CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212477Orig1s000

PRODUCT QUALITY REVIEW(S)

FDA U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 212477
Assessment # 2

Drug Product Name	ledipasvir and sofosbuvir, LDV and SOF, (GS-5885 and GS-7977)
Dosage Form	Oral Pellets
Strength	33.75 mg /150 mg; 45 mg/200 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Gilead Sciences, Inc.
US agent, if applicable	Applicant's Responsible Official: Linda Lintao, RAC, Associate Director, Regulatory Affairs

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0007	6/25/2019	Quality
eCTD 0011	8/01/2019	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	N/A	N/A
Drug Product	George Lunn	Balajee Shanmugam
Manufacturing	Nathan Davis	Rapti Madurawe
Microbiology	N/A	N/A
Biopharmaceutics	Mei Ou	Elsbeth Chikhale
Regulatory Business Process Manager	Shamika Brooks	
Application Technical Lead	Erika Englund	
Laboratory (OTR)	N/A	
Environmental	George Lunn	Balajee Shanmugam

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS, Other Documents and Consults

Refer to Review #1

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

From the Product Quality perspective, ***NDA 212477*** *is recommended for* ***Approval***. The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on August 22, 2019. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Refer to Review #1

Proposed Indication(s) including Intended Patient Population	Treatment of chronic hepatitis C in pediatric patients
Duration of Treatment	12-24 weeks
Maximum Daily Dose	The recommended doses are: 90mg/400 mg per day (adults and pediatric patients >35 kg); 45mg/200 mg per day (pediatric patients 17-35 kg) and 33.75mg/150 mg per day (pediatric patients at least 3 years of age and < 17 kg).
Alternative Methods of Administration	The oral pellets can be taken in the mouth without chewing, or with non-acidic food. The oral pellets can be administered with non-acidic food, such as pudding, chocolate syrup, mashed potato and ice cream.

B. Quality Assessment Overview

Drug Substance: Adequate

Refer to Review #1

Drug Product: Adequate

Refer to Review #1

Labeling: Adequate

Refer to Review #1

Manufacturing: Adequate

Refer to Review #1 for additional discussion.

In Review #1, there were outstanding concerns regarding the packaging process due to the OAI facility status and missing commercial manufacturing equipment. The outcome of the (b) (4) (primary packaging) was OAI due, in part, to missing commercial manufacturing equipment per the FDA-483.

An addendum to the original review (Review #2) was completed on 8/21/2019. The final outcome of the PAI review and EIR review can be found in CMS WA # 283608. The final outcome is adequate after review of FDA-483 responses and the firm response to an RAI. The inspection final classification is VAI and therefore the NDA is recommended for approval from an OPF perspective.

Biopharmaceutics: Adequate

Note, at the time that IQA #1 was finalized, the biopharmaceutics review #1 could not be archived in Panorama. This IQA includes both biopharmaceutics review #1, and the addendum to biopharmaceutics review #1, which recommended the NDA for approval.

Biopharmaceutics Review #1 described a pending IR regarding the controls in place to assure the integrity of the taste masking coat at batch release and during the shelf life of the product. The pending IR also requested a risk mitigation strategy to assure the integrity of the taste masking coat, which could include a two-phase dissolution test.

On 08/01/2019, the Applicant responded that the FDA's recommended two-stage dissolution method is not necessary because adequate formulation and manufacturing controls were developed, evaluated, and implemented to ensure the integrity of the taste-mask coating of the drug

product at the time of batch release and during its shelf life. The biopharmaceutics reviewer found that the provided information/data for the formulation design, manufacturing controls, and results of the taste assessment and coating integrity tests, fully support the integrity of the taste-mask coating of the SOF pellets, and the information also demonstrates that the coating remains intact during storage. Therefore, based on the satisfactory justification and the overall information provided, this Reviewer agrees with the Applicant's proposal of not using a two-stage dissolution method to control the quality of the proposed drug product. It is noted that the Applicant also proposes to continue testing the primary stability batches of the proposed drug product through their shelf life using the coating integrity test. The NDA is recommended for approval from a biopharmaceutics perspective.

Microbiology (if applicable): Choose an item.

N/A

C. Risk Assessment

Refer to Review #1

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

None

2. Drug Substance Deficiencies

None

3. Drug Product Deficiencies

None

4. Labeling Deficiencies

None

5. Manufacturing Deficiencies

None

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

None

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