Office of Clinical Pharmacology Review

NDA or BLA Number	N202806/S27, N204114/S29
Link to EDR	\\CDSESUB1\evsprod\NDA202806\0398 \\CDSESUB1\evsprod\NDA204114\0378
Submission Date	05/19/2023
Submission Type	Prior Approval Supplement (Priority Review)
Brand Name	Tafinlar, Mekinist
Generic Name	Dabrafenib, Trametinib
Dosage Form and Strength	TAFINLAR Capsules: 50 mg, 75 mg TAFINLAR Tablets for Oral Suspension: 10 mg MEKINIST Tablets: 0.5 mg, 2 mg MEKINIST for Oral Solution: 4.7 mg
Route of Administration	Orally at least 1 hour before or at least 2 hours after a meal
Approved Indications	Dabrafenib and trametinib combination therapy is indicated 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.
Applicant	Novartis
OCP Review Team	Lili Pan, Ph.D., Hong Zhao, Ph.D. (TL)
OCP Final Signatory	Stacy Shord, Pharm.D., Deputy Division Director

Executive Summary

Tafinlar (NDA 202806) and Mekinist (NDA 204114) in combination are approved for multiple indications, including adults and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation (tumor agnostic, accelerated approval in June 2022) and pediatric patients 1 year of age and older with low-grade glioma (LGG) with BRAF V600E mutation (approved in March 2023). The current submission is a Prior Approval Supplement (PAS) to extend the age from patients aged 6 years of age and older to patients aged 1 year of age and older for the approved tumor agnostic indication:

Dabrafenib in combination with trametinib is indicated for treatment of adult and pediatric patients 1 ~~6~~ 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.

No clinical data were provided in support of this supplement application. Novartis stated that the application is based on the benefit/risk profile and posology established for pediatric patients aged

1 to less than 6 years with LGG. An understanding of the disease in adult and pediatric patients, available safety data and pharmacokinetic information support the extrapolation. The Applicant proposed labeling changes to Indications and Usage and Pediatric Use, as well as minor editorial changes in Pharmacokinetics.

Recommended Dosage

The accelerated approval of tumor agnostic indication was for oral capsule (dabrafenib) and oral tablet (trametinib) dosage forms with minimum body weight requirement of 26 kg and the approval of pediatric LGG indication included an alternative dosage form as tablet for oral suspension (dabrafenib, NDA 217514) and oral solution (trametinib, NDA 217513) with a minimum body weight requirement of 8 kg. The recommended dosages for the solid and liquid dosage forms can be found in Table 1 and Table 2.

The approved recommended dosage for LGG indication in pediatric patients aged 1 year and older was established based on a population PK analysis that included results from 3 pediatric studies: Study G2201 in BRAF V600-positive LGG or relapsed or refractory high-grade glioma, Study A2102 in advanced BRAF V600-mutation positive solid tumors, and Study X2101 in BRAF V600 mutation positive solid tumors.

The approved recommended dosage for the tumor agnostic indication in adults and pediatric patients aged 6 years and older was established based on results from Study X2101 which was conducted in patients with BRAF V600-positive solid tumors.

Table 1. Recommended Dosage for TAFINLAR Capsules and MEKINIST Tablets in Pediatric Patients (Weight-based)

Body weight	Recommended TAFINLAR dosage	Recommended MEKINIST dosage
26 to 37 kg	75 mg orally twice daily	1 mg orally once daily
38 to 50 kg	100 mg orally twice daily	1.5 mg orally once daily
51 kg or greater	150 mg orally twice daily	2 mg orally once daily

Table 2. Recommended Dosage for TAFINLAR Tablets for Oral Suspension and MEKINIST for Oral Solution

Body weight	Recommended TAFINLAR dosage	Recommended MEKINIST dosage total volume of oral solution (trametinib content)
8 kg	(b) (4)	6 mL (0.3 mg) once daily
9 kg		7 mL (0.35 mg) once daily
10 kg		7 mL (0.35 mg) once daily
11 kg		8 mL (0.4 mg) once daily
12 to 13 kg		9 mL (0.45 mg) once daily
14 to 17 kg		11 mL (0.55 mg) once daily
18 to 21 kg		14 mL (0.7 mg) once daily
22 to 25 kg		17 mL (0.85 mg) once daily
26 to 29 kg		18 mL (0.9 mg) once daily
30 to 33 kg		20 mL (1 mg) once daily
34 to 37 kg		23 mL (1.15 mg) once daily

38 to 41 kg	(b) (4)	25 mL (1.25 mg) once daily
42 to 45 kg		28 mL (1.4 mg) once daily
46 to 50 kg		32 mL (1.6 mg) once daily
≥ 51 kg		40 mL (2 mg) once daily

Reviewer's comment: The proposed dosage of dabrafenib and trametinib in pediatric patients aged 1 to < 6 years old is the approved recommended dosage for pediatric patients with LGG with clinical data from studies including tumor agnostic patients; therefore, it is acceptable.

Labeling

Editorial changes in Pediatric Use and Pharmacokinetics sections have been updated accordingly in the labeling and they are acceptable from a clinical pharmacology perspective.

Recommendations

The Office of Clinical Pharmacology reviewed this PAS submission and found it is approvable.

Summary of Labeling Updates

The Office of Clinical Pharmacology recommends the following labeling recommendations. Note that red colored words were Applicant proposed, while blue ones are the FDA recommended modifications.

TAFINLAR USPI

- Revised **Section 8.4 Pediatric Use:** *(Adapted from OCE Pediatric Labeling Working Group Review)*

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

  The safety and effectiveness of TAFINLAR in combination with trametinib 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. Use of TAFINLAR in combination with trametinib 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), and Clinical Studies (14.6, 14.7)]*.

  The safety and effectiveness of TAFINLAR in combination with trametinib have not been established for these indications in pediatric patients less ~~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~~.

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

- Revised **Section 12.3 Pharmacokinetics**:

  Pediatric Patients

  The pharmacokinetics of dabrafenib in glioma and other solid tumors were evaluated in 243 patients aged 1 to < 18 years ~~of age~~ following a single dose or multiple doses. Pharmacokinetic parameters in patients aged 1 to ~~17~~ < 18 years are within range of values previously observed in adults give the same dose based on weight. Weight (6 to 156 kg) had a statistically significant effect on dabrafenib oral clearance in this population.

MEKINIST USPI

- Revised **Section 8.4 Pediatric Use:** *(Adapted from OCE Pediatric Labeling Working Group Review)*

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 BRAFV600E 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. 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), and 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 ~~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~~.

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

- Revised **Section 12.3 Pharmacokinetics**:

Pediatric Patients: The pharmacokinetics of trametinib in glioma and other solid tumors were evaluated in 244 patients aged 1 to < 18 years ~~old~~ 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 given the same dose based on weight. Weight (6 to 156 kg) was found to have a statistically significant effect on trametinib oral clearance in this population.

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/s/

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