PMR Fulfillment – Cross-Disciplinary Team Leader Memorandum

Application Type (NDA/BLA)	NDA and sNDA
Application Number(s)/ supplement number	217514 and 217513 202806 S-25 and 204114 S-25
Received Date	August 24, 2022
PDUFA Goal Date	May 24, 2023
Division/Office	Office of Oncologic Diseases/Division of Oncology 2
Clinical Reviewer	Michael Barbato, Jeannette Nashed
Team Leader	Diana Bradford
Signatory	Nicole Drezner
Product: Established Name (Trade name)	Trametinib (MEKINIST) tablets, for oral use; 0.5 mg, 2 mg and powder for oral solution; 4.7 mg Dabrafenib (TAFINLAR) capsules, for oral use; 50 mg, 75 mg and tablets for oral suspension; 10 mg
Applicant	Novartis Pharmaceuticals Corporation

Executive Summary:

On June 22, 2022, FDA granted accelerated approval to dabrafenib in combination with trametinib (NDA 202806 S-22 and 204114 S-22) 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. The following post-marketing requirements were included in the approval letters:

Dabrafenib (202806)

- 4298-2 Develop age appropriate pediatric formulations (dabrafenib dispersible tablets for oral suspension, and trametinib powder for oral solution), and evaluate these in Study CDRB436G2201 ("Phase II Open-label Global Study to Evaluate the Effect of Dabrafenib in Combination With Trametinib in Children and Adolescent Patients With BRAF V600 Mutation Positive Low Grade Glioma (LGG) or Relapsed or Refractory High Grade Glioma (HGG)").
  Final Report Submission: 10/2022

- 4298-3 Conduct Study CDRB436G2201 ("Phase II Open-label Global Study to Evaluate the Effect of Dabrafenib in Combination With Trametinib in Children and Adolescent Patients With BRAF V600 Mutation Positive Low Grade Glioma (LGG) or Relapsed or Refractory High Grade Glioma [HGG]") to confirm safety and efficacy in pediatric

patients with glioma one year of age and above.
Final Report Submission: 10/2022

Trametinib (204114)

- 4297-2 Develop age appropriate pediatric formulations (dabrafenib dispersible tablets for oral suspension, and trametinib powder for oral solution), and evaluate these in Study CDRB436G2201 ("Phase II Open-label Global Study to Evaluate the Effect of Dabrafenib in Combination With Trametinib in Children and Adolescent Patients With BRAF V600 Mutation Positive Low Grade Glioma (LGG) or Relapsed or Refractory High Grade Glioma (HGG)").
  Final Report Submission: 10/2022
- 4297-3 Conduct Study CDRB436G2201 ("Phase II Open-label Global Study to Evaluate the Effect of Dabrafenib in Combination With Trametinib in Children and Adolescent Patients With BRAF V600 Mutation Positive Low Grade Glioma (LGG) or Relapsed or Refractory High Grade Glioma [HGG]") to confirm safety and efficacy in pediatric patients with glioma one year of age and above.
  Final Report Submission: 10/2022

On August 17, 2022, the Applicant submitted NDA 217513 (trametinib) and NDA 217514 (dabrafenib) for new formulations of trametinib (oral solution) and dabrafenib (tablets for oral suspension) appropriate for patients who cannot swallow pills. The Applicant's proposed indication was for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy. On August 24, 2022, the Applicant submitted NDA 202806 S-25 and NDA 204114 S-25, as supplements to the NDAs for dabrafenib and trametinib, respectively, with the intent to allow the indication stated above to be granted for the existing solid dosage forms in addition to the new dosage forms. Dabrafenib is administered orally, twice daily, and trametinib is administered orally, once daily; the recommended dosages for trametinib and dabrafenib are based on age and body weight. The supplementary applications rely entirely upon data submitted to the new NDAs, 217513 and 217514. The review team has recommended regular approval for NDAs 217513 and 217514 and the associated efficacy supplements to the existing NDAs.

Assessment and Recommended Regulatory Action

The review team considers that PMRs 4297-2 and 4298-2 have been fulfilled by the submission of NDAs 217513 and 217513, applications for new age-appropriate pediatric formulations of dabrafenib and trametinib.

The study report for Study CDRB436G2201 was submitted to NDAs 217513 and 217514 (and associated supplements 202806 S-25 and 204114 S-25) to establish the safety and efficacy of dabrafenib in combination with trametinib in patients pediatric patients with glioma (specifically patients with LGG with BRAF V600E mutations) one year of age and above. Therefore, the review team considers that PMRs 4297-3 and 4298-3 requiring the conduct of the study have been fulfilled. In order to obtain results of the final analysis of overall survival from Study G2201 and obtain longitudinal analyses to understand any impact of treatment with dabrafenib and trametinib on visual acuity (an important functional outcome for patients with LGG involving the optic pathway), a post-marketing commitment will be issued with the approval letters for NDAs NDAs 217513 and 217514 (and associated supplements 202806 S-25 and 204114 S-25). The post-marketing commitment is provided below:

> Complete Study CDRB436G2201, entitled "Phase II open-label global study to evaluate the effect of dabrafenib in combination with trametinib in children and adolescent patients with BRAF V600 mutation positive Low Grade Glioma (LGG) or relapsed or refractory High Grade Glioma (HGG)", and provide the final analysis for overall survival (OS) and progression free survival once all patients with LGG have been followed for at least 2 years. Include an analysis of change in visual acuity over the course of treatment with dabrafenib and trametinib for patients who enrolled on the study due to impaired vision.

Please refer to the Approval letters for the post-marketing requirements and commitments for NDAs NDAs 217513 and 217514 (and associated supplements 202806 S-25 and 204114 S-25). The Approval letters will state that the PMRs PMRs 4297-3 and 4298-3 and 4297-2 and 4298-2 have been fulfilled.

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/

DIANA L BRADFORD
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