Medical Officer Review of Prior Approval Labeling Supplement

NDA	204114
SUPPLEMENT	s-29
SDN	1595
SUBMISSION DATE	May 19, 2023
PDUFA DATE	November 19, 2023
PRODUCT	Trametinib
SPONSOR	Novartis
CLINICAL REVIEWER	Leslie Doros
DIVISION DIRECTOR	Steven Lemery

1. RECOMMENDED REGULATORY ACTION

This reviewer recommends approval of the agreed upon labeling changes stated under Section "Conclusions" below.

2. BACKGROUND

Novartis submitted a prior approval labeling supplement to NDA 204114 s-29 on May 19, 2023, to extend the age range of the tumor agnostic indication from patients 6 years of age and older to patients 1 year of age and older. Novartis proposed the following labeling change to the USPI and Medication Guide.

Original labeling changes proposed in s-29

Revised in Highlights:

- *the treatment of adult and pediatric patients ~~6~~**1** year~~s~~ of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.*

Revised in Section 1.6:

BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors:

- *MEKINIST is indicated, in combination with dabrafenib, for the treatment of adult and pediatric patients ~~6~~**1** year~~s~~ of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.*

Revised in Section 8.4 Pediatric Use:

BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors and LGG

- *The safety and effectiveness of MEKINIST in combination with dabrafenib have been established in pediatric patients ~~6~~**1** year~~s~~ of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options; and **pediatric** patients 1 year of age and older with LGG with BRAF V600E mutation who require systemic therapy.*

- *The safety and effectiveness of MEKINIST in combination with dabrafenib have not been established in pediatric patients younger than 1 year ~~old with LGG with BRAF V600E mutation, and in patients < 6 years old with unresectable or metastatic solid tumors with BRAF V600E mutation~~.*

Revised section 12.3 Pharmacokinetics

Pediatric Patients

- *The pharmacokinetics of dabrafenib in glioma and other solid tumors were evaluated in (b) (4) patients aged 1 to < 18 years~~s~~ (b) (4) following a single dose or multiple doses. Pharmacokinetic parameters in patients aged 1 to (b) (4) **< 18** years are within range of values previously observed in adults give the same dose based on weight.*

Original labeling changes proposed to the Medication Guide

What is MEKINST?
MEKINIST is a prescription medicine used:

- *in combination with dabrafenib to treat solid tumors in adults and children ~~6~~**1** year~~s~~ and older*

3. DISCUSSION

Trametinib in combination dabrafenib was granted accelerated approval on June 22, 2022, for:

- the treatment of adult and pediatric patients ≥6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.

No additional clinical information were generated in support of this labeling change. The supplement is based on the benefit:risk profile and dosage established for the liquid formulation in pediatric glioma patients 1 to <6 years of age, and that the tumor agnostic indication can also be considered age agnostic.

4. CONCLUSIONS

The final changes to the USPI are as follows:

Highlights:

- *the treatment of adult and pediatric patients 1 year of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.*

Section 1.6:

BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors:

- *MEKINIST is indicated, in combination with dabrafenib, for the treatment of adult and pediatric patients 1 year of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no*

satisfactory alternative treatment options

Section 8.4 Pediatric Use:

BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors and LGG

- *The safety and effectiveness of MEKINIST in combination with dabrafenib have been established in pediatric patients 1 year of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options; or with LGG with BRAF V600E mutation who require systemic therapy. Use of MEKINIST in combination with dabrafenib for these indications is supported by evidence from studies X2101 and G2201 that enrolled 171 patients (1 to < 18 years) with BRAF V600 mutation-positive advanced solid tumors, of which 4 (2.3%) patients were 1 to < 2 years of age, 39 (23%) patients were 2 to < 6 years of age, 54 (32%) patients were 6 to < 12 years of age, and 74 (43%) patients were 12 to < 18 years of age [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.6, 14.7)].*

  The safety and effectiveness of MEKINIST in combination with dabrafenib have not been established for these indications in pediatric patients less than 1 year old.

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

Section 12.3 Pharmacokinetics

Pediatric Patients

- *The pharmacokinetics of trametinib in glioma and other solid tumors were evaluated in* (b) (4) *patients aged 1 to < 18 years following a single dose or multiple doses. Pharmacokinetic parameters in patients aged 1 to < 18 years are within range of values previously observed in adults give the same dose based on weight.*

The final to the Medication Guide are as follows:

What is MEKINIST?
MEKINIST is a prescription medicine used:

- *in combination with dabrafenib to treat solid tumors in adults and children 1 year and older*

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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