SUMMARY OF PRODUCT CHARACTERISTCIS

1. NAME OF THE MEDICINAL PRODUCT

Lenacapavir Gilead 464 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose vial contains lenacapavir sodium equivalent to 463.5 mg of lenacapavir in 1.5 mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear, yellow to brown solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lenacapavir Gilead injection is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents with increased HIV-1 acquisition risk, weighing at least 35 kg (see sections 4.2, 4.4 and 5.1).

4.2 Posology and method of administration

Lenacapavir Gilead should be prescribed by a healthcare professional experienced in the management of HIV prevention.

Each injection should be administered by a healthcare professional.

All individuals must be screened for HIV-1 prior to initiating lenacapavir, prior to each subsequent injection, and additionally as clinically appropriate (see sections 4.3 and 4.4). A combined antigen/antibody test as well as an HIV-RNA-based test should be negative. Prescribers are advised to perform both tests, even if the result of the HIV-RNA-based test will become available after initiation of lenacapavir. If a combined testing strategy including both tests is not available, testing should follow local guidelines.

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

Posology

The 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-month continuation dosing (subcutaneous injections) (Table 1).

Oral tablets can be taken with or without food (see Lenacapavir Gilead tablet SmPC).

Table 1: Dosing schedule for lenacapavir initiation and continuation

Time	
	Dose of lenacapavir: 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)
	Dose of lenacapavir: Continuation
Every 6 Months (26 weeks)[c] +/- 2 weeks	927 mg subcutaneous injection (2 x 1.5 mL injections[b])

a The complete initiation dosing schedule, consisting of subcutaneous injections and oral tablets, is required; the efficacy of lenacapavir 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).
c From the date of the last injection.

Missed dose

Anticipated delayed injections
During continuation dosing, if the scheduled 6-month injection is anticipated to be delayed by more than 2 weeks, lenacapavir 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 continuation injection dosage within 7 days after the last oral dose (see Table 1).

Missed injections
During the continuation period, if more than 28 weeks have elapsed since the last injection and lenacapavir tablets have not been taken for oral bridging, restart the initiation dosing schedule from Day 1 (see Table 1).

Special populations

Elderly
No dose adjustment of lenacapavir is required for elderly individuals. There are limited data available on the use of lenacapavir in individuals aged 65 years and above (see section 5.2).

Renal impairment
No dose adjustment of lenacapavir is required in individuals with mild, moderate, or severe renal impairment (creatinine clearance [CrCl] ≥ 15 mL/min). Lenacapavir 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 should be used with caution in these individuals.

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

Paediatric population
Safety and efficacy of lenacapavir in children and adolescents weighing less than 35 kg have not been established. No data are available.

Method of administration

For subcutaneous use only.

Lenacapavir injections must only be administered subcutaneously into the abdomen or thigh (two injections, with the second injection at least 5 centimetres from the first injection) by a healthcare professional (see section 6.6). Do NOT administer intradermally (see section 4.4).

For instructions on preparation and administration, see ‘Instructions for Use’ in the package leaflet. ‘Instructions for Use’ are also available as a card in the injection kit.

Following lenacapavir injection, a subcutaneous drug depot forms whereby lenacapavir is slowly released from the site of administration. In some individuals, this may lead to a nodule at the injection

site (see sections 4.8 and 5.2).

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, such as:
- antimycobacterials: rifampicin
- 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. HIV-1 negative status should be confirmed prior to initiation of lenacapavir. Individuals should be re-tested for HIV-1 prior to each subsequent injection of lenacapavir, and additionally as clinically appropriate.

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.

Lenacapavir Gilead should be used to prevent HIV-1 acquisition as part of a strategy to reduce the risk of sexually transmitted infections (STIs). Individuals should be identified for whom the required initiation and every 6-month continuation injection dosing schedule is appropriate. Non-adherence to the required initiation and continuation dosing schedule (see section 4.2) may lead to HIV-1 acquisition. Individuals should be counselled and supported on adhering to the lenacapavir administration schedule, on the use of other measures to prevent STIs, and on the importance of testing for HIV-1 and other STIs.

Mean lenacapavir plasma concentrations associated with significant antiviral activity were reached by Day 2 of the required initiation dosing and were maintained through the dosing interval of 26 weeks (see section 5.2). The exact time from initiation of lenacapavir for HIV-1 PrEP to maximal protection against HIV-1 infection is unknown.

Risk of resistance

Lenacapavir may not always be effective in preventing HIV-1 infection (see section 5.1). 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. To minimise this risk, it is essential to confirm HIV-1 negative status before each subsequent injection, and additionally

only taking Lenacapavir Gilead. 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).

These concentrations may affect the exposures of other medicinal products (i.e. sensitive CYP3A and/or P-gp substrates) that are initiated within 9 months after the last subcutaneous dose of lenacapavir (see section 4.5).

If lenacapavir 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 injection.

Injection site reactions

Injection site reactions with improper administration
Improper administration (intradermal injection) has been associated with serious injection site reactions, including necrosis and ulcer. Lenacapavir Gilead injections must only be administered subcutaneously (see section 4.2).

Slow or non-resolving injection site nodules and indurations
Administration of Lenacapavir Gilead may result in local injection site reactions (ISRs), including nodules and indurations. The healthcare professional should inform patients that nodules and indurations at the injection site may take longer to resolve than other ISRs or may not resolve (see section 4.8). The mechanism driving the persistence of injection site nodules in some individuals is not fully understood but may be related to the presence of the subcutaneous drug depot and an associated foreign body response at the injection site. Non-resolving ISRs should be subject to clinical monitoring.

Co-administration of other medicinal products

Co-administration with medicinal products that are moderate inducers of CYP3A and P-gp 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 injection, 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. Concomitant administration of lenacapavir with strong inducers of CYP3A, P-gp, and UGT1A1 is contraindicated (see section 4.3). Moderate inducers of CYP3A and P-gp may decrease plasma concentrations of lenacapavir. Concomitant administration of lenacapavir with moderate inducers of CYP3A and P-gp is not recommended (see section 4.4).

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 medicinal products

Lenacapavir is a moderate inhibitor of CYP3A and a P-gp inhibitor. Caution is advised if lenacapavir 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.

Clinical drug interaction data for lenacapavir as victim are from studies with oral lenacapavir. Clinical drug interaction data for subcutaneous lenacapavir are not available.

Table 2: Interactions between Lenacapavir Gilead and other medicinal products

Medicinal product by therapeutic areas	**Effects on concentrations. Mean percent change in AUC, C_{max}**	**Recommendation concerning co-administration with Lenacapavir Gilead**
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%	Co-administration is contraindicated (see section 4.3).
Rifabutin Rifapentine	Interaction not studied. Co-administration of rifabutin or rifapentine may decrease lenacapavir plasma concentrations.	Co-administration is not recommended (see section 4.4).
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).

Medicinal product by therapeutic areas	Effects on concentrations. Mean percent change in AUC, C_{max}	Recommendation concerning co-administration with Lenacapavir Gilead
ANTIRETROVIRAL AGENTS		
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%	Co-administration is not recommended (see section 4.4).
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] (25 mg) (substrate of P-gp)	Tenofovir alafenamide: AUC:↑ 32% C_{max}:↑ 24% Tenofovir[f]: 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.
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

Medicinal product by therapeutic areas	Effects on concentrations. Mean percent change in AUC, C_{max}	Recommendation concerning co-administration with Lenacapavir Gilead
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 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, 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%	
ANTIARRHYTHMICS		
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.
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%	

Medicinal product by therapeutic areas	Effects on concentrations. Mean percent change in AUC, C_{max}	Recommendation concerning co-administration with Lenacapavir Gilead
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 daily) (strong CYP3A inhibitor)	Lenacapavir: AUC:↑ 41% C_{max}:↔	No dose adjustment of lenacapavir is required.
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 OR LONG-ACTING CONTRACEPTIVES		
Long-acting contraceptives: Medroxyprogesterone acetate Etonogestrel Norethisterone enanthate	Observed data does not indicate clinically relevant changes in the exposure of long-acting contraceptives.	No dose adjustment of oral or long-acting contraceptives is required.
Oral contraceptives: Ethinylestradiol Progestins	Interaction not studied. Plasma concentrations of oral contraceptives may be increased when co-administered with lenacapavir.	
GENDER AFFIRMING HORMONES (feminising or masculinising)		
Estradiol Testosterone	Observed data does not indicate clinically relevant changes in the exposure of estradiol and testosterone.	No dose adjustment of these gender affirming hormones is required.
Anti-androgens Progestogen	Interaction not studied. Plasma concentrations of these medicinal products may be increased when co-administered with lenacapavir.	

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 orally 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.

4.6 Fertility, pregnancy and lactation

Individuals of childbearing potential

Individuals of childbearing potential should be counselled about the long-acting properties of lenacapavir injection.

If an individual plans a pregnancy, the benefits and the risks of initiating or continuing Lenacapavir Gilead during pregnancy should be discussed.

Pregnancy

There are limited data (130 birth outcomes) from the use of lenacapavir in pregnant women. The rates of adverse pregnancy outcomes in participants who received Lenacapavir Gilead were similar to reported background rates.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Lenacapavir Gilead may be considered during pregnancy if the expected benefit outweighs the potential risk to the foetus.

Breast-feeding

Lenacapavir is present in human milk. Lenacapavir was detected at low levels in infants who were breastfed by individuals who became pregnant while receiving Lenacapavir Gilead (see section 5.2). There is insufficient information on the effects of lenacapavir in newborns/infants.

Lenacapavir Gilead may be considered during breastfeeding if the expected benefit outweighs the potential risk to the child.

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

Summary of the safety profile

The most common adverse reaction in PURPOSE 1 and PURPOSE 2 was injection site reactions (71% and 85% respectively).

Tabulated list of adverse reactions

Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

Table 3: Tabulated list of adverse reactions

Frequency[a]	Adverse reaction
General disorders and administration site conditions	
Very common	injection site reactions[b]

a Frequency based on all adverse events in PURPOSE 1 and PURPOSE 2 (see section 5.1) attributed to lenacapavir (or to the procedure) by the investigator.

b Includes injection site nodule, pain, induration, erythema, swelling, pruritus, bruising, warmth, discolouration, oedema, ulcer, haematoma, haemorrhage, and discomfort.

Description of injection-associated adverse reactions

Local injection site reactions (ISRs)

PURPOSE 1
In PURPOSE 1, 71% of participants receiving lenacapavir experienced ISRs, compared to 38% of participants receiving placebo injections (and emtricitabine/tenofovir alafenamide [FTC/TAF] or emtricitabine/tenofovir disoproxil fumarate [FTC/TDF]). Most participants who received lenacapavir had mild (Grade 1, 50%) or moderate (Grade 2, 21%) severity ISRs. Grade 3 ISRs were reported in 4 (0.2%) participants, and included ulcer and nodule. Lenacapavir was discontinued due to ISRs in 4 (0.2%) participants.

Nodules: Injection site nodule was reported in 66% of participants who received lenacapavir and resolved more slowly than other ISRs. The median duration of nodules was 274 (180, 407) days. Of the injection site nodule events associated with Day 1 lenacapavir injections, 70% had resolved within a median time of 276 days.

Other ISRs: The other ISRs reported in more than 2% of participants who received lenacapavir were pain (34%), swelling (5%), induration (4%), and pruritus (3%). The median duration of ISRs, excluding nodules and indurations, was 9 (4 to 30) days.

PURPOSE 2
In PURPOSE 2, 85% of participants receiving lenacapavir experienced ISRs, compared to 70% of participants receiving placebo injections (and FTC/TDF). Most participants had mild (Grade 1, 66%) or moderate (Grade 2, 18%) severity ISRs. Grade 3 ISRs were reported in 14 (0.6%) participants, and included ulcer, pain, erythema, oedema, and dermatitis. Lenacapavir was discontinued due to ISRs in 26 (1.2%) participants.

Nodules: Injection site nodule was reported in 65% of participants and resolved more slowly than other ISRs. The median duration of nodules was 239 (163, 362) days. Of the injection site nodule events associated with Day 1 lenacapavir injections, 70% had resolved within a median time of 269 days.

Other ISRs: The other ISRs reported in more than 2% of participants who received lenacapavir were pain (58%), erythema (18%), induration (16%), swelling (7%), pruritus (4%), bruising (3%), and warmth (2%). The median duration of ISRs, excluding nodules and indurations, was 4 (2 to 8) days.

Paediatric population

The safety of lenacapavir was evaluated in 59 adolescents aged 16 to <18 years and weighing ≥35 kg in PURPOSE 1 and PURPOSE 2. The adverse reactions in adolescents were consistent with those in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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
There were 2 incident infections (infections that occurred after starting lenacapavir for HIV-1 PrEP)

among participants in the lenacapavir group of the PURPOSE 1 trial. Both infections occurred after the time of the primary analysis. Genotyping of virus in one of the participants revealed no lenacapavir resistance-associated capsid substitutions. The second participant had viral loads that were too low for genotyping.

There were 3 incident infections among participants in the lenacapavir group of the PURPOSE 2 trial. One of the infections occurred after the time of the primary analysis. Lenacapavir resistance-associated substitutions were detected in viruses from the 3 participants, 2 with N74D, and 1 with Q67H/K70R.

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 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
This study was conducted in sexually active cisgender women. Participants were randomised to receive lenacapavir per the recommended dosing schedule (see Table 1, section 4.2; n = 2134), once daily FTC/TAF (n = 2136), or once daily FTC/TDF (n = 1068) in a 2:2:1 ratio.

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 efficacy of lenacapavir was established by comparing the HIV-1 incidence in the lenacapavir group to the HIV-1 incidence in the FTC/TDF group. Incident HIV-1 infections were observed in none (0%) of the participants in the lenacapavir group compared to 16 (1.5%) participants in the FTC/TDF group. Lenacapavir demonstrated superiority with a 100% reduction in the risk of HIV-1 acquisition over FTC/TDF (Table 4).

Table 4: Overall HIV-1 Infection Outcomes in PURPOSE 1

	Lenacapavir n = 2134	**FTC/TDF n = 1068**	**Rate Ratio (95% CI)**
Person-years	1939	949	-
HIV-1 infections (incidence rate per 100 person-years)	0 (0.00)	16 (1.69)	Lenacapavir / FTC/TDF: 0.000 (0.000, 0.101) p < 0.0001

CI = confidence interval

PURPOSE 2
This study was conducted in sexually active cisgender men, transgender women, transgender men, and

gender nonbinary individuals. Participants were randomised to receive lenacapavir per the recommended dosing schedule (see Table 1, section 4.2; n = 2179) or once daily FTC/TDF (n = 1086) in a 2:1 ratio.

The median age of participants was 29 years (range, 17-74); 33% were White; 27% were Black, 13% were Asian; 63% were Hispanic/Latine; 22% identified as gender-diverse (transgender women, transgender men, and gender nonbinary people); and 1% were over 65 years. Baseline characteristics in the randomised participants were similar to the screened population.

The efficacy of lenacapavir was established by comparing the HIV-1 incidence in the lenacapavir group to the HIV-1 incidence in the FTC/TDF group. Incident HIV-1 infections were observed in 2 (0.1%) participants in the lenacapavir group compared to 9 (0.8%) participants in the FTC/TDF group. Lenacapavir demonstrated superiority with an 89% reduction over FTC/TDF (Table 5). HIV-1 infections in the two participants receiving lenacapavir were diagnosed using standard serologic HIV testing.

Table 5: Overall HIV-1 Infection Outcomes in PURPOSE 2

	Lenacapavir n = 2179	**FTC/TDF n = 1086**	**Rate Ratio (95% CI)**
Person-years	1938	967	-
HIV-1 infections (incidence rate per 100 person-years)	2 (0.1)	9 (0.93)	Lenacapavir / FTC/TDF: 0.111 (0.024, 0.513) p = 0.00245

CI = confidence interval

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with lenacapavir in one or more subsets of the paediatric population in prevention of HIV-1 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

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

Oral administration
Lenacapavir is absorbed following oral administration with peak plasma concentrations occurring approximately 4 hours after administration of lenacapavir. Absolute bioavailability following oral

administration of lenacapavir is low based on population pharmacokinetic analysis (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 after oral and subcutaneous administration to adult and adolescent (weighing at least 35 kg) participants are provided in Table 6. Similar exposures are achieved when lenacapavir is administered subcutaneously in the abdomen or thigh.

Table 6: Pharmacokinetic parameters of lenacapavir following oral and subcutaneous administration to adult and adolescent participants receiving Lenacapavir Gilead

Parameter Mean (%CV)[a,b]	Day 1 to end of Week 26	Steady State
AUC_{tau} (h•ng/mL)	188112 (41.0)	257332 (38.7)
C_{max} (ng/mL)	73.8 (55.6)	82.5 (48.4)
C_{trough} (ng/mL)	27.0 (58.3)	37.0 (60.7)

CV = Coefficient of Variation
a Simulated exposures utilising population PK analysis.
b Mean lenacapavir plasma concentrations reached inhibitory quotient 4 (IQ4; 4-fold greater than the *in vitro* protein adjusted 95% effective concentration) associated with significant antiviral activity by Day 2 of the required initiation dosing and were maintained above IQ4 through the dosing interval of 26 weeks.

Distribution

Lenacapavir steady state volume of distribution was 1657 litres based on population pharmacokinetic analysis. 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 based on population pharmacokinetic analysis.

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, including a limited number of elderly participants (n = 19; ≥ 65 to 78 years), 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.

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
No clinically relevant changes in lenacapavir exposure during pregnancy and postpartum were observed compared to lenacapavir exposures in non-pregnant participants.

Lactation
The median (Q1, Q3) lenacapavir concentration in human breast milk to maternal plasma ratio in participants (n = 102 matched pairs) who received Lenacapavir Gilead was 0.52 (0.38, 0.77). The median (Q1, Q3) infant plasma concentration (n = 98) was 1.63 ng/mL (0.87, 2.85) as compared to the median (Q1, Q3) matched maternal plasma concentration (n = 96) of 65.65 ng/ml (46.00, 91.10). The median (Q1, Q3) infant-to-mother plasma ratio for lenacapavir in infants (n = 98 matched pairs) who were breastfed by participants receiving Lenacapavir Gilead was 0.02 (0.01, 0.05).

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

Macrogol (E1521)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Once the solution has been drawn into the syringes, the injections should be used immediately, from a microbiological point of view. Chemical and physical in-use stability has been demonstrated for 4 hours at 25 °C outside of the package.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store below 30 °C. Store in the original outer carton in order to protect from light.

6.5 Nature and contents of container

Lenacapavir Gilead injection is packaged in a dosing kit containing:

- 2 clear glass vials, each containing 1.5 mL solution for injection. Vials are sealed with an elastomeric butyl rubber closure and aluminium overseal with flip off cap;
- 2 withdrawal needles (18-gauge, 40 mm), 2 disposable syringes, and 2 injection safety needles for subcutaneous injection (22-gauge, 13 mm).

6.6 Special precautions for disposal and other handling

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

Use aseptic technique. Visually inspect the solution in the vials for particulate matter and discoloration prior to administration. Lenacapavir Gilead injection is a yellow to brown solution. Do not use Lenacapavir Gilead injection if the solution is discoloured or if it contains particulate matter. Once the

solution is withdrawn from the vials, the subcutaneous injections should be administered as soon as possible.
The injection kit components are for single use only. 18-gauge needle is for withdrawal only. Two 1.5 mL injections are required for a complete dose.

Full instructions for use and handling of Lenacapavir Gilead injection are provided in the package leaflet (see Instructions for Use).

7. MARKETING AUTHORIZATION HOLDER

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Carrigtohill
County Cork, T45 DP77
Ireland

8. MARKETING AUTHORIZATION NUMBER

CTD13162

9. DATE OF FIRST AUTHORIZATION/RENEWAL:

09/01/2025

10. DATE OF REVISION OF THE TEXT

09/01/2025