacy of MEKINIST have not been established in children and adolescents less than 18 years of age (see WARNINGS AND PRECAUTIONS, Special Populations). Toxicology studies in rats showed dose-related thickening of the growth plate and subepiphyseal infarcts/degeneration in long bones (see PART II, TOXICOLOGY). MEKINIST is not recommended for use in children and adolescents (see WARNINGS AND PRECAUTIONS, Special Population).

CONTRAINDICATIONS

MEKINIST is contraindicated in patients who are hypersensitive to trametinib or to any ingredient in the formulation or component of the container. For a complete listing of the ingredients, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

MEKINIST tablets should be prescribed by a physician experienced in the administration of anti-cancer agents.

The following are significant adverse drug reactions identified in clinical trials conducted with MEKINIST.

- Left ventricular dysfunction (see Cardiovascular section below)
- Retinal pigment epithelial detachment and retinal vein occlusion (see Ophthalmologic section below)
- Interstitial lung disease (see Respiratory section below)
- Skin toxicity including serious cases (see Skin section below)
- Venous Thromboembolism (see Cardiovascular below)

General

Confirmation of BRAF V600 mutation using a validated test is required for selection of patients appropriate for MEKINIST therapy.

MEKINIST monotherapy was not effective in patients with BRAF V600 mutation positive unresectable or metastatic melanoma who progressed on a prior BRAF inhibitor therapy (see PART II, CLINICAL TRIALS). MEKINIST monotherapy should not be used in this patient population.

MEKINIST has not been compared with a BRAF inhibitor in a clinical study in patients with BRAF V600 mutation positive unresectable or metastatic melanoma. However, overall response rates were lower in patients treated with MEKINIST than those reported in patients treated with BRAF inhibitors.

Carcinogenesis and Mutagenesis

Carcinogenicity studies have not been performed with trametinib.

There was no indication for a genotoxic potential of trametinib after testing in standard *in vitro* assays and *in vivo* in rats (see PART II, TOXICOLOGY).

Cardiovascular

Left Ventricular Dysfunction: MEKINIST has been reported to decrease left ventricular ejection fraction (LVEF) (see ADVERSE REACTIONS). In clinical trials with patients treated with MEKINIST at the recommended dose, patients with abnormal left ventricular ejection fraction were excluded. In the randomized clinical study in patients with unresectable or metastatic melanoma, cardiac adverse events including decreased LVEF, left ventricular dysfunction, and cardiac failure were reported in 8% patients treated with MEKINIST whereas none was reported in patients in the chemotherapy arm. In clinical trials, the mean time to onset of left ventricular dysfunction and decreased LVEF was 58.5 (range: 16-526) days. Cardiac failure, left ventricular dysfunction or decreased LVEF leading to dose interruption was reported in 5% of patients, and leading to dose reduction in 3% of patients. MEKINIST was permanently discontinued in 2% of patients due to the cardiac adverse events.

LVEF should be evaluated in all patients prior to initiation of treatment with MEKINIST with a recommendation of periodic follow-up within 8 weeks of initiating therapy. LVEF should continue to be evaluated during treatment with MEKINIST, as clinically appropriate. MEKINIST is not recommended in patients with decreased LVEF at baseline. Dose modifications for managing decreased LVEF/left ventricular dysfunction are outlined in Table 3 (see DOSAGE AND ADMINISTRATION). MEKINIST should be permanently discontinued if left ventricular dysfunction cannot be resolved within 4 weeks after interruption of MEKINIST treatment or is of ≥ Grade 3 (see DOSAGE and ADMINISTRATION, Dose Modifications). MEKINIST should be used with caution in patients with conditions that could impair left ventricular function.

Venous Thromboembolism: Deep vein thrombosis (DVT) and Pulmonary embolism (PE) can occur with MEKINIST. Across clinical studies in patients receiving MEKINIST as monotherapy (n=329), DVT was reported in 3 patients (1%) and PE was reported in 12 (4%) patients.

If patients develop symptoms of pulmonary embolism or deep vein thrombosis, such as shortness of breath, chest pain, or arm or leg swelling, they should immediately seek medical care.

Electrocardiography: The effect of MEKINIST on ECG intervals has not been established as a dedicated ECG study has not been completed. MEKINIST was associated with a concentration-dependent prolongation of the PR interval in a phase I study (see ACTION AND CLINICAL PHARMACOLOGY, PR Interval Prolongation). Caution should be observed in patients with pre-existing conduction system disease (e.g. first degree, second degree or third degree AV block) or a history of syncope of unknown etiology. There are no data regarding concomitant use of MEKINIST with medications that result in PR interval prolongation. Nonetheless, these medications should be used with caution with MEKINIST (see DRUG INTERACTIONS).

Hypertension: Elevations in blood pressure have been reported in association with MEKINIST in patients with or without pre-existing hypertension. In a retrospective review of blood pressure measured every 3 weeks in the randomized clinical study in patients with unresectable or metastatic melanoma, there was a statistically significant increase in mean systolic and diastolic pressure in the MEKINIST arm versus the chemotherapy arm at week 3 and 6, and diastolic pressure at week 9 following initiation of treatments. The comparator adjusted mean increase in systolic pressure was 5 mmHg and the diastolic pressure 4 mmHg. In this randomized study, hypertension as an adverse event was reported in 35 patients (17%) of which 28 (13%) were Grade 3. Blood pressure should be monitored during MEKINIST treatment, with control of hypertension by standard therapy as appropriate (See Monitoring and Laboratory Tests below).

Ophthalmologic

Retinal Pigment Epithelial Detachment: Retinal pigment epithelial detachments (RPED) can occur during treatment with MEKINIST (see ADVERSE REACTIONS). Across all clinical trials of MEKINIST, 14 cases (0.8%) of RPED were reported. The drug-induced RPEDs were often bilateral, multifocal, occurring in the macular region of the retina, and were associated with symptoms such as blurred vision and decreased visual acuity. In the 14 cases, RPED symptoms resolved after a median of 11.5 days (range 3-71 days) following interruption of dosing with MEKINIST, although optical coherence tomography abnormalities persisted beyond a month in some cases. Recurrence was reported in some patients who had experienced ≥ Grade 2 RPED after MEKINIST was re-initiated at reduced doses.

Perform ophthalmological evaluation any time a patient reports new visual disturbances and compare to baseline, if available. Withhold MEKINIST if RPED is diagnosed. If resolution of RPED is documented on repeat ophthalmological evaluation within 3 weeks MEKINIST can be resumed at a reduced dose. If RPED recurs, MEKINIST should be permanently discontinued.

Retinal Vein Occlusion (RVO): RVO has been reported in patients treated with MEKINIST (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions). The incidence of RVO was 0.2% across all clinical trials of MEKINIST. RVO may lead to macular edema, acute and progressive loss of vision, neovascularization, and glaucoma. Full recovery may not occur in patients developing RVO on MEKINIST treatment. Patients with hypertension, diabetes, hypercholesterolemia, or glaucoma are at higher risk for RVO. MEKINIST is not recommended in patients with a history of RVO. In patients who experience RVO, treatment with MEKINIST should be permanently discontinued.

Respiratory

Interstitial Lung Disease: In the clinical study in patients with unresectable or metastatic melanoma, interstitial lung disease or pneumonitis was reported in 2.8% of patients treated with MEKINIST (n = 211) compared to none in patients in the chemotherapy arm (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions). All six cases were serious (including one fatal case) leading to permanent discontinuation of MEKINIST. MEKINIST should be permanently discontinued if pneumonitis is diagnosed (see DOSAGE AND ADMINISTRATION, Dose Modifications).

Sexual Function/Reproduction

There is no information on the effect of MEKINIST on human fertility. In animals, no fertility studies have been performed. In a repeat-dose toxicity study, adverse effects were seen on female reproductive organs in rats at sub-therapeutic exposures. There were no effects on male reproductive organs; however, systemic exposures at doses tolerated by animals were lower than exposure at the recommended therapeutic dose (see PART II, TOXICOLOGY). MEKINIST may impair fertility in humans.

Skin

Skin Toxicity: In clinical studies with MEKINIST, skin toxicities of all grades have occurred in 87% of patients. Severe skin toxicities have occurred in 12% of patients. These skin toxicities included rash, dermatitis acneiform, and palmar-plantar erythrodysesthesia syndrome (see ADVERSE REACTIONS). Skin toxicities leading to dose reduction and interruption were reported in 12% and 12% of patients, respectively.

Serious skin infections including dermatitis, folliculitis, paronychia, cellulitis, and infective skin ulcer were also reported. In the randomized study in patients with unresectable or metastatic melanoma, six percent of patients treated with MEKINIST

compared to none in the chemotherapy arm required hospitalization and intravenous antibiotics due to serious skin toxicity or secondary infections.

Skin toxicity and infections should be monitored during MEKINIST treatment. MEKINST should be permanently discontinued if Grade 2 intolerable or ≥ Grade 3 skin toxicity occurs (see DOSAGE AND ADMINISTRATION, Dose Modifications).

Special Populations

Pregnant Women: There are no adequate and well-controlled studies of MEKINIST in pregnant women. Animal studies have shown reproductive toxicity. In rabbits, post-implantation loss, including total loss of pregnancy, and foetal toxicity, consisting of decreased body weight and ossification defects, occurred at sub-therapeutic systemic trametinib exposure levels (see PART II, TOXICOLOGY). MEKINIST should not be administered to pregnant women. Women of childbearing potential should use effective methods of contraception during therapy and for 4 months following discontinuation. If MEKINIST is used during pregnancy, or if the patient becomes pregnant while taking MEKINIST, the patient should be informed of the potential hazard to the fetus.

Nursing Women: No studies have been conducted with MEKINIST in nursing mothers. MEKINIST should not be administered to nursing mothers. It is not known whether trametinib is excreted in human milk. Because many drugs are excreted in human milk, a risk to the nursing infant cannot be excluded. A decision should be made whether to discontinue nursing or to discontinue MEKINIST taking into account the importance of MEKINIST to the mother.

Pediatrics: The safety and efficacy of MEKINIST have not been established in children and adolescents less than 18 years of age. MEKINIST may affect bone growth (see PART II, TOXICOLOGY). MEKINIST is not recommended for use in children and adolescents.

Geriatrics: In clinical studies with MEKINIST in patients with unresectable or metastatic melanoma (n= 329), 67 patients (20%) were 65 years of age and older, and 13 patients (4%) were 75 years of age and older. Higher rates of discontinuation and dose interruptions/ reductions were reported in elderly patients than the younger patients (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions).

Gender: Female patients with lower body weights had higher systemic exposure of trametinib compared to male patients (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions). Common and Grade 3 adverse reactions were reported more frequently in female than male patients in the randomized clinical trial (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions).

Renal impairment: A pharmacokinetic study in patients with renal impairment has not been conducted. Renal impairment is unlikely to have a clinically relevant effect on trametinib pharmacokinetics given the low renal excretion of trametinib.

Based on a population pharmacokinetic analysis, mild or moderate renal impairment had no significant effect on the oral clearance and systemic exposure of trametinib (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics). There are no data with MEKINIST in patients with severe renal impairment.

Hepatic impairment: A pharmacokinetic study in patients with hepatic impairment has not been conducted.

Based on a population pharmacokinetic analysis, trametinib oral clearance was not significantly different in patients with mild hepatic impairment compared to patients with normal hepatic function (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics). There are no clinical data in patients with moderate or severe hepatic impairment.

Monitoring and Laboratory Tests

Confirmation of BRAF V600 mutation using a validated test is required for selection of patients appropriate for MEKINIST therapy.

LVEF should be evaluated in all patients prior to initiation of treatment with MEKINIST with a recommendation of periodic follow-up within 8 weeks of initiating therapy. LVEF should continue to be evaluated during treatment with MEKINIST, as clinically appropriate (see DOSAGE AND ADMINISTRATION).

Blood pressure should be measured at baseline and monitored during treatment with MEKINIST (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions).

A thorough ophthalmological evaluation should be performed at baseline, if clinically warranted. Perform ophthalmological evaluation any time a patient reports new visual disturbances and compare to baseline, if available.

Patients should be monitored for skin toxicity 2 weeks after initiating MEKINIST treatment and periodically thereafter or, as clinically warranted (see DOSAGE AND ADMINISTRATION, Dose Modifications, Table 3).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety of MEKINIST has been evaluated in an integrated population of 329 patients with unresectable or metastatic melanoma treated with MEKINIST 2 mg orally once daily in clinical trials with median duration of treatment of 3.8 (range: 0.03-24.5) months.

Almost all patients (>99%) treated with MEKINIST reported at least one adverse reaction. The most common adverse reactions (≥ 20%) included rash, diarrhea, fatigue, peripheral edema, nausea, dermatitis acneiform and vomiting. Serious adverse drug reactions were reported in 22% of patients treated with MEKINIST. Serious adverse drug reactions reported in ≥1% of patients included cellulitis, pulmonary embolism, anemia, dyspnoea, pneumonitis and vomiting.

Adverse reactions leading to permanent discontinuation were reported in 10% of patients treated with MEKINIST. The most common adverse reactions leading to permanent discontinuation were ejection fraction decreased/left ventricular dysfunction, pneumonitis, and alanine aminotransferase increased. Adverse reactions leading to dose reduction and interruption were reported in 26% and 36%, respectively. The most common adverse reactions leading to dose reductions or interruptions included rash, ejection fraction decreased/left ventricular dysfunction, dermatitis acneiform, diarrhoea and peripheral edema.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The adverse drug reactions described in this section were those reported in a randomized, open-label study where patients with unresectable or metastatic melanoma were randomized to receive MEKINIST 2 mg orally once daily or chemotherapy (dacarbazine 1,000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 every 3 weeks). Patients who received at least one dose of study drug were included in the safety population. The median duration of study treatment was 4.8 (range: 0.3-16.3) months for MEKINIST arm and 2.1 (range: 0.1-14.0) months for chemotherapy arm.

The incidence of adverse events resulting in permanent discontinuation of study medication was 12% for patients treated with MEKINIST and 9% for patients treated with chemotherapy. The incidence of adverse events leading to dose reductions was 32% for MEKINIST and 10% for chemotherapy. The incidence of adverse events leading to dose delay/interruption was 38% for MEKINIST and 24% for chemotherapy.

Fatal treatment-emergent adverse events were reported in 1.9% of patients in the MEKINIST arm (myocardial infarction, renal failure, hepatic and renal failure, death of unknown cause) and in 2% of patients in the chemotherapy arm (pneumonia, pseudomembranous colitis). Two fatal adverse events (infected skin ulcer, pneumonitis) were reported in patients treated with MEKINIST after crossover from the chemotherapy arm.

Adverse reactions were reported in >99% and 93% of patients in the safety population treated with MEKINIST and chemotherapy, respectively. The majority of patients (97% in the MEKINIST arm and 80% in the chemotherapy arm) reported adverse events considered drug-related by the investigators. Among the commonly reported adverse events, rash, diarrhea, peripheral edema, dermatitis acneiform, dry skin, pruritis, paronychia and hypertension were more frequent in patients in the MEKINIST™ arm, while nausea, vomiting and constipation were more frequent in patients in the chemotherapy arm. Table 1 lists the adverse reactions with an incidence of ≥10% in patients receiving MEKINIST.

Table 1 Adverse Reactions (%) Occurring in ≥10% of Patients Treated With MEKINIST

	MEKINIST 2mg QD (N = 211)		Chemotherapy[b] (N = 99)	
Adverse Drug Reactions by System Organ Class and Preferred Term	**All Grades[a]**	**Grade 3/4**	**All Grades[a]**	**Grade 3/4**
Any adverse reaction	>99	52	93	32
Gastrointestinal disorders	70	7	65	5
Diarrhea	44	<1	17	2
Nausea	22	<1	39	1
Constipation	16	<1	23	1
Vomiting	15	1	20	2
General disorders and administrative site conditions	64	9	55	6
Fatigue	29	4	28	3
Edema peripheral	29	<1	3	0
Infections and Infestations	42	7	21	1
Paronychia	11	0	1	0
Folliculitis	10	<1	2	0
Skin and subcutaneous tissue disorders	92	13	36	0
Rash	59	7	10	0
Dermatitis acneiform	19	<1	2	0
Alopecia	18	<1	19	0
Dry Skin	13	0	1	0
Pruritus	11	2	1	0
Vascular Disorders	30	15	16	4
Hypertension	17	13	7	3

	MEKINIST 2mg QD (N = 211)		Chemotherapy[b] (N = 99)	
Adverse Drug Reactions by System Organ Class and Preferred Term	**All Grades[a]**	**Grade 3/4**	**All Grades[a]**	**Grade 3/4**
Hemorrhage	13	<1	0	0
Nervous system disorders	33	4	38	3
Headache	14	1	15	0
Respiratory, thoracic and mediastinal disorders	29	7	20	0
Cough	11	0	6	0
Investigations	31	11	19	8
Aspartate aminotransferase increased	10	2	1	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4
[b] Chemotherapy included patients on dacarbazine (DTIC) 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 every 3 weeks

Elderly patients (≥65 years) reported the following adverse reactions more frequently than the younger counterpart (<65 years): peripheral edema, pruritus, decreased appetite, rash pustular, paraesthesia, lymphoma, pain in extremity, vision blurred, blood creatine phosphokinase increased, blood lactate dehydrogenase increased, erythema, edema, syncope, weight decreased and periorbital edema. Grade 3 adverse events (57% vs. 37%) and serious adverse events (26% vs. 16%) were also reported more frequently in elderly than younger patients. In addition, a higher percentage of elderly patients compared to younger patients experienced adverse events leading to dose interruption (45% vs. 32%), reduction (47% vs. 22%) or permanent discontinuation (21% vs. 6%).

Female patients reported the following adverse reactions more frequently than male patients: peripheral edema, alopecia, vomiting, dry skin, pruritus, stomatitis, dry mouth, abdominal pain/abdominal pain upper, epistaxis, mucosal inflammation, rash pustular, eczema, palmar-plantar erythrodysesthesia syndrome and periorbital edema.

Less Common Clinical Trial Adverse Drug Reactions (<10%)

Treatment emergent adverse events considered clinically significant in studies with MEKINIST at the recommended dose (n = 329) are presented below. As the list includes adverse events from the integrated safety population of three clinical trials, some adverse events with frequency >10% are not included in Table 1.

Blood and lymphatic system disorders: Anemia (9%), thrombocytopenia (2%), neutropenia (2%)

Cardiac disorders: Ejection fraction decreased (5%), left ventricular dysfunction (4%), cardiac failure (<1%)

Cardiovascular disorders: Pulmonary embolism (4%), deep vein thrombosis (1%)

Eye disorders: Vision blurred (6%), periorbital edema (3%), dry eye (3%), visual impairment (2%), retinal pigment epithelial detachment (<1%), papilledema (<1%), retinal detachment (<1%), retinal vein occlusion (<1%)

Gastrointestinal disorders: Abdominal pain (13%), dry mouth (10%), stomatitis (7%), dysphagia (2%)

General disorders and administration site conditions: Pyrexia (12%), mucosal inflammation (7%), face edema (7%), asthenia (5%), sudden death (<1%)

Hepatobiliary disorders: Alanine aminotransferase increased (8%), blood alkaline phosphatase increased (5%), cytolytic hepatitis (<1%), blood bilirubin increased (<1%)

Immune system disorders: Hypersensitivity (1%), corneal graft rejection (<1%)

Infections and infestations: Cellulitis (5%), rash pustular (3%), erysipelas (2%), eye infection (2%), fungal skin infection (<1%)

Metabolism and nutrition disorders: Hypoalbuminemia (6%), dehydration (4%)

Musculoskeletal and connective tissue disorders: Arthralgia (10%), back pain (7%), pain in extremity (7%), muscle spasm (5%), joint swelling (2%), blood creatine phosphokinase increased (2%), rhabdomyolysis (<1%)

Nervous system disorders: Dizziness (8%), dysgeusia (6%), syncope (2%)

Reproductive system and breast disorders: Scrotal edema (<1%)

Respiratory, thoracic and mediastinal disorders: Cough (11%), dyspnoea (11%), epistaxis (8%), pulmonary embolism (4%), pneumonitis (2%), interstitial lung disease (<1%)

Skin and subcutaneous tissue disorders: Erythema (5%), palmar plantar erythrodysesthesia syndrome (4%), skin chapped (4%), skin fissures (3%), dermatitis (2%), hyperkeratosis (1%), skin ulcer (1%)

Vascular disorders: Lymphedema (7%)

Abnormal Hematologic and Clinical Chemistry Findings

Table 2 lists the laboratory adverse events with an incidence of ≥1% in patients receiving MEKINIST in the randomized study in patients with unresectable or metastatic melanoma.

Table 2 Abnormal Laboratory Adverse Events (%) Occurring in ≥1% of Patients Treated With MEKINIST

Adverse Events by Preferred Term	MEKINIST 2mg QD (N = 211)		Chemotherapy[b] (N = 99)	
	All Grades[a]	Grades 3 and 4	All Grades[a]	Grades 3 and 4
Hypoalbuminemia	4	1	1	1
Hypocalcemia	2	0	0	0
Hyponatremia	1	1	0	0
Aspartate aminotransferase increased	10	2	1	0
Alanine aminotransferase increased	9	3	3	0
Blood alkaline phosphatase increased	6	1	1	0
Blood lactate dehydrogenase increased	4	<1	0	0
Blood creatinine phosphokinase increased	4	2	1	0
Blood albumin decreased	2	<1	1	1
Hemoglobin decreased	1	<1	1	0
White blood cell count decreased	1	0	2	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4
[b] Chemotherapy included patients on dacarbazine (DTIC) 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 every 3 weeks

DRUG INTERACTIONS

Overview

Formal clinical drug interaction studies with MEKINIST have not been conducted.

Trametinib is metabolized predominantly via deacetylation by hydrolytic enzymes. In microsomes and hepatocytes, trametinib was metabolically stable with low intrinsic clearance. The NADPH-dependent (oxidative) metabolism of ^{14}C-trametinib was very low in both human liver microsomes (~1%) and recombinant CYPs (~3%).

Drug-Drug Interactions

Effects of Trametinib on Drug Metabolizing Enzymes and Transporters: Based on *in vitro* studies, trametinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2D6 and CYP3A4. The inhibition of CYP2C8, CYP2C9 and CYP2C19 *in vitro* occurred at concentrations that are at multiples of therapeutic concentrations of trametinib (9- to >100 fold) and therefore drug interactions with sensitive CYP2C8, CYP2C9, and CYP2C19 substrates are not anticipated.

In vitro, trametinib was an inducer of CYP3A4 and an inhibitor of the transporters OATP1B1, OATP1B3, Pgp and BCRP. Based on the clinical trametinib systemic exposure relative to the *in vitro* inhibition or induction values, trametinib treatment is unlikely to have an effect on the kinetics of substrates of CYP3A4 and the transporters.

Effects of Other Drugs on Trametinib: *In vitro* data suggest that the pharmacokinetics of trametinib is unlikely to be affected by other drugs. Trametinib metabolism by CYP enzymes is minor and trametinib is not a substrate for the efflux transporters Pgp or BCRP. Trametinib is deacetylated via hydrolytic enzymes which are not generally associated with drug interaction risk.

Drugs that Prolong the PR Interval: MEKINIST may be associated with concentration-dependent prolongation of the PR interval (See WARNINGS AND PRECAUTIONS, Cardiovascular; ACTION AND CLINICAL PHARMACOLOGY, PR Interval Prolongation). Caution should therefore be exercised when MEKINIST is administered concomitantly with other drugs that prolong the PR interval, including, but not limited to, antiarrhythmics, beta blockers, non-dihydropyridine calcium channel blockers, digitalis glycosides, sphingosine-1 phosphate receptor modulators, and some HIV protease inhibitors.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Recommended Dose

The recommended dose of MEKINIST is 2 mg given orally once daily with a full glass of water.

MEKINIST should be taken without food, at least one hour before or two hours after a meal (see ACTION AND CLINICAL PHARMACOLOGY; Pharmacokinetics).

It is recommended that patients continue treatment until disease progression or the development of unacceptable toxicity.

Dose modifications

The management of adverse reactions may require treatment interruption, dose reduction, or treatment discontinuation (see Table 3). Discontinue MEKINIST treatment permanently if a dose reduction below 1 mg once daily is required.

Table 3 Recommended Dose Modifications for MEKINIST

Target Organ	Adverse Reaction[a]	Dose Modification
Cutaneous	Grade 2 rash	Reduce dose of MEKINIST by 0.5 mg or discontinue MEKINIST in patients taking MEKINIST 1 mg daily
	Intolerable Grade 2 rash that does not improve within 3 weeks following dose reduction Grade 3 or 4 rash	Withhold MEKINIST for up to 3 weeks If improved within 3 weeks, resume MEKINIST at a lower dose (reduced by 0.5 mg or discontinue MEKINIST in patients taking MEKINIST 1 mg daily
	Intolerable Grade 2 or Grade 3 or 4 rash that does not improve within 3 weeks despite interruption of MEKINIST dosing	Permanently discontinue MEKINIST
Cardiac	Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline and is below institutional lower limits of normal (LLN) from pre-treatment value	Withhold MEKINIST for up to 4 weeks
	Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline and is below LLN that improves to normal LVEF value within 4 weeks following interruption of MEKINIST	If improved within 4 weeks, resume MEKINIST at a lower dose (reduced by 0.5 mg) or discontinue MEKINIST in patients taking MEKINIST 1 mg daily
	Symptomatic congestive heart failure	Permanently discontinue MEKINIST
Cardiac	Absolute decrease in LVEF of greater than 20% from baseline that is below LLN Absolute decrease in LVEF of 10% or greater from baseline and is below LLN that does not improve to normal LVEF value within 4 weeks following interruption of MEKINIST	Permanently discontinue MEKINIST

Target Organ	Adverse Reaction[a]	Dose Modification
Ocular	Grade 2-3 retinal pigment epithelial detachments (RPED)	Withhold MEKINIST for up to 3 weeks
	Grade 2-3 RPED that improves to Grade 0-1 within 3 weeks	If improved within 3 weeks, resume MEKINIST at a lower dose (reduced by 0.5 mg) or discontinue MEKINIST in patients taking MEKINIST 1 mg daily
	Retinal vein occlusion Grade 2-3 RPED that does not improve to at least Grade 1within 3 weeks Recurrence of RPED (any Grade) after dose interruption or reduction	Permanently discontinue MEKINIST
Pulmonary	Interstitial lung disease/pneumonitis	Permanently discontinue MEKINIST
Other	Grade 3 adverse reaction	Withhold MEKINIST for up to 3 weeks
	If Grade 3 adverse reaction improves to Grade 0-1 following interruption of MEKINIST within 3 weeks	Reduce dose of MEKINIST by 0.5 mg or discontinue MEKINIST in patients taking MEKINIST 1 mg daily
	Grade 4 adverse reaction Grade 3 adverse reaction that does not improve to Grade 0-1 within 3 weeks	Permanently discontinue MEKINIST

[a] The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE)

Pediatrics: MEKINIST is not recommended in this population (see INDICATIONS AND CLINICAL USE).

Geriatrics: No dose adjustment is required in patients over 65 years (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Renal impairment: No dosage adjustment is required in patients with mild or moderate renal impairment. There are no clinical data with MEKINIST in patients with severe renal impairment; the need for starting dose adjustment is unknown (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Hepatic impairment: No dosage adjustment is required in patients with mild hepatic impairment. There are no clinical data in patients with moderate or severe hepatic impairment; the need for starting dose adjustment is unknown(see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Missed Dose

If a dose is missed, MEKINIST should not be taken if it is less than 12 hours until the next dose.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There were no cases of MEKINIST dose above 4 mg once daily reported from the clinical trials. Doses of up to 4 mg orally once daily or loading doses of up to 10 mg on two consecutive days, have been administered to limited numbers of patients in a clinical study. Doses above the recommended 2 mg orally once daily regimen were associated with increased toxicities including retinal pigment epithelial detachment.

There is no specific antidote for overdosage of MEKINIST, and treatment of overdose should consist of general supportive measures. Hemodialysis is not expected to enhance the elimination as trametinib is highly bound to plasma proteins.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Trametinib is an orally bioavailable, small molecule inhibitor of mitogen-activated extracellular signal regulated kinase 1 and 2 (MEK1 and MEK2). MEK1 and MEK2 are critical components of the mitogen-activated protein kinase (MAPK) pathway. The RAS effector pathway RAF-MEK-ERK, is an essential, shared element of mitogenic signaling involving tyrosine kinase receptors, leading to a wide range of cellular responses, including growth, differentiation, inflammation, and apoptosis. Mutant BRAF and RAS proteins subsequently signal through MEK1 and MEK2 leading to consecutive activation of the MAPK pathway and stimulation of cell growth. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 50% of melanoma. Trametinib is a potent, reversible, and selective allosteric inhibitor of MEK1 and MEK2 activation and kinase activity. The IC_{50} values for the unphosphorylated form of MEK1 and MEK2 are 0.7 nM and 0.9 nM, respectively. The IC_{50} values for the phosphorylated form of MEK1 and MEK2 are 13.2 nM and 10.7 nM, respectively. Trametinib inhibits growth of BRAF V600 mutant melanoma cell lines and demonstrates anti-tumour effects in BRAF V600 mutant melanoma xenograft models.

Pharmacodynamics

In patients (n=5-6) with BRAF mutant melanoma, administration of trametinib (1 mg or 2 mg once daily) resulted in dose-dependent changes in biomarkers including inhibition

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

PR Interval Prolongation: A dedicated clinical ECG study has not been conducted. The effect of MEKINIST on ECG intervals was assessed as part of the first time in human study to determine the relationship between the manually read ECG interval parameters and plasma concentrations of trametinib using a nonlinear mixed effect model. Data were available from 50 patients with a total of 498 matched ECG interval and plasma concentration values collected on day 1 and day 15. The slope (95% CI) of the exposure-relationship with PR was positive (0.371 [0.223, 0.519] msec/ng/mL) indicating an increase in PR interval with increasing trametinib concentrations. A median increase of 8.3 msec in the PR interval is predicted at the geometric mean C_{max} value of 22.2 ng/mL, with an upper 95th percentile limit of 10.9 msec. At the maximum C_{max} value of 32.9 ng/mL, a median increase of 12.2 msec of the PR interval is predicted, with an upper 95th percentile limit of 16.2 msec. The slopes of the relationship between trametinib concentration and QTc, QRS, and heart rate were not statistically significant.

Pharmacokinetics

The pharmacokinetics of trametinib were characterized following single- and repeat-oral administration and were adequately described by a 2-compartment model with dual sequential first-order absorption in patients.

Absorption: Trametinib is absorbed orally with median time to achieve peak concentrations of 1.5 hours post-dose (see Table 4). The mean absolute bioavailability of a single 2 mg tablet dose is 72% relative to an intravenous (IV) microdose. The increase in exposure (C_{max} and AUC) was dose-proportional following repeat dosing. Following administration of 2 mg daily, geometric mean C_{max}, $AUC_{(0-\tau)}$ and predose concentration were 22.2 ng/mL, 370 ng*hr/mL (see Table 4) and 12.1 ng/mL, respectively with a low peak:trough ratio (1.8). Inter-subject variability was low (<28%).

Administration of a single dose of trametinib with a high-fat, high-calorie meal resulted in a 70% and 24% decrease in C_{max} and $AUC_{(0-168h)}$, respectively compared to fasted conditions (see DOSAGE AND ADMINISTRATION).

Distribution: Binding of trametinib to human plasma proteins is 97.4%. Trametinib has a volume of distribution of 1060 L determined following administration of a 5μg IV microdose.

Metabolism: *In vitro* studies demonstrated that trametinib is metabolized predominantly via deacetylation alone or with mono-oxygenation or in combination with glucuronidation biotransformation pathways. Following a single dose (2 mg) of [14C]-trametinib, about 50% of circulating radioactivity is represented as parent. The deacetylation is mediated by hydrolytic enzymes, such as carboxyl-esterases or amidases. The deacetylated metabolite (M5) has been shown to be active based on *in vitro* studies. However, based on its exposure (~10%) relative to parent, it is unlikely to contribute to the clinical activity of trametinib.

Excretion: Trametinib accumulates with repeat daily dosing with a mean accumulation ratio of 6.0 following a 2 mg once daily dose. Mean terminal half-life is 127 hours (5.3 days) after single dose administration in a study with a 7 day sampling period (see Table 4), although a longer terminal phase (11 days) has been observed with a longer sampling period (10 days), presumably due to elimination from deep compartments. Steady-state was estimated to be achieved by Day 15-20 following administration of 2 mg once daily. The mean accumulation ratio of patients receiving continuous dosing of 2mg once daily was 6.5 (95% CI: 5.5, 7.6) on Day 15 over Day 1. Trametinib plasma IV clearance is 3.21 L/hr.

Total dose recovery is low after a 10-day collection period (<50%) following administration of a single oral dose of radiolabeled trametinib as a solution, due to the long half-life. Fecal excretion is the major route of elimination after [^{14}C]-trametinib oral dose, accounting for >80% of excreted radioactivity recovered while urinary excretion accounted for <19% of excreted radioactivity recovered. Less than 0.1% of the excreted dose was recovered as parent in urine.

Table 4 Summary of Trametinib's Pharmacokinetic Parameters in Patients with Cancer

Study	T_{max} (h) Median (Min, Max)	C_{max} (ng/mL) Geometric Mean (95% CI)	AUC[a] (ng*hr/mL) Geometric Mean (95% CI)	$t_{1/2}$ (hr) Geometric Mean (95% CI)
Single 2.0 mg Dose (n=22)[b]	1.5 (1.0, 4.0)	9.1 (7.2, 11.6)	415 (359, 479)	127 (113, 143)
Repeat Dose (Day 15)[c, d] (n=13)	1.8 (1.0, 3.0)	22.2 (18.7, 26.4)	370 (320, 427)	NA

Abbreviations: CI, confidence interval; NA, not applicable

[a] AUC refers to AUC(0-∞) for single dose and AUC(0-τ) for repeat dose

[b] Data is from the Phase I food effect study (fasting conditions)

[c] 2.0 mg once daily; includes patients who received loading dose regimens

[d] Data is from the Phase I first time in human study

Special Populations and Conditions

Pediatrics: No studies have been conducted to investigate the pharmacokinetics of trametinib in pediatric patients.

Geriatrics: Based on a population pharmacokinetics analysis, age had no relevant clinical effect on trametinib pharmacokinetics.

Gender: Based on a population pharmacokinetic analysis, sex and body weight were found to influence trametinib oral clearance. At a median weight of 79 kg, female patients had 21% lower trametinib clearance (4.9 vs. 6.2 L/h) and 25% higher AUC (402 vs. 322 ng•h.mL) than males.

Race: There is insufficient data to evaluate potential differences in the pharmacokinetics of trametinib by race or ethnicity.

Hepatic Insufficiency: A clinical pharmacokinetic study has not been conducted in patients with hepatic impairment. Based on a population pharmacokinetic analysis, trametinib oral clearance to trametinib was not significantly different in patients with mild hepatic impairment (defined by total bilirubin ≤ ULN and AST > ULN, or total bilirubin > 1.0-1.5x ULN with any AST level) relative to those with normal hepatic function. No data are available in patients with moderate or severe hepatic impairment (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency: A clinical pharmacokinetic study in patients with renal impairment has not been conducted. The pharmacokinetics of trametinib were characterized in 223 patients enrolled in clinical trials with trametinib who had mild renal impairment and 35 patients with moderate renal impairment. Based on a population pharmacokinetic analysis mild (60≤ GFR <90 mL/min/1.73m^2) and moderate renal impairment (30≤ GFR <60 mL/min/1.73m^2) had no effect on trametinib oral clearance (<6% decrease for either renal impaired group compared to normal renal function). No data are available in patients with severe renal impairment (see DOSAGE AND ADMINISTRATION).

STORAGE AND STABILITY

Store refrigerated, 2-8°C. Protect from light and moisture. Do not remove desiccant. Dispense in original bottle.

DOSAGE FORMS, COMPOSITION AND PACKAGING

MEKINIST 0.5 mg tablets are yellow, modified oval, biconvex, film-coated tablets with ‘GS’ debossed on one face and ‘TFC’ on the opposing face. Available in bottles of 30 tablets. Bottles contain a silica gel desiccant.

MEKINIST 1.0 mg tablets of are white, round, biconvex, film-coated tablets with ‘GS’ debossed on one face and ‘LHE’ on the opposing face. Available in bottles of 30 tablets. Bottles contain a silica gel desiccant.

MEKINIST 2.0 mg tablets are pink, round, biconvex, film-coated tablets with ‘GS’ debossed on one face and ‘HMJ’ on the opposing face. Available in bottles of 14 or 30 tablets. Bottles contain a silica gel desiccant.

MEKINIST tablets contain 0.5, 1.0, or 2.0 mg of trametinib and the following nonmedicinal ingredients: croscarmellose sodium, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, silicon dioxide (colloidal), and sodium lauryl sulphate. The tablet coating contains: hypromellose polyethylene glycol, and titanium

dioxide. In addition, the 0.5 mg tablets contain iron oxide yellow and the 2.0 mg tablets contain iron oxide red and polysorbate 80.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

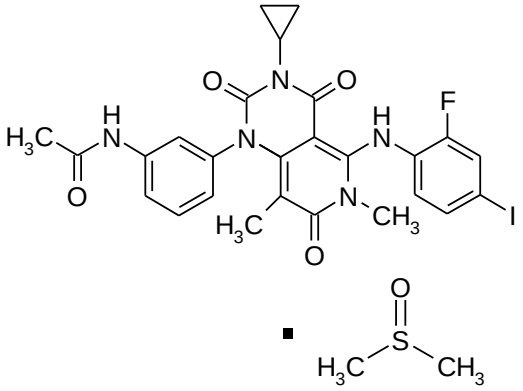
Common name: trametinib dimethyl sulfoxide

Chemical name: equimolecular combination of N-(3-{3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl}phenyl)acetamide with (methylsulfinyl)methane

Molecular formula: $C_{26}H_{23}FIN_5O_4.C_2H_6OS$

Molecular mass: 693.53 (DMSO solvate of parent)
615.39 (non-solvated parent)

Structural formula:



Tablets are formulated to contain trametinib DMSO solvate equivalent to the labelled amount of trametinib as the unsolvated parent.

Physicochemical properties: Trametinib dimethyl sulfoxide is a white to almost white solid. Trametinib dimethyl sulfoxide has low solubility (0.2 − 0.3 µg/mL) in the pH range of 2 to 8 in aqueous media at 37°C. Trametinib dimethyl sulfoxide is soluble in organic solvents (3.8 mg/mL in dimethyl sulfoxide (DMSO)) at 20°C.
pKa (basic) = 0.25

CLINICAL TRIALS

Trial Design

The efficacy and safety of MEKINIST were evaluated in a Phase III randomized, multi-centre, international, open label study comparing MEKINIST to chemotherapy in patients with unresectable or metastatic BRAF V600E or V600K mutation-positive cutaneous melanoma. Screening included central laboratory testing of BRAF mutation (V600E or V600K) using a BRAF mutation assay conducted on the most recent tumour sample available.

Patients may have received up to one prior chemotherapy in unresectable or metastatic setting. Patients previously treated with a BRAF or MEK inhibitor were excluded. Patients were randomized 2:1 to receive MEKINIST 2 mg once daily or chemotherapy (dacarbazine 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 every 3 weeks). Treatment for all patients continued until disease progression, death or withdrawal. Patients in the chemotherapy arm were allowed to cross-over to MEKINIST therapy after independent confirmation of progression.

The Intent to Treat (ITT) population included all randomized patients with BRAF V600E, or V600K mutation-positive unresectable or metastatic melanoma with or without a prior history of brain metastases.

The primary efficacy population included patients with unresectable or metastatic BRAF V600E mutation-positive cutaneous melanoma without a prior history of brain metastases. The primary efficacy endpoint was progression-free survival (PFS). The secondary endpoints included PFS in the ITT population as well as overall survival (OS), overall response rate (ORR), and duration of response in the primary efficacy and ITT populations.

Study demographics and Baseline Characteristics

Study demographics and baseline characteristics were balanced between treatment groups in the primary efficacy population and the ITT population (see Table 5).

Table 5 Summary of patient demographics and baseline characteristics in pivotal clinical trial of MEKINIST (ITT Population)

	MEKINIST (N=214)	Chemotherapy[a] (N=108)	Total (N=322)
Age (years)			
Median (Min. – Max.)	54.5 (23-85)	54.0 (21-77)	54.0 (21 -85)
Age Category, n (%)			
<65 years	165 (77)	86 (80)	251 (78)
≥65 years	49 (23)	22 (20)	71 (22)
Sex, n (%)			
Male	120 (56)	53 (49)	173 (54)
Female	94 (44)	55 (51)	149 (46)
Baseline lactate dehydrogenase, n (%)			
≤ULN	134 (63)	66 (61)	200 (62)
>ULN	77 (36)	42 (39)	119 (37)
Unknown	3 (1)	0	3 (<1)
Any prior therapy, n (%)			
No	14 (7)	7 (6)	31 (10)
Yes	200 (93)	101 (94)	291 (90)
Prior chemotherapy in unresectable or metastatic setting, n (%)			
No	143 (67)	70 (65)	213 (66)
Yes	71 (33)	38 (35)	109 (34)
Prior immunotherapy, n (%)[b]			
No	146 (68)	78 (72)	224 (70)
Yes	68 (32)	30 (28)	98 (30)
Prior biologic therapy, n (%)			
No	198 (93)	95 (88)	293 (91)
Yes	16 (7)	13 (12)	29 (9)
ECOG PS at Baseline, n (%)			
ECOG 0	136 (64)	69 (64)	205 (64)
ECOG 1	78 (36)	39 (36)	117 (36)
Stage at screening, n (%)			
IIIC, IV M1a, or IV M1b	69 (32)	45 (42)	114 (35)
IV M1c	144 (67)	63 (58)	207 (64)
Unknown	1 (<1)	0	1 (<1)
Number of disease sites at Baseline, n (%)			
≥3 sites	123 (57)	56 (52)	179 (56)
<3 sites	91 (43)	52 (48)	143 (44)
BRAF mutation status, n (%)			
V600E	184 (86)	97 (90)	281 (87)
V600K	29 (14)	11 (10)	40 (12)
V600E/V600K	1 (<1)	0	1 (<1)
History of brain metastases, n (%)			
No	205 (96)	106 (98)	311 (97)
Yes	9 (4)	2 (2)	11 (3)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PS = performance status; ULN = upper limit of normal

[a] Chemotherapy included patients on dacarbazine (DTIC) 1,000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 every 3 weeks.

[b] The majority of patients received adjuvant interferon. Patients were not permitted ipilimumab in the unresectable or metastatic setting.

Study results

In the primary efficacy population, MEKINIST demonstrated a statistically significant improvement in investigator-assessed PFS (HR = 0.44; [95% CI: 0.31, 0.64], N=273, P<0.0001) which represents a 56% reduction in the risk of tumour progression or death for patients treated with MEKINIST compared with those treated with chemotherapy. Comparable PFS results were observed in the ITT population (HR = 0.45; [95% CI: 0.33, 0.63], N=322, P<0.0001; see Table 6 and Figure 1). Similar PFS results were seen based on an Independent Review Committee evaluation. At the time of the primary analysis, the median follow-up were 4.9 months for patients treated with MEKINIST and 4.8 months for those treated with chemotherapy.

At the time of primary analysis, OS data were not mature with 20% events reported in the ITT population and 51 (47%) patients in the chemotherapy arm had crossed over to receive MEKINIST after a confirmed disease progression. An updated analysis was conducted with 63% events. See Table 6 for results.

The investigator-assessed best confirmed overall response rate (ORR) was 22% in the MEKINIST arm compared to 8% in the chemotherapy arm (see Table 6). However, in the MEKINIST treatment arm, the confirmed overall response rate was 10% in patients with BRAF V600K mutation compared to 24% in those with BRAF V600E mutation.

Treatment effect with MEKINIST was observed across all subgroups. However, in patients with BRAFV600K mutation, the investigator-assessed best confirmed overall response rate was 10% in the MEKINIST arm (n = 29) compare to 18% in the chemotherapy arm (n = 11).

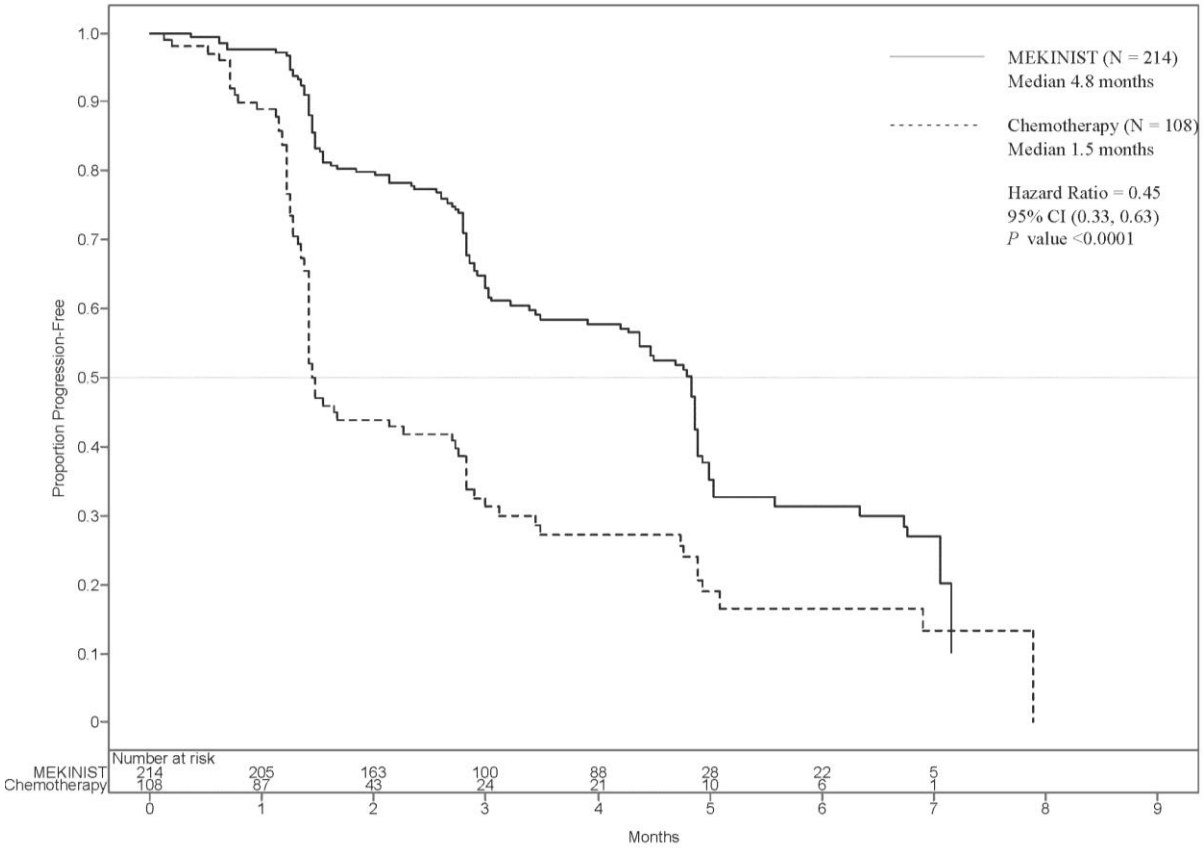
Table 6 Investigator-Assessed Efficacy Results

Endpoint	MEKINIST	Chemotherapy[a]
Primary Efficacy Population	**(N = 178)**	**(N = 95)**
Progression-free Survival		
Number of events, n (%)	96 (54)	68 (72)
Median PFS (months)	4.8	1.4
(95% CI)	(3.5, 4.9)	(1.4, 2.7)
Hazard Ratio[b]	0.44	
(95% CI)	(0.31, 0.64)	
P value[b]	<0.0001	
ITT Population	**(N = 214)**	**(N = 108)**
Progression-free Survival		
Number of events, n (%)	118 (55)	77 (71)
Median PFS (months)	4.8	1.5
(95% CI)	(4.3, 4.9)	(1.4, 2.7)
Hazard Ratio[b]	0.45	
(95% CI)	(0.33, 0.63)	
P value[b]	<0.0001	
Overall Survival		
Primary analysis: Overall Survival[c]		
Died, n (%)	35 (16)	29 (27)
Hazard Ratio[b]	0.54	
(95% CI)	(0.32, 0.92)	
P value[b]	0.014	
Overall Survival censored at the time of crossover		
Died, n (%)	35 (16)	15 (14)
Hazard Ratio[b]	0.59	
(95% CI)	(0.30, 1.18)	
P value[b]	0.073	
Updated Overall Survival		
Died, n (%)	137 (64)	67 (62)
Hazard Ratio[b]	0.78	
(95% CI)	(0.57, 1.06)	
P value	0.091	
Median overall survival (months)	15.6	11.3
(95% CI)	(5.9, 9.2)	(7.2, 14.8)
Overall Response		
Best Response, n (%)		
CR	4 (2)[d]	0
PR	43 (20)	9 (8)
ORR (CR+PR), (%)	22	8
(95% CI)	(16.6, 28.1)	(3.9, 15.2)
Duration of Response	**(N = 47)**	**(N = 9)**
Median, months	5.5	NR(5.0, NR)
(95% CI)	(4.1, 5.9)	

ITT = Intent to treat; PFS = Progression-free survival; CI = Confidence interval; CR = Complete response; PR = Partial response; NR = Not reached

[a] Chemotherapy included patients on dacarbazine (DTIC) 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 every 3 weeks.
[b] Hazard ratios are estimated using a Pike estimator. A hazard ratio <1 indicates a lower risk with this treatment. Hazard Ratio and p-value from stratified log-rank test are adjusted for prior chemotherapy for unresectable or metastatic disease and baseline LDH.
[c] Fifty-one (47%) patients crossed over to receive MEKINIST following disease progression.
[d] The four patients were reported as 2 PR, 1 stable disease and 1 'not evaluable' by the Independent Review Committee.

Figure 1 Investigator-Assessed Progression-Free Survival (ITT population)



Lack of efficacy in patients previously treated with BRAF inhibitors

In a single arm Phase II study, efficacy of MEKINIST was evaluated in 40 patients with BRAFV600E or V600K mutation positive unresectable or metastatic cutaneous melanoma who had received prior treatment with a BRAF inhibitor. At baseline, the median age was 58 (range: 23-76) years, 63% were male, 100% were Caucasian, 98% had ECOG performance status of 0 or 1. No patient achieved a confirmed complete or partial response after treatment with MEKINIST at 2 mg once daily (see INDICATIONS AND CLINICAL USE; WARNINGS AND PRECAUTIONS, General).

DETAILED PHARMACOLOGY

Refer to PART I, ACTION AND CLINICAL PHARMACOLOGY.

SAFETY PHARMACOLOGY

In vitro, trametinib inhibited hERG channel repolarization in HEK293 cells in a concentration dependent manner, with an IC_{50} of 1.54 μM (950 ng/mL). In a rabbit left ventricular wedge assay, trametinib had no significant effect on QT interval at concentrations up to 30 μM (18450 ng/mL, limit of solubility). In this preparation, significant decreases in isometric contractile force occurred at concentrations of 10 and 30 μM. A single intravenous infusion of trametinib in dogs given 1 mg/kg over 10 minutes produced no changes in electrocardiogram (ECG) parameters, blood pressure, or heart rate during the 30 minute post-dose measurement period. The highest plasma concentrations were determined at the end of the 10 minute infusion and the mean was 2.5±0.4 μM (1500 ng/mL). Single oral trametinib doses of up to 0.075 mg/kg in dogs produced no changes in arterial blood pressure, heart rate, body temperature, or ECG intervals, including QTc. Based on estimated exposures, the C_{max} at this dose would be less than therapeutic (< 22 ng/mL).

In vitro, trametinib was a selective inhibitor of MEK1 and MEK2 with no affinity for other kinases at concentrations up to 10 μM (6154 ng/mL). Trametinib showed no significant binding activity (IC_{50}> 10 μM, 6154 ng/mL) in a screen for a number of receptors, enzymes, and ion channels.

TOXICOLOGY

Trametinib administration in non-clinical toxicology studies resulted in dose-dependent findings attributed primarily to its pharmacologic mechanism of action (inhibition of MAPK which leads to inhibition of cell proliferation in tissues with high proliferative rates including gastrointestinal, integument, and hematopoietic systems). These effects occurred in animals at systemic trametinib exposures generally below those achieved at

the oral therapeutic dose of 2 mg/day in cancer patients (C_{max} = 22.2 ng/mL; AUC = 370 ng.h/mL). Other findings included effects on phosphate homeostasis and soft tissue mineralization, liver, bone, ovary, and the developing embryo or fetus.

Skin lesions were seen in rats and dogs, but were more prevalent in rats where they included acanthosis, erosion, and ulceration as well as inflammatory responses in more severe cases.

Adverse gastrointestinal tract effects were observed in all repeated dose toxicology studies and were more common in dogs than rats. In both species, gastrointestinal-related clinical effects included reduced food consumption, body weight loss, and abnormal feces. Microscopic findings in dogs included erosions and/or neutrophilic inflammation and were observed throughout the GI tract and were accompanied by lymphoid depletion in gut-associated lymphoid tissue (GALT). In rats, erosion and ulceration of stomach and cecum mucosal epithelium were seen in exploratory studies and erosion, inflammation, and hyperplasia of the glandular mucosa seen in the 13 week pivotal study.

Hematopoietic effects were seen in rats and dogs. Microscopic changes in rats included hematopoietic cell and lymphoid necrosis, bone marrow hypocellularity, and splenic necrosis in short term studies and hematopoietic cell necrosis in a 13-week study. In dogs, lymphoid depletion in GALT and thymus, bone marrow hypocellularity, and myeloid hyperplasia were seen in one or more studies. Total WBC count was frequently increased, due mainly to increased neutrophils, and likely related to the inflammatory lesions in the skin and gastrointestinal tract. Decreases in RBC parameters and reticulocyte count were seen in most of the rat studies and all dog studies.

Trametinib caused dose-dependent serum phosphatemia in rats and dogs and presumably the related soft tissue mineralization in rat tissues including stomach, kidney, heart, lung, aorta, cornea, and liver, that was shown to be due to calcium deposition. In the exploratory studies, myocardial necrosis, hepatocellular necrosis, renal cortical tubular degeneration, and alveolar/bronchiolar lesions and hemorrhage seen at non-tolerated doses were usually associated with tissue mineralization.

Thickening of the growth plate was observed in the long bones of rats with subepiphyseal infarcts/degeneration observed at higher doses. Serum and urine biomarkers indicated that both bone resorption (urinary deoxypyridinoline-to-creatinine ratio) and formation (serum crosslinked C-telopeptide of type 1 collagen, osteocalcin, tartrate-resistant acid phosphatase) occurred in rats in a 3-day investigative study.

In repeat-dose studies in rats, hepatocellular necrosis and transaminase elevations were seen after 8 weeks at ≥0.062 mg/kg/day (approximately 0.8 times human clinical exposure based on AUC). Mild aminotransferase and alkaline phosphatase increases at ≥0.03 mg/kg/day in dogs correlated with sinusoidal neutrophilia and Kupffer cell activation may have been related to gastrointestinal toxicity.

In mice, lower heart rate, heart weight and left ventricular function were observed without cardiac histopathology after 3 weeks at ≥ 0.25 mg/kg/day trametinib (approximately 3 times human clinical exposure based on AUC) for up to 3 weeks. In adult rats, myocardial mineralization and/or necrosis associated with increased serum phosphorus were seen ≥0.3 mg/kg/day. In juvenile rats, increased heart weight with no histopathology was observed at 0.35 mg/kg/day (approximately 2 times adult human clinical exposure based on AUC).

Trametinib was phototoxic in an in vitro mouse fibroblast 3T3 Neutral Red Uptake (NRU) assay at significantly higher concentrations than clinical exposures (IC_{50} at 2.92 μg/mL, ≥ 130 times the clinical exposure based on C_{max}).

Carcinogenesis and Mutagenesis

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

Reproductive Toxicology

Fertility: No formal fertility studies were conducted. Trametinib may impair female fertility in humans. In adult rat repeat dose studies with female rats given trametinib for up to 13 weeks, alterations in follicular maturation, consisting of increases in cystic follicles and decreases in corpora lutea, were observed at doses ≥ 0.016 mg/kg/day (approximately 0.3 times the human clinical exposure based on AUC). Decreases in corpora lutea were also observed in a 6 week juvenile rat repeat dose study at 0.05/0.35 mg/kg/day. Additionally, in juvenile rats given trametinib, decreased ovarian weights, slight delays in hallmarks of female sexual maturation (vaginal opening and increased incidence of prominent terminal end buds within the mammary gland) and slight hypertrophy of the surface epithelium of the uterus were observed. All of these effects were reversible following an off-treatment period and likely attributable to the pharmacology of trametinib. However, in adult rat and dog toxicity studies up to 13 weeks in duration, there were no treatment effects observed on male reproductive tissues; although systemic exposure to trametinib was at sub-therapeutic levels.

Pregnancy: In reproductive toxicity studies in rats, maternal and developmental toxicity (decreased fetal weights) were seen at ≥0.031 mg/kg/day (approximately 0.3 times human clinical exposure based on AUC). In pregnant rabbits, maternal toxicity and post-implantation loss, including total loss of pregnancy, and foetal toxicity, consisting mainly of incomplete ossification, defects occurred at ≥0.039 mg/kg/day (approximately 0.1 times human clinical exposure based on AUC) and a low incidence of skeletal malformations was seen at ≥0.077 mg/kg/day (approximately 1/6th the human therapeutic AUC).

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PART III: CONSUMER INFORMATION

Pr MEKINIST®
Trametinib Tablets

This leaflet is part III of a three-part "Product Monograph" published when MEKINIST was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MEKINIST. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

MEKINIST is a medicine used to treat a type of skin cancer called melanoma that has spread to other parts of the body or cannot be removed by surgery.

MEKINIST should only be used for people whose cancer has a particular change (mutation) in a gene called "BRAF". You should have your cancer tested for this change in the BRAF gene before starting treatment with MEKINIST.

What it does:

MEKINIST targets proteins made from the modified BRAF gene and slows down or stops the growth of cancer cells.

When it should not be used:

Do not use MEKINIST if you are allergic to trametinib, or any of the other ingredients in MEKINIST (see What the important nonmedicinal ingredients are).

What the medicinal ingredient is:

Trametinib

What the important nonmedicinal ingredients are:

Croscarmellose sodium, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, silicon dioxide (colloidal), and sodium lauryl sulphate.

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

What dosage forms it comes in:

MEKINIST is available as film-coated tablets in strengths of 0.5 mg, 1.0 mg or 2.0 mg.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

MEKINIST should be prescribed and managed by a physician experienced in the administration of anti-cancer agents. Serious side effects include:

- Heart problems
- Eye problems
- Lung complications
- Skin problems, including serious cases of rash, with or without infections
- Blood clots in the veins (deep vein thrombosis) and in the lung (pulmonary embolism)

BEFORE you use MEKINIST talk to your doctor or pharmacist if:

- You are pregnant, maybe pregnant or are planning to become pregnant. You must use effective birth control while you are taking MEKINIST and for 4 months after you stop taking it. You must make sure that you do not get pregnant while receiving MEKINIST, but if you do, inform your doctor immediately. MEKINIST can harm an unborn baby.
- You are breastfeeding. Do not breastfeed if you are taking MEKINIST.
- You have any **heart problems** such as heart failure or problems with the way your heart beats. Your doctor should check your heart function before you start taking MEKINIST and during treatment.
- You have any **eye problems** including blockage of the vein draining the eye (retinal vein occlusion) or swelling in the eye which may be caused by fluid blockage. Your doctor may arrange for you to have an eye exam before you take MEKINIST and while you are taking it.
- You have any **skin problems** including rash or acne-like rash.
- You have any **lung or breathing problems**, including difficulty in breathing often accompanied by a dry cough, shortness of breath and fatigue. Your doctor may arrange to check your lung function before you start taking MEKINIST.

- You have **high blood pressure** (hypertension).
- You have **liver or kidney problems**.

MEKINIST should only be used to treat melanomas with a change (mutation) in the BRAF gene. Your doctor will take a tumour tissue sample, to test whether MEKINIST is suitable for you.

MEKINIST is not recommended in children and adolescents (< 18 years of age).

Heart Problems: MEKINIST can affect how well your heart pumps with each beat. People may be more likely to develop this side effect if they have an existing heart problem. You will be checked for any heart problems while you are taking MEKINIST. Signs and symptoms of heart problems include:

- Feeling like your heart is pounding, racing, or beating irregularly
- Dizziness
- Tiredness
- Feeling lightheaded
- Shortness of breath
- Swelling in the legs

Eye (Vision) Problems: MEKINIST can cause eye problems, including blindness. MEKINIST is not recommended if you have ever had, or are at risk of certain eye conditions including blockage of the vein draining the eye (retinal vein occlusion). Your doctor may advise an eye exam before you take MEKINIST and while you are taking it. Your doctor will ask you to stop taking MEKINIST and refer you to a specialist, if you develop signs and symptoms in your vision that include:

- Colour dots
- Halo (seeing a blurred outline around objects)
- Blurred vision

Lung problems: MEKINIST can cause lung complications, such as interstitial lung disease or pneumonitis and in some cases these can be fatal.

Skin Problems: MEKINIST can cause rash, acne-like rash and infections. Tell your doctor if you develop a rash.

Blood Clots: MEKINIST can cause blood clots in your arms and legs, which can travel to your lungs and can lead to death. Get medical help right away if you have any of 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, especially one larger than the other
- a cool or pale arm or leg

INTERACTIONS WITH THIS MEDICATION

Tell your doctor and pharmacist about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements.

The following list includes some, but not all, of the drugs that may interact with MEKINIST to affect the electrical activity of your heart:

- Antiarrhythmics (drugs that stabilize the heart rhythm function, such as quinidine, procainamide, amiodarone, sotalol, etc.)
- Beta-blockers used to lower blood pressure
- HIV protease inhibitors

It is important to take MEKINIST without food, because food may affect the way MEKINIST is absorbed into your body.

PROPER USE OF THIS MEDICATION

Usual dose:

The usual dose of MEKINIST is one 2.0 mg tablet once a day.

How to take MEKINIST:

Take MEKINIST on an empty stomach at least one hour before or two hours after food.

Swallow the tablet with a full glass of water.

Take MEKINIST at about the same time each day.

Always take MEKINIST exactly as your doctor has told you to. Your doctor may decide that you should take a lower dose if you get side effects.

Don't take more MEKINIST than your doctor has recommended.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take it as soon as you remember. Do not take it if it is close (within 12 hours) to your next dose. Just take the next dose at your regular time. **Do not take more than 1 dose of MEKINIST at a time.**

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, MEKINIST can cause side effects.

Very common side effects – these may affect more than 1 in 10 people:

- Diarrhea
- Feeling sick (*nausea*), being sick (*vomiting*)
- Constipation
- Stomach ache
- Dry mouth
- Lack of energy or feeling weak or tired
- Swelling of hands or feet
- Unusual hair loss or thinning
- Fever (high temperature)
- Cough
- Shortness of breath
- Bleeding (from the gums, eyes, lungs, vagina, rectum and blood in urine)
- Headache
- Nail disorders such as nail bed changes, nail pain, infection and swelling of the cuticles
- High blood pressure - MEKINIST can cause new or worsening high blood pressure (hypertension). Your doctor should check your blood pressure during treatment with MEKINIST. Tell your doctor if you develop high blood pressure, your blood pressure worsens, or you have severe headache, lightheadedness, or dizziness.

Common side effects – these may affect up to 1 in 10 people:

- Inflammation of the follicles in the skin
- Skin rash with pus-filled blisters
- Redness, chapping or cracking of the skin
- Infection of the skin (*cellulitis*)
- Red, painful hand and feet
- Nose bleeds
- Sore mouth or mouth ulcers, inflammation of mucous membranes
- Swelling of the face, localized tissue swelling
- Blurred vision
- Swelling around the eyes
- Eyesight problems
- Feeling weak
- Abnormal heart scans related to how the heart pumps blood
- Abnormal blood test results related to the liver
- Decreased red blood cells (*anemia*)
- Abnormal test related to *creatine phosphokinase*, an enzyme found mainly in heart, brain, and skeletal muscle
- Dehydration (low levels of water or fluid)

Uncommon side effects – these may affect up to 1 in 100 people:

- Swelling of nerves at the back of the eye
- Separation of the light-sensitive membrane in the back of the eye from its supporting layers (*retinal detachment*)

Tell your doctor or pharmacist if any of the side effects listed are or becomes severe or troublesome, or if you notice any side effects not listed in this leaflet.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Very Common	Skin rash, acne-like rash, redness of the face, dry or itching skin		✓	
Common	**Blood clots:** chest pain, sudden shortness of breath or trouble breathing, pain in your legs with or without swelling, swelling in your arms and legs, a cool or pale arm or leg			✓
Uncommon	**Heart problems:** feeling like your heart is pounding, racing, or beating irregularly, dizziness, tiredness, feeling lightheaded, shortness of breath, and swelling in the legs		✓	
	Eye problems: Seeing flashes of light, colour or black dots (floaters), blurred outline around objects (halo), partial loss of vision. These problems can arise from: ▪ Retinal Vein Occlusion (RVO): Blurred or reduced vision. This usually happens in one eye and could occur abruptly ▪ Retinal Pigment Epithelial Detachment (RPEP): Blurred or distorted vision		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
	Lung complications (inflammation of the lung)**:** shortness of breath and cough			✓
	Allergic reaction: Rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.			✓
	Rhabdomyolysis: muscle pain that you cannot explain, muscle tenderness or weakness, generalized weakness (especially if you don't feel well), brownish or discoloured urine		✓	

This is not a complete list of side effects. For any unexpected effects while taking MEKINIST, *contact your doctor or pharmacist.*

HOW TO STORE IT

Keep out of the reach and sight of children.

Store in a refrigerator between 2-8°C in the original package. This medicine is to be protected from light and moisture. Do not remove desiccant.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

http://www.novartis.ca or by contacting the sponsor,

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This leaflet was prepared by:

Novartis Pharmaceuticals Canada Inc.

Last revised: July 31, 2015

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