Professional Information

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Lenacapavir 300 mg Tablet Gilead

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains lenacapavir sodium equivalent to 300 mg of lenacapavir.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Beige, capsule-shaped, film-coated tablets of dimensions 10 mm x 21 mm, debossed with “GSI” on one side of the tablet and “62L” on the other side of the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lenacapavir Gilead tablet is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to prevent sexually acquired HIV-1 in adults and adolescents weighing at least 35 kg for:

- oral loading
- oral bridging

(see sections 4.2 and 5.1).

4.2 Posology and method of administration

All individuals must be screened for HIV-1 prior to initiating Lenacapavir Gilead and routinely thereafter as clinically appropriate (see sections 4.3 and 4.4).

Individuals must have a negative HIV-1 test prior to initiating Lenacapavir Gilead.

If recent (<1 month) exposures to HIV-1 are suspected or clinical symptoms consistent with acute HIV-1 infection are present, HIV-1 status should be reconfirmed.

Prior to starting Lenacapavir Gilead, healthcare professionals should select individuals for whom the required initiation and 6-monthly maintenance injection dosing schedule is appropriate, and counsel individuals about the importance of adherence to scheduled Lenacapavir Gilead dosing visits (see section 4.4).

Posology

The Lenacapavir Gilead dosing schedule in adults and adolescents weighing at least 35 kg consists of a required initiation dosing (subcutaneous injections and oral tablets) followed by once every 6-months maintenance dosing (subcutaneous injections) (Table 1).

Initiation

On Day 1, the required dose is 927 mg of Lenacapavir Gilead administered by subcutaneous injection and 600 mg taken orally. On Day 2, the required dose is 600 mg taken orally.

Table 1: Dosing schedule for Lenacapavir Gilead initiation

Time	
Dose of Lenacapavir Gilead: Initiation[a]	
Day 1	927 mg subcutaneous injection (2 x 1,5 ml injections[b]) 600 mg orally (2 x 300 mg tablets)
Day 2	600 mg orally (2 x 300 mg tablets)

[a] The complete initiation dosing schedule, consisting of subcutaneous injections and oral tablets, is required; the efficacy of Lenacapavir Gilead has only been established with this dosing schedule.

[b] Two injections, with the second injection at least 5 centimetres from the first injection (see Method of Administration in the Lenacapavir Gilead solution for injection Professional Information).

Missed initiation dose

If the Day 1 or Day 2 oral initiation dose (600 mg) is missed, it should be taken as soon as possible. Day 1 and Day 2 doses should not be taken on the same day.

Planned missed injections

During the maintenance dosing, if an individual plans to miss a scheduled 6-month injection visit by more than 2 weeks, Lenacapavir Gilead tablets may be used for oral bridging on an interim basis (for up to 6 months if needed), until

injections resume. Oral bridging should be initiated within 26 to 28 weeks from the last injection. The dosing schedule is 300 mg (1 tablet) taken orally once every 7 days. Resume the maintenance injection dosage within 7 days after the last oral dose.

Vomiting

If the individual vomits within 3 hours of taking an oral dose of Lenacapavir Gilead, another oral dose should be taken. If the individual vomits more than 3 hours after taking an oral dose of Lenacapavir Gilead there is no need to take another oral dose of Lenacapavir Gilead, and the scheduled dosing regimen should continue.

Special populations

Elderly

No dose adjustment of Lenacapavir Gilead is required for elderly individuals (see section 5.2).

Renal impairment

No dose adjustment of Lenacapavir Gilead is required in individuals with mild, moderate, or severe renal impairment (creatinine clearance [CrCl] ≥ 15 mL/min). Lenacapavir Gilead has not been studied in individuals with end stage renal disease (CrCl < 15 mL/min or on renal replacement therapy) (see section 5.2), therefore Lenacapavir Gilead should be used with caution in these individuals.

Hepatic impairment

No dose adjustment of Lenacapavir Gilead is required in individuals with mild or moderate hepatic impairment (Child-Pugh Class A or B). Lenacapavir Gilead has not been studied in individuals with severe hepatic impairment (Child-Pugh Class C) (see section 5.2), therefore Lenacapavir Gilead should be used with caution in these individuals.

Paediatric population

Safety and efficacy of Lenacapavir Gilead has been established in adolescents weighing at least 35 kg.

Method of administration

For oral use.

Lenacapavir Gilead tablets should be taken orally with or without food (see section 5.2). The film-coated tablet should not be chewed, crushed, or split, because the effects on lenacapavir absorption have not been studied.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Use in individuals with unknown HIV-1 status (see section 4.4).
Co-administration with strong inducers of CYP3A, P-gp, and UGT1A1, other than rifampicin, such as:

- anticonvulsants: carbamazepine, phenytoin
- herbal products: St. John's wort (*Hypericum perforatum*) (see section 4.5).

4.4 Special warnings and precautions for use

Prevention strategy

Lenacapavir Gilead should only be used to prevent HIV-1 acquisition in individuals confirmed to be HIV-negative. Confirm HIV-1 negative status prior to initiation of Lenacapavir Gilead and routinely thereafter as clinically appropriate in individuals receiving Lenacapavir Gilead.

Use Lenacapavir Gilead to prevent HIV-1 acquisition as part of a strategy to reduce the risk of sexually transmitted infections (STIs). Select individuals for whom the required initiation and every 6-month maintenance injection dosing schedule is appropriate. Non-adherence to the required initiation and maintenance dosing schedule (see section 4.2) may lead to HIV-1 acquisition. Counsel and support individuals on adhering to the Lenacapavir Gilead administration schedule, on the use of other measures to prevent STIs, and on the importance of testing for HIV-1 and other STIs.

Risk of resistance

There is a risk of developing resistance to lenacapavir if an individual acquires HIV-1 either before or when receiving Lenacapavir Gilead, or following discontinuation of Lenacapavir Gilead. Lenacapavir Gilead alone does not constitute a complete regimen for HIV-1 treatment. Individuals who are confirmed to have HIV-1 must immediately begin a complete HIV-1 treatment regimen to reduce the risk of developing resistance.

Long-acting properties

Residual concentrations of lenacapavir may remain in the systemic circulation of individuals for prolonged periods (up to 12 months or longer).

If Lenacapavir Gilead is discontinued and it is clinically appropriate to continue PrEP, alternative forms of PrEP should be considered and initiated within 28 weeks of the last Lenacapavir Gilead injection.

Co-administration of other medicines

Co-administration with medicinal products that are moderate inducers of CYP3A and P-gp, other than rifabutin, is not recommended (see section 4.5).

Co-administration with medicinal products that are strong inhibitors of CYP3A, P-gp, and UGT1A1 together (i.e. all 3 pathways) is not recommended (see section 4.5).

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on the pharmacokinetics of lenacapavir

Lenacapavir is a substrate of CYP3A, P-gp and UGT1A1. Strong inducers of CYP3A, P-gp, and UGT1A1 may significantly decrease plasma concentrations of lenacapavir which may result in reduced effectiveness of Lenacapavir Gilead. Concomitant administration of Lenacapavir Gilead with strong inducers of CYP3A, P-gp, and UGT1A1, other than rifampicin, is contraindicated (see section 4.3); dose adjustment of Lenacapavir Gilead is required if rifampicin is co-administered (see Table 2). Moderate inducers of CYP3A and P-gp may decrease

plasma concentrations of lenacapavir. Concomitant administration of Lenacapavir Gilead with moderate inducers of CYP3A and P-gp, other than rifabutin, is not recommended (see section 4.4); dose adjustment of Lenacapavir Gilead is required if rifabutin is co-administered (see Table 2).

Strong inhibitors of CYP3A, P-gp and UGT1A1 together (i.e., all 3 pathways) may significantly increase plasma concentrations of lenacapavir, therefore co-administration is not recommended (see section 4.4).

Strong CYP3A4 inhibitors alone or strong inhibitors of CYP3A4 and P-gp together do not result in a clinically meaningful increase in lenacapavir exposure.

Effect of lenacapavir on the pharmacokinetics of other medicines

Lenacapavir is a moderate inhibitor of CYP3A and a P-gp inhibitor. Caution is advised if Lenacapavir Gilead is co-administered with a sensitive CYP3A and/or P-gp substrate with a narrow therapeutic index. Lenacapavir is not a clinically meaningful inhibitor of BCRP and does not inhibit OATP.

Table 2: Interactions between Lenacapavir Gilead and other medicines

Medicinal product by therapeutic areas	**Effects on concentrations. Mean percent change in AUC, C_{max}**	**Recommendation concerning co-administration with Lenacapavir Gilead**
ANTICONVULSANTS		
Carbamazepine Phenytoin	Interaction not studied. Co-administration of carbamazepine, oxcarbazepine, phenobarbital, or phenytoin with lenacapavir may decrease lenacapavir plasma concentrations.	Co-administration is contraindicated (see section 4.3).
Oxcarbazepine Phenobarbital		Co-administration is not recommended (see section 4.4). Alternative anticonvulsants should be considered.
HERBAL PRODUCTS		
St. John's wort *(Hypericum perforatum)*	Interaction not studied. Co-administration of St. John's wort may decrease lenacapavir plasma concentrations.	Co-administration is contraindicated (see section 4.3).
ANTIMYCOBACTERIALS		

Rifampicin[a,b] (600 mg once daily) (strong inducer of CYP3A, and an inducer of P-gp and UGT)	Lenacapavir: AUC: ↓84 % C_{max}: ↓55 %	If rifampicin or rifabutin is co-administered, maintain the usual Lenacapavir Gilead dosing schedule and administer additional dose(s) of Lenacapavir Gilead as follows: <u>Rifampicin:</u> • In individuals receiving Lenacapavir Gilead, rifampicin may be co-administered starting at least 2 days after Lenacapavir Gilead is first initiated. • On the day rifampicin is initiated, administer 927 mg of Lenacapavir Gilead subcutaneously (2 x 1,5 ml injections) and 600 mg of Lenacapavir Gilead orally (2 x 300 mg tablets), and • On the day after rifampicin initiation, administer 600 mg of Lenacapavir Gilead orally (2 x 300 mg tablets). • If rifampicin is co-administered for longer than 6 months, continue to administer additional doses of Lenacapavir Gilead as described
Rifabutin Rifapentine	Interaction not studied. Co-administration of rifabutin and rifapentine may decrease lenacapavir plasma concentrations.	

		above, every 6 months following the day of rifampicin initiation. <u>Rifabutin:</u> • On the day rifabutin is initiated, administer 463,5 mg of Lenacapavir Gilead subcutaneously (1 x 1,5 ml injection). • If rifabutin is co-administered for longer than 6 months, continue to administer additional doses of Lenacapavir Gilead as described above, every 6 months following the day of rifabutin initiation. After stopping rifampicin or rifabutin, maintain the usual Lenacapavir Gilead dosing schedule. Concomitant administration with rifapentine is not recommended.
ANTIRETROVIRAL MEDICINES		
Atazanavir/cobicistat [b,c,d] (300 mg/150 mg once daily) (strong inhibitor of CYP3A, and an inhibitor UGT1A1 and P-gp)	Lenacapavir: AUC: ↑ 321 % C_{max}: ↑ 560 %	Co-administration of lenacapavir and strong inhibitors of CYP3A, P-gp, and UGT1A1 is not recommended (see section 4.4).

Efavirenz [b,c,d] (600 mg once daily) (moderate inducer of CYP3A and an inducer of P-gp)	Lenacapavir: AUC:↓ 56 % C_{max}:↓ 36 %	
Cobicistat [b,c,d] (150 mg once daily) (strong inhibitor of CYP3A and an inhibitor of P- gp)	Lenacapavir: AUC: ↑ 128 % C_{max}:↑ 110 %	No dose adjustment of lenacapavir is required.
Darunavir/cobicistat [b,c,d] (800 mg/150 mg once daily) (strong inhibitor of CYP3A, and an inhibitor and inducer of P-gp)	Lenacapavir: AUC:↑ 94 % C_{max}:↑ 130 %	
Tenofovir alafenamide[c,e,f] (25 mg) (substrate of P-gp)	Tenofovir alafenamide: AUC:↑ 32 % C_{max}:↑ 24 % Tenofovir[h]: AUC:↑ 47 % C_{max}:↑ 23 %	No dose adjustment of tenofovir alafenamide is required.
ERGOT DERIVATIVES		
Dihydroergotamine Ergotamine	Interaction not studied. Plasma concentrations of these medicinal products may be increased when co-administered with lenacapavir.	Caution is warranted when dihydroergotamine or ergotamine, is co-administered with Lenacapavir Gilead.
PHOSPHODIESTERASE-5 (PDE-5) INHIBITORS		
Sildenafil Tadalafil Vardenafil	Interaction not studied. Plasma concentration of PDE-5 inhibitors may be increased when co-administered with lenacapavir.	Use of PDE-5 inhibitors for pulmonary arterial hypertension: Co-administration with tadalafil is not recommended. Use of PDE-5 inhibitors for erectile dysfunction: Sildenafil: A starting dose of 25 mg is recommended. Vardenafil: No more than 5 mg in a 24-hour period. Tadalafil:

		• For use as needed: no more than 10 mg every 72 hours • For once daily use: dose not to exceed 2,5 mg
CORTICOSTEROIDS (systemic)		
Dexamethasone Hydrocortisone/cortisone	Interaction not studied. Plasma concentrations of corticosteroids may be increased when co-administered with lenacapavir. Plasma concentrations of lenacapavir may decrease when co- administered with systemic dexamethasone.	Co-administration of Lenacapavir Gilead with corticosteroids whose exposures are significantly increased by CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. Initiate with the lowest starting dose and titrate carefully while monitoring for safety. Caution is warranted when systemic dexamethasone is co-administered with Lenacapavir Gilead, particularly for long-term use. Alternative corticosteroids should be considered.
HMG-CoA REDUCTASE INHIBITORS		
Lovastatin Simvastatin	Interaction not studied. Plasma concentrations of these medicinal products may be increased when co-administered with lenacapavir.	Initiate lovastatin and simvastatin with the lowest starting dose and titrate carefully while monitoring for safety (e.g. myopathy).
Atorvastatin		No dose adjustment of atorvastatin is required.
Pitavastatin[c,e] (2 mg single dose; simultaneous or 3 days after lenacapavir) (substrate of OATP)	Pitavastatin: AUC:↔ C_{max}:↔	No dose adjustment of pitavastatin and rosuvastatin is required.

Rosuvastatin[c,e] (5 mg single dose) (substrate of BCRP and OATP)	Rosuvastatin: AUC: ↑ 31 % C_{max}: ↑ 57 %	
ANTIDYSRHYTHMICS		
Digoxin	Interaction not studied. Plasma concentration of digoxin may be increased when co-administered with lenacapavir.	Caution is warranted and therapeutic concentration monitoring of digoxin is recommended.
SEDATIVES/HYPNOTICS		
Midazolam[c,e] (2,5 mg single dose; oral; simultaneous administration) (substrate of CYP3A)	Midazolam: AUC: ↑ 259 % C_{max}: ↑ 94 % 1-hydroxymidazolam[g]: AUC: ↓ 24 % C_{max}: ↓ 46 %	Caution is warranted when midazolam or triazolam, is co-administered with Lenacapavir Gilead.
Midazolam[c,e] (2,5 mg single dose; oral;1 day after lenacapavir) (substrate of CYP3A)	Midazolam: AUC: ↑ 308 % C_{max}: ↑ 116 % 1-hydroxymidazolam[g]: AUC: ↓ 16 % C_{max}: ↓ 48 %	
Triazolam	Interaction not studied. Plasma concentration of triazolam may be increased when co-administered with lenacapavir.	
ANTICOAGULANTS		
Direct Oral Anticoagulants (DOACs) Rivaroxaban Dabigatran Edoxaban	Interaction not studied. Plasma concentration of DOAC may be increased when co-administered with lenacapavir.	Due to potential bleeding risk, dose adjustment of DOAC may be required. Consult the Summary of Product Characteristics of the DOAC for further information on use in combination with moderate CYP3A inhibitors and/or P-gp inhibitors.
ANTIFUNGALS		
Voriconazole[a,b,h] (400 mg twice daily/200 mg twice	Lenacapavir: AUC:↑ 41 % C_{max}:↔	No dose adjustment of lenacapavir is required.

daily) (strong CYP3A inhibitor)		
Itraconazole Ketoconazole	Interaction not studied. Plasma concentration of lenacapavir may be increased when co-administered with itraconazole or ketoconazole.	
H2-RECEPTOR ANTAGONISTS		
Famotidine[a,b] (40 mg once daily, 2 hours before lenacapavir)	Famotidine: AUC:↑ 28 % C_{max}:↔	No dose adjustment of famotidine is required.
ORAL CONTRACEPTIVES		
Ethinylestradiol Progestins	Interaction not studied. Plasma concentrations of ethinylestradiol and progestins may be increased when co-administered with lenacapavir.	No dose adjustment of ethinylestradiol and progestins is required.
GENDER AFFIRMING HORMONES (feminising or masculinising)		
17β-estradiol Anti-androgens Progestogen Testosterone	Interaction not studied. Plasma concentrations of these medicinal products may be increased when co-administered with lenacapavir.	No dose adjustment of these gender affirming hormones is required.

a Fasted.
b This study was conducted using lenacapavir 300 mg single dose administered orally.
c Fed.
d These antiretroviral medicinal products are probes for the referenced enzymes/transporters and are not to be co- administered with lenacapavir for PrEP.
e This study was conducted using lenacapavir 600 mg single dose following a loading regimen of 600 mg twice daily for 2 days, single 600 mg doses of lenacapavir were administered with each co -administered medicinal product.
f Tenofovir alafenamide is converted to tenofovir *in vivo*.
g Major active metabolite of midazolam.
h This study was conducted using voriconazole 400 mg loading dose twice daily for a day, followed by 200 mg maintenance dose twice daily.

In vitro studies

Lenacapavir is not a substrate, inducer, or inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. Lenacapavir is not an inducer of CYP3A4.

Lenacapavir is not an inhibitor of UGT1A1, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE 2-K.

Lenacapavir is not a substrate of BCRP, OATP1B1, or OATP1B3.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women (369 pregnancy outcomes) indicate no malformative or feto/neonatal toxicity of lenacapavir. The rates of adverse pregnancy outcomes in participants who received Lenacapavir Gilead were similar to reported background rates. Lenacapavir exposures during each trimester of pregnancy and postpartum were comparable to those in non-pregnant participants (see section 5.2).

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, foetal development, parturition or postnatal development (see section 5.3).

The use of Lenacapavir Gilead may be considered during pregnancy, if clinically appropriate.

Breast-feeding

Lenacapavir is present in human milk. Lenacapavir was detected at very low levels in infants who were breastfed by individuals who became pregnant while receiving Lenacapavir Gilead (see section 5.2). No adverse effects of lenacapavir in breastfed infants have been observed.

Lenacapavir Gilead can be used during breast-feeding.

Fertility

There are no data on the effects of lenacapavir on human male or female fertility. Animal studies indicate no effects of lenacapavir on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Lenacapavir Gilead is expected to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

No adverse reactions to Lenacapavir Gilead taken orally were identified in adults or adolescents in PURPOSE 1 and PURPOSE 2.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting reporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

If overdose occurs the individual must be monitored for signs or symptoms of adverse reactions (see section 4.8). Treatment of overdose with Lenacapavir Gilead consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the individual. As lenacapavir is highly protein bound, it is unlikely to be significantly removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, other antivirals, ATC code: J05AX31

Mechanism of action

Lenacapavir is a multistage, selective inhibitor of HIV-1 capsid function that directly binds to the interface between capsid protein (CA) subunits. Lenacapavir inhibits HIV-1 replication by interfering with multiple, essential steps of the viral lifecycle, including capsid-mediated nuclear uptake of HIV-1 proviral DNA (by blocking nuclear import proteins binding to capsid), virus assembly and release (by interfering with Gag/Gag-Pol functioning, reducing production of CA subunits), and capsid core formation (by disrupting the rate of capsid subunit association, leading to malformed capsids).

Antiviral activity and selectivity *in vitro*

The antiviral activity of lenacapavir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, PBMCs, primary monocyte/macrophage cells, and CD4+ T-lymphocytes. The EC_{50} and selectivity (CC_{50}/EC_{50}) values ranged from 30 to 190 pM and 140,000 to >1,670,000, respectively, for wild-type (WT) HIV-1 virus. The protein-adjusted EC_{95} for lenacapavir was 4 nM (3,87 ng per ml) in the MT-4 T-cell line for wild-type HIV-1 virus.

Lenacapavir displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including subtypes A, A1, AE, AG, B, BF, C, D, E, F, G, H.

Lenacapavir was 15- to 25-fold less active against HIV-2 isolates relative to HIV-1.

Resistance

In cell culture

HIV-1 variants with reduced susceptibility to lenacapavir have been selected in cell culture. In vitro resistance selections with lenacapavir identified 7 mutations in CA: L56I, M66I, Q67H, K70N, N74D/S, and T107N singly or in dual combination. Phenotypic susceptibility to lenacapavir was reduced 4- to >3,226-fold, relative to WT virus.

In clinical trials

In the PURPOSE 1 trial of sexually active cisgender women, no participants receiving Lenacapavir Gilead acquired HIV-1 during the trial. In the PURPOSE 2 trial of sexually active cisgender men, transgender women, transgender men, and gender nonbinary individuals, genotyping was performed on 2 participants receiving Lenacapavir Gilead who acquired HIV-1 during the trial and who had HIV- 1 RNA ≥200 copies/ml. Lenacapavir resistance-associated N74D capsid substitutions were observed in both participants.

Cross resistance

The *in vitro* antiviral activity of lenacapavir was determined against a broad spectrum of HIV-1 site-directed mutants and patient-derived HIV-1 isolates with resistance to the 4 main classes of antiretroviral agents (NRTIs, NNRTIs, INSTIs and PIs; n = 58), as well as to viruses resistant to maturation inhibitors (n = 32), and to viruses resistant to the entry inhibitors (EI) class (fostemsavir, ibalizumab,

maraviroc, and enfuvirtide; n = 42). These data indicated that lenacapavir remained fully active against all variants tested, thereby demonstrating a non-overlapping resistance profile. In addition, the antiviral activity of lenacapavir in patient isolates was unaffected by the presence of naturally occurring Gag polymorphisms.

Effects on electrocardiogram

In a parallel-design thorough QT/QTc study, lenacapavir had no clinically relevant effect on the QTcF interval. At supratherapeutic exposures of lenacapavir (16-fold higher than the therapeutic exposures of lenacapavir), the predicted mean (upper 90 % confidence interval) increase in QTcF interval was 2,6 (4,8) msec, and there was no association (p = 0,36) between observed lenacapavir plasma concentrations and change in QTcF.

Clinical data

The efficacy and safety of Lenacapavir Gilead in preventing the acquisition of HIV-1 were evaluated in two randomised, double-blind, active-controlled, multinational trials (PURPOSE 1 and PURPOSE 2).

PURPOSE 1 was in sexually active cisgender women. Background HIV-1 incidence was calculated in the screened population (n = 8094). Participants were randomised to receive Lenacapavir Gilead (n = 2134), or one of the two active control treatment in a 2:2:1 ratio.

PURPOSE 2 was in sexually active cisgender men, transgender women, transgender men, and gender nonbinary individuals. Background HIV-1 incidence was calculated in the screened population (n = 4634). Participants were randomised to receive Lenacapavir Gilead (n = 2179) or active control treatment (n = 1086) in a 2:1 ratio.

PURPOSE 1

In PURPOSE 1, the median age of participants was 21 years (range, 16-26); and 99,9 % were Black. Baseline characteristics in the randomised participants were similar to the screened population.

The primary outcome was diagnosis of incident HIV-1 infection per 100 person-years compared with the background HIV incidence, as determined by a recent infection testing algorithm. Incident HIV-1 infections were observed in none (0 %) of the participants in the Lenacapavir Gilead group compared to 16 (1,5 %)

participants in one of the active control arms. Lenacapavir Gilead demonstrated superiority with a 100 % reduction in the risk of HIV-1 acquisition over background HIV-1 incidence and over one of the active control arms.

PURPOSE 2

In PURPOSE 2, the median age of participants was 29 years (range, 17-74); 67 % were non-White; 63 % were Hispanic/Latine; and 22 % identified as gender-diverse (transgender women, transgender men, and gender nonbinary people). Baseline characteristics in the randomised participants were similar to the screened population.

The primary outcome was diagnosis of incident HIV-1 infection per 100 person-years compared with the background HIV incidence, as determined by a recent infection testing algorithm. Incident HIV-1 infections were observed in 2 (0,1 %) participants in the Lenacapavir Gilead group compared to 9 (0,8 %) participants in the control arm. Lenacapavir Gilead demonstrated superiority with a 96 % reduction in the risk of HIV-1 acquisition over background HIV-1 incidence and an 89 % reduction over the control arm. HIV-1 infections in the two participants receiving Lenacapavir Gilead were diagnosed using standard serologic HIV testing, with no evidence of delayed diagnosis of HIV-1.

5.2 Pharmacokinetic properties

Absorption

Subcutaneous administration

Absolute bioavailability of lenacapavir following subcutaneous administration was 91 %. Subcutaneously administered lenacapavir forms a drug depot whereby lenacapavir is slowly released from the site of administration, with peak plasma concentrations occurring 77 to 84 days post dose.

Oral administration

Lenacapavir is absorbed following oral administration with peak plasma concentrations occurring approximately 4 hours after administration of Lenacapavir Gilead. Absolute bioavailability following oral administration of lenacapavir is low (approximately 4 to 7 %). Lenacapavir is a substrate of P-gp.

Lenacapavir AUC, C_{max} and T_{max} were comparable following administration of a low fat (~400 kcal, 25 % fat) or high fat (~1000 kcal, 50 % fat) meal relative to

fasted conditions. Oral lenacapavir can be administered without regard to food.

Pharmacokinetic parameters

The population pharmacokinetic parameter estimates of Lenacapavir Gilead after oral and subcutaneous administration to adult participants are provided in Table 4. Similar exposures are achieved when Lenacapavir Gilead is administered subcutaneously in the abdomen, upper buttocks, thigh, or back of upper arm.

Table 4: Pharmacokinetic parameters of lenacapavir following oral and subcutaneous administration to adult participants receiving Lenacapavir Gilead

Parameter Mean (%CV)[a]	**Day 1 to end of Week 26**	**Steady State**
AUC_{tau} (h•ng/ml)	188108 (41,0)	257334 (38,7)
C_{max} (ng/ml)	73,8 (48,6)	82,4 (40,4)
C_{trough} (ng/ml)	27,0 (51,1)	36,9 (53,5)

CV = Coefficient of Variation

a Simulated exposures utilising population PK analysis.

Distribution

Lenacapavir steady state volume of distribution was 1657 litres. Lenacapavir is highly bound to plasma proteins (99,8 %).

Biotransformation

Following a single intravenous dose of radiolabelled-lenacapavir to healthy subjects, 76 % of the total radioactivity was recovered from faeces and < 1 % from urine. Unchanged lenacapavir was the predominant moiety in plasma (69 %) and faeces (33 %). Metabolism played a lesser role in lenacapavir elimination. Lenacapavir was metabolised via oxidation, N-dealkylation, hydrogenation, amide hydrolysis, glucuronidation, hexose conjugation, pentose conjugation, and glutathione conjugation; primarily via CYP3A and UGT1A1. No single circulating metabolite accounted for > 10 % of plasma drug-related exposure.

Elimination

The median half-life following oral and subcutaneous administration ranged from 10 to 12 days, and 8 to 12 weeks, respectively. Systemic clearance of lenacapavir was 3,4 L/h.

Linearity/non-linearity

The single dose pharmacokinetics of lenacapavir after oral administration are non-linear and less than dose proportional over the dose range of 50 to 1800 mg.

The single dose pharmacokinetics of lenacapavir after subcutaneous injection (309 mg/ml) are dose proportional over the dose range of 309 to 927 mg.

Other special populations

Age, sex, gender identity, race, ethnicity, and weight

Population pharmacokinetic analysis using data from trials in adults and adolescents weighing at least 35 kg did not identify any clinically relevant differences in the exposure of lenacapavir due to age, sex assigned at birth, gender identity, race, ethnicity, or weight.

Adolescents

The population pharmacokinetic parameter estimates of Lenacapavir Gilead after oral and subcutaneous administration to adolescents (weighing at least 35 kg) are provided in Table 5.

Table 5: Pharmacokinetic parameters of lenacapavir following oral and subcutaneous administration to adolescent participants receiving Lenacapavir Gilead[a]

Parameter Mean (% CV)[a]	**Day 1 to end of Week 26**	**Steady State**
AUC_{tau} (h•ng/ml)	205420 (42,1)	279630 (39,3)
C_{max} (ng/ml)	81,4 (50,8)	90,1 (41,7)
C_{trough} (ng/ml)	29,1 (51,4)	39,8 (53,7)

CV = Coefficient of Variation

a Simulated exposures utilising population PK analysis.

Hepatic impairment

The pharmacokinetics of a single 300 mg oral dose of lenacapavir were evaluated in a dedicated Phase 1 trial in participants with moderate hepatic impairment (Child-Pugh Class B). Lenacapavir mean exposures (total and unbound) were 1,47- to 2,84-fold and 2,61- to 5,03-fold higher for AUC_{inf} and C_{max}, respectively in individuals with moderate hepatic impairment (Child-Pugh B) compared to

participants with normal hepatic function. However, this increase is not considered clinically relevant based on lenacapavir exposure-response. The pharmacokinetics of lenacapavir have not been studied in individuals with severe hepatic impairment (Child-Pugh C) (see section 4.2).

Renal impairment

The pharmacokinetics of a single 300 mg oral dose of lenacapavir were evaluated in a dedicated study in participants with severe renal impairment (estimated creatinine clearance ≥ 15 and < 30 ml/minute). Lenacapavir exposures were increased (84 % and 162 % for AUC_{inf} and C_{max}, respectively) in participants with severe renal impairment compared with participants with normal renal function; however, the increase was not considered clinically relevant. The pharmacokinetics of lenacapavir have not been studied in individuals with end-stage renal disease, including those on dialysis (see section 4.2). As lenacapavir is approximately 99,8 % protein bound, dialysis is not expected to alter exposures of lenacapavir.

Pregnancy

Lenacapavir exposures during pregnancy and postpartum in participants who received Lenacapavir Gilead were between -22 % to +12 % (C_{max}) and -10 % to +15 % (C_{trough}) of those observed in non- pregnant participants. These exposure changes are not considered clinically relevant.

Lactation

The median lenacapavir concentration in human breast milk to maternal plasma ratio in participants (n = 8) who received Lenacapavir Gilead was 0,63 (range: 0,29 to 1,90). The median infant-to-mother plasma ratio for lenacapavir in infants (n = 11) who were breastfed by individuals receiving Lenacapavir Gilead was 0,05 (range: 0,00 to 0,20).

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction and development.

Lenacapavir was not mutagenic or clastogenic in conventional genotoxicity assays.

Lenacapavir was not carcinogenic in a 6-month rasH2 transgenic mouse study at doses of up to 300 mg/kg/dose once every 13 weeks, which resulted in exposures approximately 88 times the exposure in humans at the recommended human dose (RHD).

In a 2-year rat carcinogenicity study, there were lenacapavir-treatment induced subcutaneous primary sarcomas associated with fibrosis and inflammation present at the injection sites in animals administered 927 mg/kg/dose once every 13 weeks. 11/110 animals manifested sarcomas at the high dose where each animal had up to 16 injection sites – corresponding to an incidence of <1 % total injection sites across animals at the high dose. Drug concentrations in the injection depot sites are difficult to determine but systemically, the 927 mg/kg dose corresponds to 44 times the exposure in humans at the RHD. At the no-observed-adverse-effect level (NOAEL), the 309 mg/kg/dose corresponds to 25 times the exposure in humans at the RHD. Rats are prone to sarcoma formation at the subcutaneous injection site, but a clinical relevance cannot be excluded considering the long duration of the drug depot in humans. There were no neoplasms associated with systemic exposure to lenacapavir at any dose.

In offspring from rat and rabbit dams treated with lenacapavir during pregnancy, there were no toxicologically significant effects on developmental endpoints.

In rats, male and female fertility was not affected at lenacapavir exposures up to 9 (male) and 6 (female) times the human exposure at the RHD. In rats and rabbits, embryofoetal development was not affected at exposures up to 20 and 159 times the human exposure, respectively, at the RHD. In rats, pre- and postnatal development was not affected at exposures up to 6 times the human exposure at the RHD.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol (E421)

Microcrystalline cellulose (E460)

Croscarmellose sodium (E468)

Copovidone

Magnesium stearate (E572)

Poloxamer

Film coat

Polyvinyl alcohol (E1203)

Titanium dioxide (E171)

Macrogol (E1521)

Talc (E553b)

Iron oxide yellow (E172)

Iron oxide black (E172)

Iron oxide red (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30 °C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Lenacapavir Gilead tablets are packaged in white high-density polyethylene (HDPE) bottle containing polyester coil and silica gel desiccant. Each bottle is capped using a white, continuous thread, child- resistant polypropylene screw cap with an induction sealed, aluminium-faced liner. Pack size of 4 tablets.

6.6 Special precautions for disposal

Any unused medicines or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

60/20.2.8/0811

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 October 2025

10 DATE OF REVISION OF THE TEXT

Not applicable

Mee Towindo Digitally signed by Mee Towindo
Date: 2025.10.30 08:09:20 +02'00'