CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215973Orig1s000
215974Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	215973 & 215974
PDUFA Goal Date	February 28, 2022
TTT #	2022-24
Reviewer Name	Theresa Ng, PharmD, BCPS
Team Leader	Yasmeen Abou-Sayed, PharmD
Associate Director for REMS	Laura Zendel, PharmD, BCPS
Design and Evaluation	
Review Completion Date	December 13, 2022
Subject	Evaluation of Need for a REMS
Established Name	lenacapavir
Trade Name	Sunlenca
Name of Applicant	Gilead Sciences
Therapeutic Class	inhibitor of HIV-1 capsid function
Formulation	oral and subcutaneous injection (SC)

Dosing Regimen

Initiation Option 1 (simplified dosing regimen)	
Day 1	927 mg by subcutaneous injection (2 x 1.5 mL injections) and 600 mg orally (2 tablets)
Day 2	600 mg orally (2 tablets)
Initiation Option 2	
Day 1	600 mg orally (2 tablets)
Day 2	600 mg orally (2 tablets)
Day 8	300 mg orally (1 tablet)
Day 15	927 mg by subcutaneous injection (2 x 1.5 mL injections)
Maintenance	
927 mg by subcutaneous injection (2 x 1.5 mL injections) every 6 months (26 weeks) from the date of the last injection +/-2 weeks.	

Table of Contents

1 Introduction

This is an addendum to the risk evaluation and mitigation strategy (REMS) review which was completed by the Division of Risk Management (DRM) in the previous review cycle for Sunlenca (lenacapavir) New Drug Applications (NDAs) 215973 (subcutaneous [SC] injection) and 215974 (oral tablet) and submitted to DARRTS on February 22, 2022 (DARRTS reference ID: 4941682).[1] Sunlenca is proposed for (b) (4) [redacted]. Efficacy and safety were demonstrated for lenacapavir (LEN) over placebo based on the interim analyses of the clinical trials in the first review cycle of this application.[2] There were low rates of adverse events (AEs), serious adverse events (SAEs), and treatment emergent adverse events (TEAEs) except for injection site reactions (ISRs). The review team determined that labeling and routine pharmacovigilance was adequate to ensure the benefits of the drug outweighs the risks of injection site reactions (ISRs) and a REMS would not be necessary for Sunlenca (lenacapavir). However, as approval of the lenacapavir oral tablet (NDA 215974) is contingent on the approval of lenacapavir subcutaneous (SC) injection (NDA 215973), complete response letters (CRLs) were issued for both NDAs due to product quality deficiencies for the injection formulation related to the (b) (4) [redacted] and glass contamination.[3] Of note, the European Medicines Agency (EMA) recently granted marketing authorization to lenacapavir in August 2022.

Gilead submitted a Class 2 resubmission of the complete response consisting of supplemental efficacy and safety updates to the CAPELLA (up to Week 52) and CALIBRATE (up to Week 54), and product quality data to address the deficiencies in the CRLs issued on June 27, 2022.[4] This addendum serves to finalize DRM's review of Sunlenca (lenacapavir), NDAs 215973 and 215974.

1.1 Regulatory History

The following is a summary of the regulatory history for NDA 215973 and 215974 relevant to this review:

- 6/28/2021: The applicant submitted NDAs 215973 and 215974 for the (b) (4) [redacted]
- 2/28/ 2022: The Agency issued a CRL to both NDAs 215973 and 215974 due to CMC compatibility and microbiology data
- 6/27/2022: The Applicant submitted a Class 2 resubmission of NDAs 215973 and 215974 in response to the CRLs
- 8/17/2022: EMA granted lenacapavir marketing authorization. Risk minimization measures include prescribing information and antiretroviral pregnancy registry to collect data on risk of birth defects with antiretroviral drugs.

2 Benefit Assessment

Reference ID: 5093194

In the initial review cycle, the clinical reviewers determined that LEN demonstrated superior efficacy over placebo in the treatment of heavily treatment experience (HTE) patients with HIV (PWH) in the Phase 2/3 pivotal study, Study GS-US-200-4625 also known as CAPELLA , and was further supported by a Phase 2 study, Study GS-US-200-4334 also known as CALIBRATE.[2]

For this review cycle, Gilead provided further efficacy data in support of LEN with results up to Week 52 for CAPELLA and Week 54 for CALIBRATE. Per the study protocol, Week 26 and Week 52 HIV-1 RNA levels were planned to be evaluated as secondary endpoints for CAPELLA. The clinical reviewer concluded that the proportions of subjects who achieved virologic suppression (HIV-1 RNA <50 copies/mL) with LEN for CAPELLA for both cohorts 1 and 2 at Week 52 were reasonably consistent (30/36 [83%]) with those at Week 26 (29/36 [81%]).

For CALIBRATE, the primary endpoint was the proportion of subjects with virologic suppression at Week 54. The clinical reviewer determined the LEN combined arm in CALIBRATE had a similar response rate to CAPELLA (86.6%) , which supports the efficacy results of CAPELLA; the difference and 95% confidence interval (CI) between the LEN and comparator arm was -5.3 (CI: -17.3, 6.7) (see the Division of Antivirals (DAV's) Class 2 Resubmission integrated review for specific details of the extended data analyses).[5]

3 Risk Assessment

Gilead provided additional cumulative safety updates to Week 52 for CAPELLA and Week 54 for CALIBRATE. As in the first review cycle, additional support for the safety of LEN includes interim data from Study GS-US-200-5709 (an ongoing, phase 1 study in healthy participants).

At the time of the NDA resubmissions, 1508 individuals were enrolled in clinical studies and received at least one dose of LEN, regardless of route (SC, per oral [PO], or intravenous [IV]), formulation, or population (healthy, patient living with HIV [PLWH]). The total number of PLWH who received SC LEN at the proposed dose/duration was 195. In CAPELLA, the mean (standard deviation [SD]) exposure was 596.5 days (102.8 days). No new safety signals were identified with the safety data updates. Overall, there were no SAEs and very few ≥ Grade 3 adverse events (AEs) that were considered by the investigator to be study-drug related in any of the studies. Since the first cycle review, one additional death was reported in CAPELLA due to hypoxemic respiratory failure/ pneumonia. The study investigators concluded that it was not drug-related, and the clinical reviewer agreed with their assessment. There were no additional deaths reported in CALIBRATE since the first cycle review. Most laboratory abnormalities were generally not clinically significant (Grade 1 or 2) and occurred in subjects who had previous underlying conditions such as diabetes.

LEN associated resistance substitutions was detected in 53% (n=9) of the confirmed virologic failure subjects and four virologic failure subjects had emergent resistance substitutions to components of the optimized background regimen (OBR) in CAPELLA. The clinical reviewer concluded though LEN resistance substitutions do not confer cross-resistance to other antiretrovirals (ARVs), it is important to use LEN as a component of a complete ARV regimen as LEN resistance emerges readily in patients with history of virologic failures.

Reference ID: 5093194

Injection site reactions (erythema, swelling, pain, nodule, inflammation, induration, site mass) remain as the most common adverse drug reaction (ADR) for LEN SC injection (CAPELLA: 65.3% and CALIBRATE (55.3%); most ISRs were Grade 1 or 2 in severity. Subjects with ADRs for injection site nodules and undulations, respectively, were reported in 18 (25%) and 11 (15%), in CAPELLA, and 15 (15%), and 13 (13%) in CALLIBRATE. For some subjects, the duration of induration and nodules were much longer (lasting approximately 1 to 12 months) than other injection site reactions (e.g., erythema, pain and swelling; lasting approximately 1 day to 3 weeks). In total, 3 of 105 participants (2.9%) in the SC LEN total group discontinued study drug due to ISRs (injection site induration, injection site erythema, and injection site swelling); all were nonserious and Grade 1 in severity. However, due to a lack of understanding of the histopathology at the injection sites in these patients, and the unique properties of the drug product solution, the clinical reviewer is not able to determine whether there is permanent tissue damage associated with this. DAV consulted the Division of Dermatology and Dentistry (DDD) for recommendations on labeling and additional safety information for the applicant to submit.[6] To communicate the ISRs in labeling, DDD agreed with an expanded characterization of ISRs in Section 6 (Adverse Reactions) but felt inclusion of ISRs as a Warning (Section 5) was not necessary as there were no reports of AEs that were considered serious or life-threatening. DDD recommended that injection site nodules be followed to resolution or stabilization, where possible, in ongoing trials. The clinical reviewer agreed with the need for additional information to fully understand if there are any contributing factors of injections site reactions with LEN, particularly for subjects who have prolonged resolution with nodules and indurations. A postmarketing requirement will be required to further characterize ISRs.

4 Discussion

As the approval of the lenacapavir oral tablet (NDA 215974) is contingent on the approval of lenacapavir subcutaneous (SC) injection (NDA 215973), Complete Response Letters (CRLs) were issued in the first review cycle on February 28, 2022, due to product quality deficiencies including 1) incompatibility between drug product and borosilicate glass vials, and 2) incomplete information with respect to Container Closure Integrity Testing for the lenacapavir SC product. Gilead submitted a response to the CRLs on June 27, 2022, to address the deficiency identified in the CRLs and provide updated efficacy and safety updates in its NDA application resubmission. At the time of this review, the reviewers from the Chemistry Manufacturing and Controls (CMC) division reported in the wrap-up meeting that the product quality data are under review and the Applicant's responses to the product deficiencies identified in the CRLs are generally satisfactory (see CMC's product quality review).[a] This addendum focuses on the additional clinical and safety data submitted in the Class 2 resubmission to the CR.

As noted in the first review cycle, the interim analyses from the pivotal trial CAPELLA consisting of data up to Week 26 and supported by the phase 2 supportive trial, CALLIBRATE, with data up to Week 28, demonstrated superior efficacy of lenacapavir in combination with OBR in the treatment of patients with HIV-1 infection with multidrug resistant HIV-1 infection failing their current antiretroviral regimen. Except for ISRs, the safety profile was considered acceptable. In this current review cycle, Gilead

[a] Internal Wrap-up meeting discussion, dated November 14, 2022.

Reference ID: 5093194

submitted data up to Week 52 for CAPELLA and Week 54 for CALLIBRATE. The clinical reviewer concluded the extended data from CAPELLA and CALLIBRATE further supported the efficacy of lenacapavir that was demonstrated in the initial review cycle. No new safety signals were identified with the supplemental safety data. ISRs continue to be the most common adverse drug reaction with lenacapavir subcutaneous injection with some subjects experiencing prolong durations of nodules and undulations. Resistance emergence data reinforced the need to use LEN as a component of a complete antiretroviral (ARV) regimen as LEN resistance emerges readily in patients with history of virologic failures. There were no events in the lenacapavir NDA resubmission safety update that changed the clinical reviewer's opinion about the benefit/risk assessment of lenacapavir for treatment of multi-drug resistant HIV-1 infection in HTE subjects. As noted earlier, lenacapavir (both oral and subcutaneous presentations) was recently approved by the EMA in August 2022; (b) (4) .

DRM determined that a REMS is not necessary to ensure the benefits of lenacapavir outweigh the risks. DRM agrees with DAV that labeling and postmarketing pharmacovigilance are adequate to ensure the benefits outweigh the risks of ISRs. Labeling will include expanded adverse reaction information on ISRs (section 6) as recommended by DDD. In addition, a postmarketing study will be required to further characterize the ISRs.

9 Conclusion & Recommendations

Based on the available data, no new safety signals were identified in this Class 2 resubmission and a REMS is not necessary to ensure the benefits outweigh the risk of injection site reactions associated with Sunlenca for subcutaneous injection. This addendum serves to finalize DRM's REMS review for Lenacapavir NDAs 215973 and 215974.

10 Appendices

10.1 References

1. Ng T. DRM. REMS Review for Lenocapavir NDA 215973 and 215974, dated February, 22, 2022.
2. FDA. DAV. Integrated Review of Lenacapavir NDAs 21573 and 21574, dated February 28, 2022.
3. FDA. DAV. Complete Response Letter for Lenacapavir NDA 215972 and 215974, dated February 28, 2022.
4. Gilead. Class 2 responses to the CRLs to NDA 215973 and 215974, dated June 27, 2022/.
5. DAV. Draft Integrated Review for NDA 215973 and 215974, accessed December 5, 2022.
6. Brown P. DDD. Consult #2116: Lenacapavir (NDA 215973, NDA 215974), dated December 29, 2021.

Reference ID: 5093194

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Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	215973 & 215974
PDUFA Goal Date	February 28, 2022
OSE RCM #	2021-1277
Reviewer Name	Theresa Ng, PharmD, BCPS
Team Leader	Yasmeen Abou-Sayed, PharmD
Associate Director for REMS	Laura Zendel, PharmD, BCPS
Design and Evaluation	
Review Completion Date	February 22, 2022
Subject	Evaluation of Need for a REMS
Established Name	lenacapavir
Trade Name	Sunlenca
Name of Applicant	Gilead Sciences
Therapeutic Class	inhibitor of HIV-1 capsid function
Formulation	oral and subcutaneous injection
Dosing Regimen	Initiation: 927 mg by subcutaneous injection (2 x 1.5 mL injections) and 600 mg orally (2 tablets) on Day 1; 600 mg orally (2 tablets) on Day 2. Maintenance: 927 mg by subcutaneous injection (2 x 1.5 mL injections) every 6 months (26 weeks) +/-2 weeks.

Reference ID: 5101080

Table of Contents

Reference ID: 5101080

Executive Summary

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Sunlenca (lenacapavir), subcutaneous and tablet formulations, is necessary to ensure the benefits outweigh its risks. Gilead Sciences, Inc. submitted New Drug Applications (NDAs) 215973 and 215974 for lenacapavir with the proposed indication for the treatment of (b) (4) . The risk associated with the use of lenacapavir includes injection site reactions. The applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRM) is currently not able to determine whether a REMS is needed to ensure the benefits of lenacapavir outweigh its risks. The pivotal clinical trial demonstrated efficacy of lenacapavir to treat heavily-treatment-experienced (HTE) patients with multiple drug resistant HIV-1 by acting as a selective inhibitor of HIV-1 capsid function. The major risk associated with lenacapavir is injection site reactions, including induration and nodules. Injection site reactions were not reported as serious or severe and did not require drug discontinuation in the clinical trials. However, the mechanism of injection site reactions is unclear. In addition, particulate contaminants were observed in the glass vials containing the product solution. This is due to the incompatibility of (b) (4) drug solution and the bosilicate glass vials. Until further analysis to assess the contributing factors of injection site reactions, and comprehensive compatibility data for alternative glass vials are provided, the benefit-risk profile of lenacapavir cannot be determined. For this review cycle, the review team recommends a Complete Response for this application.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Sunlenca (lenacapavir) is necessary to ensure the benefits outweigh its risks. Gilead Sciences, Inc submitted New Drug Applications (NDAs) 215973 and 215974 for lenacapavir with the proposed indication for the treatment of (b) (4) . This application is under review in the Division of Antiviral Products (DAV). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Lenacapavir, a new molecular entity, is a first-in-class, multistage, selective inhibitor of HIV-1 capsid function proposed for the treatment of (b) (4) .[a] Lenacapavir inhibits HIV-1 at multiple points in the

[a] FDAAA factor (F): whether the drug is a new molecular entity

Reference ID: 5101022

viral lifecycle, including interfering with capsid-mediated nuclear uptake of pre-integration complexes and impairing virion production and proper capsid core formation.[1]

Lenacapavir is proposed to be available as a both an oral 300 mg tablet (NDA 215974) and a 309 mg/mL solution (NDA 215973) in a single-dose vial for subcutaneous injection. The proposed treatment regimen in adults (b) (4) consists of a two-day initiation dosing period and once every 6 months maintenance dosing. On treatment Day 1, the recommended dose is 927 mg by subcutaneous injection and 600 mg orally. On treatment Day 2, the recommended dose is 600 mg orally. For maintenance, the recommended dose is 927 mg by subcutaneous injection once every 6 months from the date of the last injection (+/- 2 weeks). During the maintenance period, if more than 28 weeks have elapsed since the last injection and if clinically appropriate to continue treatment, restart the initiation dosage regimen from Day 1.[2,b] Lenacapavir injection is for administration into the abdomen by a healthcare provider. Lenacapavir solution (NDA 215973) was granted fast track designation on March 23, 2018 and for oral tablet (NDA 215974) on September 19, 2018. Breakthrough therapy designation was granted for lenacapavir on May 30, 2019.

2.2 Regulatory History

The following is a summary of the regulatory history for NDA 215973 and 215974 relevant to this review:

- 03/23/2018: Fast Track designation granted for lenacapavir solution (NDA 215973) for subcutaneous injection.
- 09/19/2018: Fast Track designation granted for lenacapavir tablet (NDA 215974) for oral administration.
- 5/30/2019: Breakthrough Therapy designation granted for lenacapavir (NDA 215974).
- 6/28/2021: Gilead submitted NDAs 215973 and 215974.
- 8/26/2021: Priority review granted for lenacapavir NDAs 215973 and 215974.
- 11/19/2021: Mid-Cycle meeting communication – a REMS is not anticipated at this time.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

HIV-1 is a life-threatening and serious disease. HIV-1 is a transmissible virus that attacks and weakens the immune system. There are thirty-eight million people infected worldwide and approximately 26 million on ARV treatment.[3,c] People with HIV have a high risk of morbidity related to HIV-1 disease

[b] FDAAA factor (D): The expected or actual duration of treatment with the drug

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

Reference ID: 5101082

progression, opportunistic infections, comorbidities, and HIV/AIDS-related death.[d] There remains a high unmet medical need for new well-tolerated therapies for individuals failing currently available therapies as a result of multi-drug resistance and have limited treatment options due to medication intolerance or safety considerations.

3.2 Description of Current Treatment Options

Most currently approved antiretroviral (ARV) drugs target 1 of the following 4 steps of the HIV lifecycle: the inhibition of viral entry, reverse transcription, viral DNA integration, or the proteolysis of viral polyproteins essential for virion maturation. The goal of therapy is to achieve durable HIV-1 viral suppression. Standard-of-care for patients failing currently available therapies as a result of multi-drug resistance requires the use of at least 2, preferably 3, fully active anti-retroviral agents which include drugs from different classes. The classes of anti-HIV drugs include non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), and integrase and fusion inhibtors.[4] Treatment side effects can include nausea, vomiting, or diarrhea, heart disease, kidney/liver damage, weakened bones, abnormal cholesterol levels, and higher blood sugar.[5] Some new regimens are comprised of more than 3 ARV agents.

For patients with multi-drug resistant HIV-1 infection, providers must individually tailor combination treatment regimens based on previous antiretroviral exposure, cumulative viral resistance testing, drug safety and tolerability and comorbid conditions. When options are limited, using a newly approved agent such as ibalizumab and fostemsavir is recommended. Ibalizumab, a CD4-directed post-attachment HIV-1 inhibitor used in combination with other antiretrovirals, is administered intravenously as a single loading dose of 2000mg followed by a maintenance dose of 800 mg every 2 weeks. The drug does not have a Boxed Warning but has hypersensitivity reactions including infusion-related reactions, immune reconstitution inflammatory syndrome, and embryo-fetal toxicity listed as Warnings & Precautions. Fostemsavir, a gp120-directed attachment inhibitor, used in combination with other antiretrovirals is administered as one 600 mg tablet taken orally twice daily.[3] The drug does not have a Boxed Warning but has immune reconstitution inflammatory syndrome, QTc prolongation with higher than recommended doses, elevations in hepatic transaminases in patients with hepatitis B or C virus co-infection, and risk of adverse reactions or loss of virologic response due to drug interactions listed as Warnings & Precautions.

4 Benefit Assessment

The efficacy and safety of lenacapavir for the treatment of HIV-1 infection in adults (b) (4) with multidrug resistant HIV-1 infection failing their current antiretroviral regimen was derived from a Phase 2/3 study, Study GS-US-200-4625 [NCT04150068], and further supported by a Phase 2 study, Study GS-US-200-4334 [NCT04143594].

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

Reference ID: 5101022

Study 4625 (CAPELLA) is an ongoing Phase 2/3, ongoing, randomized, placebo-controlled, multicenter study in North America and the Dominican Republic of lenacapavir in combination with an optimized background regimen in HTE patients with HIV (PWH) with multidrug resistance. Patients were randomized in a blinded fashion and in a 2:1 ratio to receive either oral lenacapavir 600 mg on Days 1 and 2 and 300 mg on Day 8 (Cohort 1A) or placebo (Cohort 1B) during the Functional Monotherapy Period while they continued their failing regimen. Patients were enrolled into Cohort 2 when Cohort 1 was full or if they did not meet the criteria for randomization into Cohort 1. Similarly, patients in Cohort 2 received oral lenacapavir 600 mg on Days 1 and 2 and 300mg on Day 8 during the Oral Lead-in Period while continuing their optimized background regimen (OBR). During the maintenance period (i.e., 14 days after the first dose of oral lenacapavir), participants in cohort 1A and 2 received subcutaneous injection of lenacapavir 927 mg and every 6 months (26 weeks) thereafter and initiated their OBR on Day 1 subcutaneous.[6] Participants in cohort 1B received oral lenacapavir 600 mg on Days 15 and 16 and 300 mg on day 22 and initiated their OBR on Day 15; they received subcutaneous lenacapavir injection 927 mg while continuing their OBR. Overall, 72 patients were enrolled: 24 patients in Cohort 1A, 12 in Cohort 1B, and 36 in Cohort 2. Patient demographics amongst the cohorts were similar. The majority were male (75%) and White (40%). The median age was 52 years (Cohort 1 and 2 were 54 years and 49 years, respectively) and median BMI was 25 kg/m^2. Baseline disease characteristics for both cohorts were consistent with the profile of the HTE population.

The primary efficacy endpoint is the proportion of participants in Cohort 1 achieving a reduction in HIV-1 RNA of ≥ 0.5 $\log_{10}$ copies/mL from baseline at the end of the 14-day Functional Monotherapy Period. Secondary efficacy endpoints include the proportion of participants in Cohort 1 with HIV-1 RNA < 50 and < 200 copies/mL at Weeks 26 and 52 using the FDA-defined snapshot algorithm[e]. Only Week 26 data is submitted for this application as the study is ongoing. In this study, lenacapavir met the primary endpoint of superiority to placebo and the secondary endpoint.[5] Close to 88% of participants who received lenacapavir had a reduction in HIV-1 RNA of ≥ 0.5 log10 copies/mL from baseline than those who received placebo (16.7%)(P<0.0001). For the secondary endpoint, the percentages of patients with HIV-1 RNA < 50 and < 200 copies/mL at Week 26 were 81% and 89% respectively.[f] The clinical review team stated that because this study was uncontrolled during the maintenance period and the analysis included follow-up through only Week 26, there is some uncertainty surrounding contribution of lenacapavir to the durability of virologic response. In addition, the clinical reviewer noted emergence of lenacapavir genotype resistance was found in 4 patents (36%) with virological failures in this study's HTE HIV-1 patients and that it is important for lenacapavir to be used as a component of a complete active ARV regimen.

[e] The FDA Snapshot algorithm defines success of antiretroviral therapy (ART) by viral load < 50 cp/mL without ART change (mostly for adverse events [AEs]). Notably, a viral load <50 cp/mL but with a drug-related AE is regarded as treatment success. However, drug-related AEs might increase the risk of ART failure.

[f] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

Reference ID: 5101082

Study 4334 (CALIBRATE) is an ongoing phase 2 randomized, open-label, active-controlled, multicenter study of lenacapavir in combination with other ARV agents in treatment-naïve PWH. One hundred eighty-three patients were randomized in a 2:2:2:1 ratio to 1 of 4 treatment groups comparing lenacapavir with study defined HIV regimens. Patient demographic and baseline disease characteristics were similar across the treatment groups. The study participants were mostly male (93%), and the median age was 29 years with a median BMI of 25.8 kg/m^2. There was a balance between race and ethnicity.

The primary efficacy endpoint is the proportion of participants with HIV-1 RNA< 50 copies/mL at Week 54 as determined by the US FDA-defined snapshot algorithm. Because the majority of participants had not yet reached Week 54 at the time of the NDA submission, the primary endpoint was not analyzed. Secondary efficacy endpoints include the proportion of participants with HIV-1 RNA < 50 copies/mL at Weeks 28, 38, and 80 (US FDA-defined snapshot algorithm) and changes from baseline in HIV-1 RNA and CD4 cell count at week 28, 38, 54, and 80. Only Week 28 is reported as of the NDA submission, as the study is ongoing. Lenacapavir met the secondary endpoint at Week 28 where close to 94% of patients had HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm.

5 Risk Assessment & Safe-Use Conditions

The safety assessment of lenacapavir was primarily based on patients from Studies 4625 and 4334. In the analysis of Study 4625, the percentage of patients who received Lenacapavir in cohorts 1 and 2 who experienced adverse events (AEs) was 91.7% (66 of 72 patients) and 4 patients (5.6%) experienced serious AEs (SAEs).[3] There was one subject reported in Study 4625 who experienced an AE of immune reconstitution inflammatory syndrome (IRIS) attributed to ongoing medical history of chronic hepatitis B. One patient in cohort 2 died in the study, experiencing an AE of cancer not related to study drug; the clinical reviewer concurs with this finding.

Similar percentages of AEs and SAEs were seen in Study 4334. In Study 4334, 87% (136 of 157 patients) experienced AEs, 8 patients (5%) experienced SAEs, and 1.9% of patients (2 of 105 patients) discontinued study drug prematurely due to AEs of injection site induration; both occurrences were nonserious and Grade 1 in severity. No Grade 3 or higher AEs was seen in Study 4334. In Study 4625, Grade 3 or higher AEs were reported for 13 participants (18.1%) primarily related to injection site reactions (ISRs), rash, abdominal abscess and immune reconstitution inflammatory syndrome. No Grade 3 or higher AEs were reported in Study 4334 for >1 participant in any treatment group. There were no deaths by week 28 in Study 4334.

5.1 Injection Site Reactions (ISRs)

The most commonly reported treatment-related adverse events in Study 4625 for the lenacapavir arm were ISRs. Approximately 29% of patients on lenacapavir experienced injection site swelling, 26% experienced erythema, 25% experienced injection site pain, 19% experienced nodules and 13% experienced induration at the injection site. One patient discontinued study drug due to a treatment emergent adverse event (TEAE) of injection site nodules, but is categorized as Grade 1 in severity. Four patients (13.9%) in cohort 1 and 8 patients (22.2%) in cohort 2 experienced Grade 3 or higher AEs. Similarly, in Study 4334, the most commonly reported treatment-related AEs were ISRs in patients who

Reference ID: 5101082

received lenacapavir. Approximately 15% experienced injection site swelling, 14% experienced injection site erythema, and 14% experienced injection site pain. Injection site nodules and induration occurred at 19% and 12% respectively. The clinical reviewer noted that in Studies 4625 and 4334, the durations of induration and nodules were much longer (approximately 6-12 months) than other injection site reactions (e.g., erythema, pain and swelling lasting approximately 1 to 3 weeks). The maximum size for the majority of injection site injection site nodules and indurations were approximately 1 to 4 cm and appeared more visible in participants who were leaner with little fat tissue in the abdomen. No biopsies or histopathologic examinations were obtained from any subjects experiencing injection site nodules or indurations.

The review team had concerns of incompatibility of the borosilicate vials with the (b) (4) drug product solution. Reviewers from the Office of Product Quality (OPQ) observed particulate contaminants in the glass vials containing the product solution.[6] Without histological analysis, it is unknown whether the particulates from the glass vial delamination contributed to the injection site reactions.

6 Expected Postmarket Use

The likely prescribers will be infectious disease specialists in outpatient or inpatient settings. The subcutaneous injections are to be administered into the abdomen by a healthcare provider in a healthcare setting while the oral tablets may be taken by the patients at home or in the healthcare provider setting. These prescribers should be familiar with how to manage the injection site reactions that are associated with lenacapavir as ISRs are a common risk of injectable drug products.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for lenacapavir beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

HIV-1 is a life-threatening and serious disease. HTE patients infected with multi-drug resistant HIV-1 who cannot achieve complete virologic suppression with antiretroviral therapy have a high risk of morbidity related to HIV-1 disease progression, opportunistic infections, comorbidities, and HIV/AIDS-related death. Standard-of-care for patients failing currently available therapies as a result of multi-drug resistance contain at least 2, preferably 3, fully active anti-retroviral agents which include drugs from different classes. The clinical reviewer concluded that the clinical trials demonstrated effectiveness of lenacapavir in the treatment of HTE in PWH and the safety data appears to show low rates of AEs, SAEs, and TEAEs with the exception of injection site reactions.

However, this application will be issued a Complete Response (CR) as there are safety concerns related to the compatibility of the lenacapvir injectable solution and glass vials containing the product solution. The Office of Product Quality (OPQ) analyzed the drug substance data submitted by the Applicant and reported concerns of particulates observed in the glass vials containing lenacapavir.[6] Lenacapivir sodium is formulated as a concentrated, a single strength injection product, composed (w/w) of (b) (4)% active ingredient (b) (4)% water and (b) (4)% polyethylene glycol (PEG) 300 in a glass vial; the role of PEG is to

Reference ID: 5101082

(b) (4) resulting in a high pH solution (pH 9 to 10). After subcutaneous administration, (b) (4) which then releases lenacapavir to the circulatory system over a six-month period. Gilead initially proposed to market the product with two different vials: borosilicate glass vials and aluminosilicate glass vials, but focused primarily on the borosilicate vials. Significant pitting of the borosilicate glass vials was observed after filling and (b) (4) process and (b) (4). The Applicant subsequently proposed to withdraw the borosilicate glass vials in the submission and provided further data in support of aluminosilicate glass vials; however, the OPQ reviewer determined that the data currently submitted did not appear sufficient. In addition, the OPQ reviewer noted that the Applicant has not submitted adequate responses to multiple inquiries regarding the Container Closure Integrity Test information after the (b) (4). Therefore, considering the drug product solutions unusually high pH coupled with the (b) (4) and the incompatibility of the borosilicate vials with the drug product solution, the OPQ reviewer concluded that this application cannot be approved without a comprehensive report of the stability batches over the period of time to unambiguously demonstrate that the aluminosilicate glass vials are compatible with proposed high pH and (b) (4) of lenacapavir injection formulation. In addition, without further histological analysis, the role of glass particulates seen in the product solution and injection site reaction is not clear.

9 Conclusion & Recommendations

Based on the available data, this reviewer is unable to determine whether a REMS is necessary to ensure the benefits outweigh the risks.

Though efficacy was established with lenacapavir for the treatment of HTE in PWH, the review division recommends a Complete Response due to deficiencies in product quality and safety concerns of incompatibility of lenacapavir solution and the glass vials and concerns of its involvement in injection site reactions. Because the benefit-risk has not been determined, at this time, we are unable to formulate recommendations for risk management, specifically REMS.

10 Appendices

10.1 References

1. Gilead Sciences. Clinical Overview for Sunlenca (lenacapavir), June 28, 2021
2. Gilead Sciences. U.S Prescribing Information for Sunlenca (lenacapavir), June 28, 2021
3. Gilead Sciences. Summary of Clinical Safety for Sunlenca (lenacapavir), June 28, 2021
4. Sax, Paul., & Rajesh T. Gandhi & Allyson Bloom. Acute and early HIV infection: Treatment *UpToDate*. 2020. www.uptodate.com/contents/acuteandearlyhivinfectiontreatment. Accessed August 15, 2021.
5. Gilead Sciences. Summary of Clinical Efficacy for Sunlenca (lenacapavir), June 28, 2021
6. Claffrey D. OPQ. Integrated Quality Review for lenacapavir, NDA 215973, dated January 12, 2022.

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