ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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).

<u>Posology</u>

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 as clinically appropriate. Lenacapavir Gilead alone does not constitute a complete regimen for HIV-1 treatment and mutations have emerged in some individuals with undetected HIV-1 infection who were

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. SCIENTIFIC OPINION HOLDER

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Carrigtohill
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8. SCIENTIFIC OPINION NUMBER

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10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Lenacapavir Gilead 300 mg film-coated tablets

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 (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 reduce the risk of sexually acquired HIV-1 infection in adults and adolescents with increased HIV-1 acquisition risk, weighing at least 35 kg for:

- oral loading
- oral bridging

(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.

All individuals must be screened for HIV-1 prior to initiating lenacapavir 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) (Table 1), followed by once every 6-month continuation dosing (subcutaneous injections).

Initiation
On Day 1, the required dose is 927 mg of lenacapavir 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 initiation

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)

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 in the Lenacapavir Gilead solution for injection SmPC).

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.

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.

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

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 oral use.

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

studied. For individuals who are unable to swallow the tablet whole, the tablet may be split in half and both halves taken one after the other, ensuring that the full dose is taken immediately.

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, and additionally as clinically appropriate in individuals receiving lenacapavir.

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. Nonadherence 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 as clinically appropriate. Lenacapavir Gilead alone does not constitute a complete regimen for HIV-1 treatment and mutations have emerged in some individuals with undetected HIV-1 infection who were 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.

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 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. 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
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.

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

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

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

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

No adverse reactions to lenacapavir 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 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. 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 in the Lenacapavir Gilead solution for injection SmPC; n = 2134), once daily emtricitabine/tenofovir alafenamide (FTC/TAF) (n = 2136), or once daily emtricitabine/tenofovir disoproxil fumarate (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 3).

Table 3: 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 in the Lenacapavir Gilead solution for injection SmPC; 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 4). HIV-1 infections in the two participants receiving lenacapavir were diagnosed using standard serologic HIV testing.

Table 4: 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 5. Similar exposures are achieved when lenacapavir is administered subcutaneously in the abdomen or thigh.

Table 5: 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 population

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

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

7. SCIENTIFIC OPINION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

8. SCIENTIFIC OPINION NUMBER

EMEA/H/W/006659/001

9. DATE OF FIRST SCIENTIFIC OPINION /RENEWAL OF THE SCIENTIFIC OPINION

Date of first Scientific Opinion: 24 July 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE SCIENTIFIC OPINION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Gilead Sciences Ireland UC
IDA Business & Technology Park
Carrigtohill
County Cork
Ireland

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City
CA 94404
USA

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE SCIENTIFIC OPINION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The scientific opinion holder shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The scientific opinion holder shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the scientific opinion and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (SOLUTION FOR INJECTION)

1. NAME OF THE MEDICINAL PRODUCT

Lenacapavir Gilead 464 mg solution for injection
lenacapavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

It also contains macrogol (E1521) and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
2 single-dose vials
2 withdrawal needles
2 syringes
2 injection needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE SCIENTIFIC OPINION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. SCIENTIFIC OPINION NUMBER

EMEA/H/W/006659/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL (SOLUTION FOR INJECTION)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Lenacapavir Gilead 464 mg solution for injection
lenacapavir
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INSTRUCTIONS FOR USE CARD FOR HEALTHCARE PROFESSIONALS ONLY (SOLUTION FOR INJECTION)

1. NAME OF THE MEDICINAL PRODUCT

Lenacapavir Gilead 464 mg solution for injection
lenacapavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

463.5 mg/1.5 mL

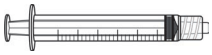
3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

For Healthcare Professionals Only
INSTRUCTIONS FOR USE

VIAL x2

SYRINGE x2



18G, 40 mm WITHDRAWAL NEEDLE x2

22G, 13 mm INJECTION NEEDLE x2

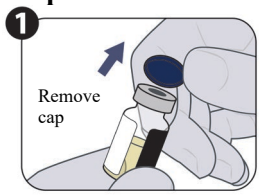
NOTE: all components are for single use

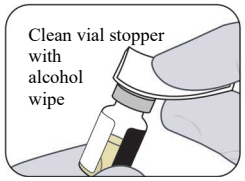
5. METHOD AND ROUTE(S) OF ADMINISTRATION

ATTENTION!
- **TWO 1.5 mL injections** are required to complete dose
- 18G needle is for **withdrawal only**

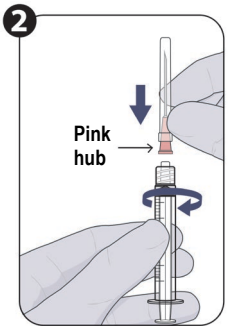
Make sure that:
- Vial and prepared syringe contain a **yellow-to-brown solution** with **no particles**
- Contents are **not damaged**
- Product is **not expired**

Prepare Vial

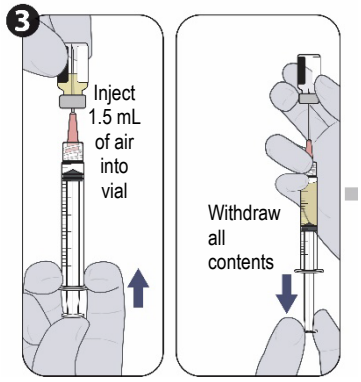




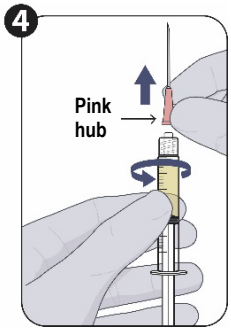
Attach 18G Withdrawal Needle to Syringe



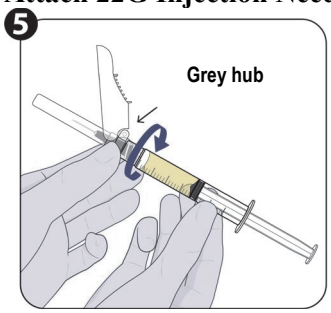
Fill Syringe



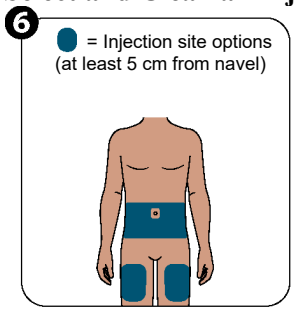
Remove 18G Withdrawal Needle from Syringe



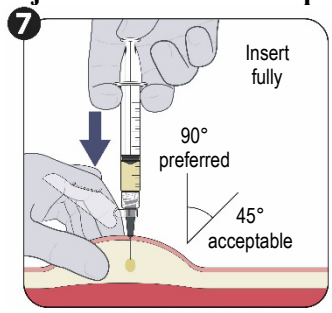
Attach 22G Injection Needle to Syringe, Expel Air Bubbles, and Prime to 1.5 mL



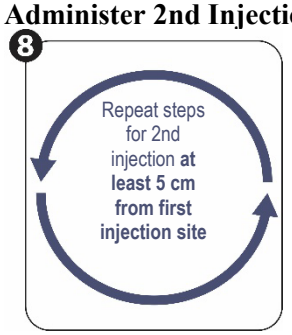
Select and Clean an Injection Site



Inject 1.5 mL of Lenacapavir Gilead Subcutaneously



Administer 2nd Injection



PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE AND CARTON LABELLING (FILM-COATED TABLET)

1. NAME OF THE MEDICINAL PRODUCT

Lenacapavir Gilead 300 mg film-coated tablets
lenacapavir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

4 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE SCIENTIFIC OPINION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. SCIENTIFIC OPINION NUMBER

EMEA/H/W/006659/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Lenacapavir Gilead [Carton only]

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included [Carton only]

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN
[Carton only]

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Lenacapavir Gilead 464 mg solution for injection
lenacapavir

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Lenacapavir Gilead is and what it is used for

Lenacapavir Gilead contains the active substance lenacapavir. It is a long acting antiretroviral medicine known as a capsid inhibitor. Lenacapavir, the active substance in Lenacapavir Gilead, binds to proteins of the HIV-1 virus's outer layer, disrupting its ability to multiply and spread.

Lenacapavir Gilead is used to help **prevent HIV-1 infection in adults and adolescents** weighing at least 35 kg who are at an increased risk of getting HIV-1. This is called *pre-exposure prophylaxis (PrEP)*. It should be used in combination with safer sex practices.

2. What you need to know before you are given Lenacapavir Gilead

Do not receive Lenacapavir Gilead

- If you are **allergic** to lenacapavir or any of the other ingredients of this medicine (listed in section 6).

- If you **do not know if you have HIV**. **You must get tested** to make sure that you do not already have HIV before you start treatment with Lenacapavir Gilead. Lenacapavir Gilead can only prevent HIV if you don't already have it.

- If you are taking any of these medicines:
  - **rifampicin**, used to treat some bacterial infections such as tuberculosis
  - **carbamazepine**, **phenytoin**, used to prevent seizures
  - **St. John's wort** (*Hypericum perforatum*), a herbal remedy used for depression and anxiety

→ **Do not receive Lenacapavir Gilead and tell your doctor or nurse immediately** if you think any of these apply to you**.**

Warnings and precautions

- **Just taking Lenacapavir Gilead may not stop you from getting HIV. Take extra measures to help prevent HIV while you are receiving Lenacapavir Gilead**

- Always practice safer sex. Use condoms to reduce contact with semen, vaginal fluids, or blood.
- Do not share or re-use needles or other injection or drug equipment.
- Get tested for other sexually transmitted infections such as syphilis and gonorrhoea. These infections make it easier for HIV to infect you.

- **Get tested for HIV** when your doctor or nurse tells you. You must get tested before starting Lenacapavir Gilead and before every injection to make sure that you stay HIV negative while receiving this medicine.

- **Keep all your appointments** to get your Lenacapavir Gilead injections on time. Talk to your doctor or nurse if you are thinking about stopping injections: stopping may increase your risk of getting HIV. If you do stop, or miss your scheduled injections, you may need to take other medicines or precautions to reduce your risk of getting HIV, and possibly developing viral resistance.

- **Tell your doctor or nurse straight away** if you think you were infected with HIV. They may want to do more tests to make sure you still do not have HIV.

- If you get a flu-like illness, it could mean you have recently been infected with HIV. These may be signs of HIV infection:
  - tiredness
  - fever
  - joint or muscle aches
  - headache
  - vomiting or diarrhoea
  - rash
  - night sweats
  - enlarged lymph nodes in the neck or groin

→ **Tell your doctor or nurse about any flu-like illness**, either in the month before starting Lenacapavir Gilead, or at any time while taking Lenacapavir Gilead.

Talk to your doctor or nurse if you have any more questions about how to prevent getting HIV.

- **Lenacapavir Gilead injection is a long-acting medicine**
  If you stop Lenacapavir Gilead injections, lenacapavir (the active substance in Lenacapavir Gilead) may remain in your body for a year or more after your last injection, **but the amount in your body may be too low to protect you from getting HIV**.

- **Reactions where Lenacapavir Gilead is injected**

→ A hardened mass or lump may occur at the injection site. In some cases, such lumps have remained for more than a year and in some cases may not go away. If this has not gone away at the time of the next injection, alert your doctor. For more information, see section 4, *Possible side effects*.

Children and adolescents

Do not give this medicine to anyone weighing less than 35 kg because it has not been studied in these individuals.

Other medicines and Lenacapavir Gilead

Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines. Lenacapavir Gilead may interact with other medicines. This may keep Lenacapavir Gilead

or other medicines from working properly, or may make side effects worse. In some cases, your doctor or nurse may need to adjust your dose or check your blood levels.

Medicines that must never be taken with Lenacapavir Gilead:

- **rifampicin**, used to treat some bacterial infections, such as tuberculosis
- **carbamazepine, phenytoin**, used to prevent seizures
- **St. John's wort** (*Hypericum perforatum*), a herbal remedy used for depression and anxiety

→ If you are taking any of these medicines, **do not receive Lenacapavir Gilead injection and tell your doctor or nurse immediately**.

Talk to your doctor or nurse in particular if you are taking:

- medicines used to treat some bacterial infections, such as tuberculosis, containing:
  - rifabutin or rifapentine
- anticonvulsants used to treat epilepsy and prevent seizures, containing:
  - oxcarbazepine or phenobarbital
- medicines used to treat migraine, containing:
  - dihydroergotamine or ergotamine
- medicines used to treat impotence and pulmonary hypertension, containing:
  - sildenafil or tadalafil
- medicine used to treat impotence, containing:
  - vardenafil
- corticosteroids (also known as 'steroids') taken orally or given by injection used to treat allergies, inflammatory bowel diseases, and other illnesses involving inflammation in your body, containing:
  - dexamethasone or hydrocortisone/cortisone
- medicines used to lower cholesterol, containing:
  - lovastatin or simvastatin
- antiarrhythmics used to treat heart problems, containing:
  - digoxin
- medicines used to help you sleep, containing:
  - midazolam or triazolam.
- anticoagulants used to prevent and treat blood clots, containing:
  - rivaroxaban, dabigatran or edoxaban

→ **Tell your doctor or nurse if you are taking any of these medicines** or if you start taking any of these medicines while receiving Lenacapavir Gilead. Do not stop any treatment without contacting your doctor or nurse.

Lenacapavir Gilead is a long-acting medicine. If after talking to your doctor or nurse you decide to stop taking this medicine, you should know low levels of lenacapavir can remain in your system for many months after your last injection. Some other medicines may be affected by the low levels of lenacapavir in your system if you take them within 9 months after your last Lenacapavir Gilead injection. You should check with your doctor or nurse if such medicines are safe for you to take after you stop Lenacapavir Gilead.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, nurse or pharmacist for advice before taking this medicine.

If you are breast-feeding, or thinking about breast-feeding, you should discuss it with your doctor or nurse.

Driving and using machines

Lenacapavir Gilead is not expected to have any effect on your ability to drive or use machines.

Lenacapavir Gilead contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per injection, that is to say essentially 'sodium-free'.

3. How Lenacapavir Gilead is given

You must have a negative HIV test before starting Lenacapavir Gilead and before every injection.

You will take tablets by mouth and your doctor or nurse will give you injections under the skin (subcutaneously) when you start Lenacapavir Gilead. After that, you will have injections every 6 months.

Day 1:
- **Two tablets** taken by mouth. These can be taken with or without food.
- **Two injections** given by your doctor or nurse. The two injections will be given at the same time at least 5 centimetres apart from each other and may be given into your abdomen (tummy) or thigh.

Day 2:
- **Two tablets** taken by mouth, as above.

Every 6 months:
- **Two injections** given by your doctor or nurse, as above.

If you have difficulty swallowing the tablet whole, you can split it in half. Take both halves of the tablet one after the other to get the full dose. Do not store the split tablet.

It is important to keep your scheduled appointments every 6 months (26 weeks) to receive your injections of Lenacapavir Gilead. This will continue to help protect you from getting HIV.
- Schedule your appointment with your doctor or nurse to make sure you will receive your next injections on time.
- You must receive your next injections within 28 weeks of your last injection.

If you are given more Lenacapavir Gilead injection than you should

Your doctor or a nurse will give this medicine to you, so it is unlikely that you will be given too much. If you are worried, speak to your doctor or a nurse.

If you miss a Lenacapavir Gilead injection appointment

- If you think you will not be able to attend an appointment for your injections, contact your doctor or nurse as soon as possible to discuss your options. If you need to delay a scheduled injection appointment, there is the option to temporarily take Lenacapavir Gilead tablets instead.
- **Using Lenacapavir Gilead tablets if you need to delay an injection appointment**
  - **Take one tablet by mouth, every 7 days until your injections resume**. Tablets can be taken with or without food.
  - It is important to continue Lenacapavir Gilead as your doctor or nurse recommends.

If you miss taking or vomit the tablets, read the package leaflet for Lenacapavir Gilead tablets to see what you should do.

Do not stop receiving Lenacapavir Gilead injections without talking to your doctor or nurse
Keep receiving Lenacapavir Gilead injections for as long as your doctor or nurse recommends. Don't stop unless your doctor or nurse advises you to. Missing Lenacapavir Gilead injections or tablets increases your risk of getting HIV.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common side effects
(may affect more than 1 in 10 people)

- **Reactions where Lenacapavir Gilead is injected**
  Symptoms may include:
  - a hardened mass or lump, which may take longer to go away than other reactions at the injection site or may not go away
  - pain and discomfort
  - inflammatory reaction such as redness, itching, and swelling
  - open sore on the skin

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Lenacapavir Gilead

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and carton after EXP. The expiry date refers to the last day of that month.

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

6. Contents of the pack and other information

What Lenacapavir Gilead contains

The active substance is lenacapavir. Each single-use vial contains 463.5 mg of lenacapavir.

The other ingredients are

Macrogol (E1521), water for injections.

What Lenacapavir Gilead looks like and contents of the pack

Lenacapavir Gilead solution for injection (injection) is a clear, yellow to brown solution with no visible particles. Lenacapavir Gilead comes in two glass vials, each containing 1.5 ml of solution for injection. These vials are included in an injection kit also containing 2 withdrawal needles (to allow your doctor or a nurse to withdraw Lenacapavir Gilead from the vial), 2 disposable syringes and 2 injection needles.

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County Cork, T45 DP77
Ireland

Manufacturer
Gilead Sciences Ireland UC
IDA Business & Technology Park
Carrigtohill
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Ireland

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City
CA 94404
USA

This leaflet was last revised in 07/2025.

Detailed information on this medicine is available on the European Medicines Agency web site:
https://www.ema.europa.eu

The following information is intended for healthcare professionals only

Instructions for Use - Lenacapavir Gilead 464 mg solution for injection

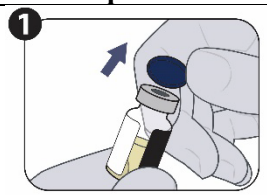
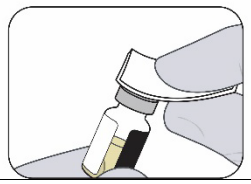
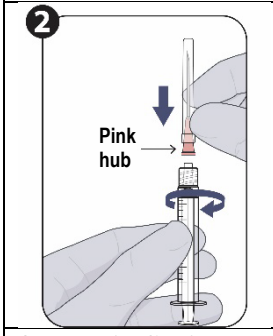
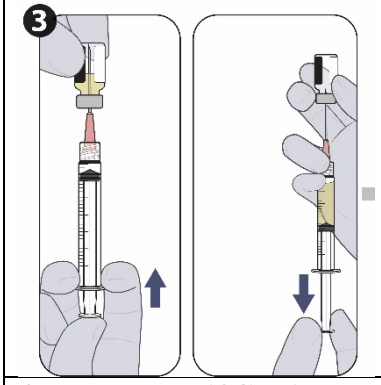
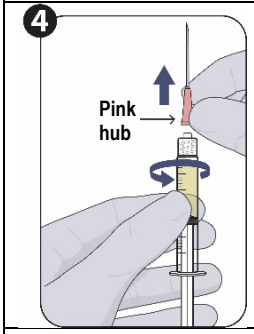
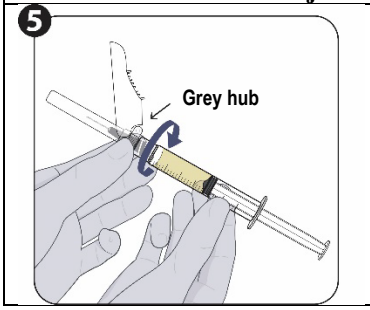
Each pack contains

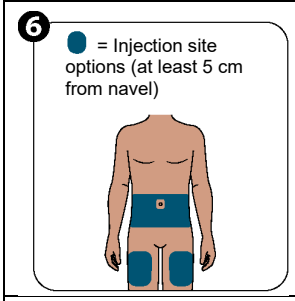
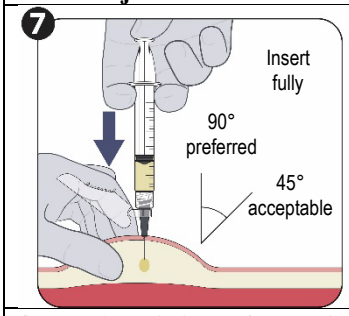
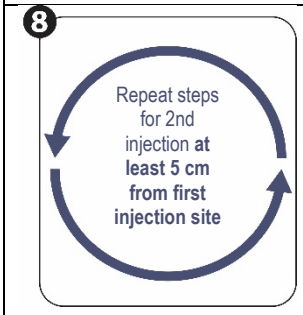
2 x vials	
2 x syringes	
2 x 18G, 40 mm withdrawal needles	
2 x 22G, 13 mm injection needles	

All the components are for single use.

A complete dose requires **two 1.5 mL injections.** 18G needle is for **withdrawal only**.

Make sure that:
- Vial contains a **yellow-to-brown solution** with **no particles**
- Contents are **not damaged**
- Product is **not expired**

1. Prepare Vial	
	Remove cap.
	Clean vial stopper with alcohol wipe.
2. Attach 18G Withdrawal Needle to Syringe	
	
3. Fill Syringe	
	• Inject 1.5 mL of air into vial. • Withdraw all contents.
4. Remove 18G Withdrawal Needle from Syringe	
	
5. Assemble 22G Injection Needle to Syringe, Expel Air Bubbles and Prime to 1.5 mL	
	

6. Select and Clean an Injection Site	
	Injection site options (at least 5 cm from navel)
7. Inject 1.5 mL Lenacapavir Gilead subcutaneously	
	
8. Administer 2nd Injection	
	

Package leaflet: Information for the patient

Lenacapavir Gilead 300 mg film-coated tablets
lenacapavir

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Lenacapavir Gilead is and what it is used for

Lenacapavir Gilead contains the active substance lenacapavir. It is a long acting antiretroviral medicine known as a capsid inhibitor. Lenacapavir, the active substance in Lenacapavir Gilead, binds to proteins of the HIV-1 virus's outer layer, disrupting its ability to multiply and spread.

Lenacapavir Gilead is used to help **prevent HIV-1 infection in adults and adolescents** weighing at least 35 kg who are at an increased risk of getting HIV-1. This is called *pre-exposure prophylaxis (PrEP)*. It should be used in combination with safer sex practices.

Your doctor will advise you to take Lenacapavir Gilead tablets when you are given Lenacapavir Gilead injections for the first time.

If you are being given Lenacapavir Gilead injections, but you plan to miss your scheduled Lenacapavir Gilead injections, you can take Lenacapavir Gilead tablets instead, until you can receive the injections again (see section 3).

2. What you need to know before you take Lenacapavir Gilead

Do not take Lenacapavir Gilead

- If you are **allergic** to lenacapavir or any of the other ingredients of this medicine (listed in section 6).

- If you **do not know if you have HIV**. **You must get tested** to make sure that you do not already have HIV before you start treatment with Lenacapavir Gilead. Lenacapavir Gilead can only prevent HIV if you don't already have it.

- If you are taking any of these medicines:
  - **rifampicin**, used to treat some bacterial infections such as tuberculosis
  - **carbamazepine**, **phenytoin**, used to prevent seizures
  - **St. John's wort** (*Hypericum perforatum*), a herbal remedy used for depression and anxiety

→ **Do not take Lenacapavir Gilead and tell your doctor or nurse immediately** if you think any of these apply to you**.**

Warnings and precautions

- **Just taking Lenacapavir Gilead may not stop you from getting HIV. Take extra measures to help prevent HIV while you are receiving Lenacapavir Gilead**
  - Always practice safer sex. Use condoms to reduce contact with semen, vaginal fluids, or blood.
  - Do not share or re-use needles or other injection or drug equipment.
  - Get tested for other sexually transmitted infections such as syphilis and gonorrhoea. These infections make it easier for HIV to infect you.

- **Get tested for HIV** when your doctor or nurse tells you. You must get tested before starting Lenacapavir Gilead and before every injection to make sure that you stay HIV negative while receiving this medicine.

- **Keep all your appointments** to get your Lenacapavir Gilead injections on time. Talk to your doctor or nurse if you are thinking about stopping injections: stopping may increase your risk of getting HIV. If you do stop, or miss your scheduled injections, you may need to take other medicines or precautions to reduce your risk of getting HIV and possibly developing viral resistance.

- **Tell your doctor or nurse straight away** if you think you were infected with HIV. They may want to do more tests to make sure you still do not have HIV.

- If you get a flu-like illness, it could mean you have recently been infected with HIV. These may be signs of HIV infection:
  - tiredness
  - fever
  - joint or muscle aches
  - headache
  - vomiting or diarrhoea
  - rash
  - night sweats
  - enlarged lymph nodes in the neck or groin.

→ **Tell your doctor or nurse about any flu-like illness**, either in the month before starting Lenacapavir Gilead, or at any time while taking Lenacapavir Gilead.

Talk to your doctor or nurse if you have any more questions about how to prevent getting HIV.

Children and adolescents

Do not give this medicine to anyone weighing less than 35 kg because it has not been studied in these individuals.

Other medicines and Lenacapavir Gilead

Tell your doctor, nurse or pharmacist if you are taking, have recently taken or might take any other medicines. Lenacapavir Gilead may interact with other medicines. This may keep Lenacapavir Gilead or other medicines from working properly, or may make side effects worse. In some cases, your doctor or nurse may need to adjust your dose or check your blood levels.

Medicines that must never be taken with Lenacapavir Gilead:

- **rifampicin**, used to treat some bacterial infections, such as tuberculosis

- **carbamazepine, phenytoin**, used to prevent seizures
- **St. John's wort** (*Hypericum perforatum*), a herbal remedy used for depression and anxiety

→ If you are taking any of these medicines, **do not take Lenacapavir Gilead and tell your doctor or nurse immediately**.

Talk to your doctor or nurse in particular if you are taking:

- medicines used to treat some bacterial infections, such as tuberculosis, containing:
  - rifabutin or rifapentine
- anticonvulsants used to treat epilepsy and prevent seizures, containing:
  - oxcarbazepine or phenobarbital
- medicines used to treat migraine, containing:
  - dihydroergotamine or ergotamine
- medicines used to treat impotence and pulmonary hypertension, containing:
  - sildenafil or tadalafil
- medicine used to treat impotence, containing:
  - vardenafil
- corticosteroids (also known as 'steroids') taken orally or given by injection used to treat allergies, inflammatory bowel diseases, and other illnesses involving inflammation in your body, containing:
  - dexamethasone or hydrocortisone/cortisone
- medicines used to lower cholesterol, containing:
  - lovastatin or simvastatin
- antiarrhythmics used to treat heart problems, containing:
  - digoxin
- medicines used to help you sleep, containing:
  - midazolam or triazolam.
- anticoagulants used to prevent and treat blood clots, containing:
  - rivaroxaban, dabigatran or edoxaban

→ **Tell your doctor or nurse if you are taking any of these medicines** or if you start taking any of these medicines while receiving Lenacapavir Gilead. Do not stop any treatment without contacting your doctor or nurse.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, nurse or pharmacist for advice before taking this medicine.

If you are breast-feeding, or thinking about breast-feeding, you should discuss it with your doctor or nurse.

Driving and using machines

Lenacapavir Gilead is not expected to have any effect on your ability to drive or use machines.

Lenacapavir Gilead contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Lenacapavir Gilead

You must have a negative HIV test before starting Lenacapavir Gilead and before every injection.

You will take tablets by mouth and your doctor or nurse will give you injections under the skin (subcutaneously) when you start Lenacapavir Gilead. After that you will have injections every 6 months.

Day 1:
- **Two tablets** taken by mouth. These can be taken with or without food.
- **Two injections** given by your doctor or nurse. The two injections will be given at the same time at least 5 centimetres apart from each other and may be given into your abdomen (tummy) or thigh.

Day 2:
- **Two tablets** taken by mouth, as above.

Every 6 months:
- **Two injections** given by your doctor or nurse, as above.

If you have difficulty swallowing the tablet whole, you can split it in half. Take both halves of the tablet one after the other to get the full dose. Do not store the split tablet.

It is important that you attend your planned appointments every 6 months (26 weeks) to receive your injections of Lenacapavir Gilead. This will continue to help protect you from getting HIV.
- Schedule your appointment with your doctor or nurse to make sure you will receive your next injections on time.
- You must receive your next injections within 28 weeks of your last injection.

If you take more Lenacapavir Gilead than you should

Contact your doctor, nurse or pharmacist immediately for advice. If you take more than the recommended dose of Lenacapavir Gilead, you may be at higher risk of side effects (see section 4, Possible side effects).

It is important not to miss a dose of Lenacapavir Gilead tablets.

If you forget to take your tablets, contact your doctor, nurse or pharmacist immediately.

If you vomit within 3 hours after taking Lenacapavir Gilead tablets, contact your doctor or nurse immediately and take another two tablets. If you vomit more than 3 hours after taking Lenacapavir Gilead you do not need to take more tablets until your next scheduled tablets or injection.

If you miss a Lenacapavir Gilead injection appointment

- If you think you will not be able to attend an appointment for your injections, contact your doctor or nurse as soon as possible to discuss your options. If you need to miss a scheduled injection appointment, there is the option to temporarily take Lenacapavir Gilead tablets instead.
- **Using Lenacapavir Gilead tablets if you have to miss an injection appointment**
  - **Take one tablet by mouth, every 7 days until your injections resume.** Tablets can be taken with or without food.
  - It is important to continue Lenacapavir Gilead as your doctor or nurse recommends.

Do not stop taking Lenacapavir Gilead without talking to your doctor or nurse.
Take Lenacapavir Gilead for as long as your doctor recommends. Don’t stop unless your doctor advises you to. Missing Lenacapavir Gilead injections or tablets increases your risk of getting HIV.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Lenacapavir Gilead

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle label after EXP. The expiry date refers to the last day of that month.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Lenacapavir Gilead contains

The active substance is lenacapavir. Each tablet contains lenacapavir sodium equivalent to 300 mg lenacapavir.

The other ingredients are

Tablet core
Mannitol (E421), microcrystalline cellulose (E460), croscarmellose sodium (E468), copovidone, magnesium stearate (E572), poloxamer (see section 2, *Lenacapavir Gilead contains sodium*).

Film-coating
Polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol (E1521), talc (E553b), iron oxide yellow (E172), iron oxide black (E172), iron oxide red (E172).

What Lenacapavir Gilead looks like and contents of the pack

Lenacapavir Gilead film-coated tablets are beige, capsule-shaped, film-coated tablets, debossed with “GSI” on one side of the tablet and “62L” on the other side of the tablet. Lenacapavir Gilead comes in a bottle of 4 tablets. Each bottle contains a silica gel desiccant that must be kept in the bottle to help protect your tablets. The silica gel desiccant is contained in a separate packet and should not be swallowed.

Scientific Opinion Holder
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Manufacturer
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IDA Business & Technology Park
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USA

This leaflet was last revised in 07/2025.

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https://www.ema.europa.eu