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APPLICATION NUMBER:

208255Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action
Division Director (DD) and Cross Discipline Team Leader (CDTL) Memorandum

Date	February 2, 2018
From	Jeffrey S. Murray MD, MPH, Deputy Director
Subject	Division Director Summary Review
NDA #	**208255**
Applicant Name	Mylan Pharmaceuticals Inc., USA (Mylan)
Date of Submission	July 25, 2017
PDUFA Goal Date	January 25, 2018
Proprietary Name / Established (USAN) Name	Symfi Lo Efavirenz 400 mg/Lamivudine 300 mg/Tenofovir disoproxil fumarate 300 mg Fixed Dose Combination (EFV 400 mg/LMV 300 mg/TDF 300 mg FDC)
Dosage Forms / Strength	Tablets
Proposed Indication(s)	As a complete regimen for the treatment of HIV in adults and adolescents at least 12 years old and weight at least 35 kg
Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Clinical/Statistical Review	Kirk Chan-Tack, M.D./Wen Zeng, Ph.D.
Office of Product Quality Review	Application Team Lead: Stephen Miller, Ph.D.
Microbiology Review	Lalji Mishra, Ph.D.
Clinical Pharmacology Review	Islam Younis, Ph.D.

OND=Office of New Drugs

1. Background

Because there are no reference listed drugs for this FDC and because the applicant is relying on FDA's previous findings for multiple aspects of the safety and efficacy of the individual agents, this NDA was submitted as a 505(b)(2) application. Mylan previously received tentative approval of the FDC EFV 600mg, LMV 300mg, and TDF 300 mg under NDA 22142 on Sept. 9, 2009. Mylan received tentative approvals for each of the individual components of this FDC under separate ANDAs and received tentative approval of the FDC EFV 400 mg, LMV 300 mg, and TDF 300 mg under NDA 208255 on March 10, 2017. This resubmission is in support of final marketing approval in the United States (U.S.), which is possible with the expiration of relevant patents and exclusivity. The tentative approval of this FDC with a reduced dose (400 mg) of EFV required an additional clinical trial to demonstrate the comparability of this dose compared to the previously approved dose. The Kirby Institute

conducted ENCORE1, owns the study data, and submitted the data as a pre-IND so that Mylan and other commercial sponsors can reference it. Mylan obtained a right-of-reference for this trial data.

The basis of approval for this fixed dose combination is summarized in my previous CDTL/Division Director Memorandum for this NDA dated March 7, 2017. Post-tentative approval the applicant was required to address several items as outlined in the tentative approval (TA) letter including:

1) draft final printed labels and labeling that comply with all U.S. regulations (uniqueness of drug product appearance per 21CFR 206; child-resistant packaging per 16 CFR 1700, etc.)
2) a proposal for addressing pediatric studies that complies with the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), which requires that all NDAs, Biological License Applications (BLAs), or supplemental applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration contain a pediatric assessment unless this requirement is waived, deferred, or inapplicable
3) a package insert that includes telephone contact for the Antiretroviral Pregnancy Registry and which requires applicants to join the pregnancy registry.

2. CMC (Chemistry, Manufacturing, Controls)

For details on CMC, refer to the Quality Assessment review prepared by multiple reviewers in collaboration with the Application Technical Lead, Stephen Miller. The review team recommends Approval of NDA 208255 for EFV 400mg/LMV 300mg/TDF 300 mg. The applicant appropriately updated the application and addressed outstanding issues needed for final approval as outlined in the TA letter.

3. Pediatrics

PREA was triggered for this application. The PeRC agreed with a waiver for requiring studies of pediatric patients weighing less than 35kg because the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients in lower weight bands. PeRC recommended adding a statement about the assessment for pediatric patients of sufficient weight to receive the doses of the component drugs included in the fixed dose combination. PeRC agreed that no further studies are necessary.

Dosing for pediatric patients weighing at least 35 kg is included in patient labeling because the approved dose of EFV 600 mg (and other components of this FDC) is the same for adults and pediatric patients in a comparable weight band (weighing at least 35 kg). In addition, the pharmacokinetics of EFV is linear, and the clinical noninferiority (HIV-RNA < 50 copies) of EFV 400 mg compared to EFV 600 mg was considered robust across multiple demographic and baseline covariates in adults.

It was determined that 3-year exclusivity for Epivir (lamivudine) was granted in error. Thus, it was not necessary to consider the exclusivity implications, if any, for purposes of this approval

4. Other Relevant Regulatory Issues

There are no unresolved regulatory issues precluding final approval action.

5. Labeling

Please refer to David Araojo's labeling memorandum that summarizes changes in the labeling since initial TA. As a condition for final marketing approval the package insert now includes information on the Antiretroviral Pregnancy Registry.

6. Decision/Action/Risk Benefit Assessment

- Regulatory Action

I fully confer with the Approval of EFV 400mg, LMV 300 mg, TDF 300 mg tablets as a complete regimen for the treatment of HIV in adults and pediatric patients weighing at least 35 kg.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEFFREY S MURRAY
02/02/2018