Sunlenca® solution for injection
(lenacapavir (as sodium) 463.5 mg)
Solution for s.c. injection

1. NAME OF THE MEDICINAL PRODUCT

Sunlenca® 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 s.c. injection (injection).
Clear, yellow to brown solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sunlenca solution for injection, in combination with other antiretroviral(s), is indicated for the treatment of adults with multidrug resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen (see sections 4.2 and 5.1).

4.2 Posology and method of administration

Therapy should be prescribed by a physician experienced in the management of HIV infection.

Each injection should be administered by a healthcare professional.

Prior to starting lenacapavir, the healthcare professional should carefully select patients who agree to the required injection schedule and counsel patients about the importance of adherence to scheduled dosing visits to help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance associated with missed doses. In addition, the healthcare professional should counsel patients about the importance of adherence to an optimised background regimen (OBR) to further reduce the risk of viral rebound and potential development of resistance.

If Sunlenca is discontinued, it is essential to adopt an alternative, fully suppressive antiretroviral regimen where possible, no later than 28 weeks after the final injection of Sunlenca (see section 4.4).

Posology

Initiation
On treatment Day 1 and Day 2, the recommended dose of Sunlenca is 600 mg per day taken orally. On treatment Day 8, the recommended dose is 300 mg taken orally. Then, on treatment Day 15, the recommended dose is 927 mg administered by subcutaneous injection.

Oral tablets can be taken with or without food (see Sunlenca tablet Prescribing Information).

Maintenance
The recommended dose is 927 mg of Sunlenca administered by subcutaneous injection once every 6 months (26 weeks) from the date of the last injection (+/- 2 weeks).

Table 1: Recommended treatment regimen for Sunlenca: initiation and maintenance dosing schedule

Treatment time	
Dose of Sunlenca: initiation	
Day 1	600 mg orally (2 x 300 mg tablets)
Day 2	600 mg orally (2 x 300 mg tablets)
Day 8	300 mg orally (1 x 300 mg tablet)
Day 15	927 mg subcutaneous injection (2 x 1.5 mL injections[a])
Dose of Sunlenca: maintenance	
Every 6 Months (26 weeks)[b] +/- 2 weeks	927 mg subcutaneous injection (2 x 1.5 mL injections[a])

a Two injections, each at a separate site in the abdomen.
b From the date of the last injection.

Missed dose
During the maintenance period, if more than 28 weeks have elapsed since the last injection and if clinically appropriate to continue Sunlenca treatment, the regimen should be restarted from Day 1 (see table 1).

Special populations

Elderly
No dose adjustment of Sunlenca is required in elderly patients (see section 5.2).

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

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

Paediatric population
The safety and efficacy of Sunlenca in children under the age of 18 years old has not been established. No data are available.

Method of administration

For subcutaneous use.

Sunlenca injections should be administered into the abdomen (two injections, each at a separate site) by a healthcare professional (see section 6.6). 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

Risk of resistance following treatment discontinuation

If Sunlenca is discontinued, to minimise the risk of developing viral resistance it is essential to adopt an alternative, fully suppressive antiretroviral regimen where possible, no later than 28 weeks after the final injection of Sunlenca.

If virologic failure is suspected, an alternative regimen should be adopted where possible.

Use of other medicinal products after discontinuation of lenacapavir

If Sunlenca is discontinued, residual concentrations of lenacapavir may remain in the systemic circulation of patients for prolonged periods. These concentrations may affect the exposures of other medicinal products (i.e. sensitive CYP3A substrates) that are initiated within 9 months after the last subcutaneous dose of Sunlenca (see section 4.5). These concentrations are not expected to affect the exposures of other antiretroviral agents that are initiated after discontinuation of Sunlenca.

Immune Reconstitution Inflammatory Syndrome

In HIV infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples include cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Opportunistic infections

Patients should be advised that Sunlenca or any other antiretroviral therapy does not cure HIV infection and that they may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of patients with HIV associated diseases.

Co-administration of other medicinal products

Co-administration with medicinal products that are moderate inducers of CYP3A and P-gp (e.g. efavirenz) 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), such as atazanavir/cobicistat 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, such as rifampicin, may significantly decrease plasma concentrations of lenacapavir resulting in loss of therapeutic effect and development of resistance, therefore co-administration is contraindicated (see section 4.3). Moderate inducers of CYP3A and P-gp, such as efavirenz, may also significantly decrease plasma concentrations of lenacapavir, therefore co-administration is not recommended (see section 4.4).

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

Strong CYP3A4 inhibitors alone (e.g. voriconazole) or strong inhibitors of CYP3A4 and P-gp together (e.g. cobicistat) do not result in a clinically meaningful increase in lenacapavir exposures.

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

Table 2: Interactions between Sunlenca and other medicinal products

Medicinal product by therapeutic areas	Effects on concentrations. Mean percent change in AUC, C_{max}	Recommendation concerning co-administration with Sunlenca
ANTIMYCOBACTERIALS		
Rifampicin[a,b,c] (600 mg once daily)	Lenacapavir: AUC: ↓84% C_{max}: ↓55%	Co-administration is contraindicated (see section 4.3).
Rifabutin	Interaction not studied. Co-administration of rifabutin may decrease lenacapavir plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	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, which may result in loss of therapeutic effect and development of resistance.	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 Sunlenca
HERBAL PRODUCTS		
St. John's wort *(Hypericum perforatum)*	Interaction not studied. Co-administration of St. John's wort may decrease lenacapavir plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	Co-administration is contraindicated (see section 4.3).
ANTIRETROVIRAL AGENTS		
Atazanavir/cobicistat[b,d,e] (300 mg/150 mg once daily)	Lenacapavir: AUC: ↑ 321% C_{max}: ↑ 560%	Co-administration is not recommended (see section 4.4).
Efavirenz[b,d,f] (600 mg once daily)	Lenacapavir: AUC:↓ 56% C_{max}:↓ 36%	
Etravirine Nevirapine Tipranavir/ritonavir	Interaction not studied. Co-administration of etravirine, nevirapine, or tipranavir/ritonavir may decrease lenacapavir plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	
Cobicistat[b,d,g] (150 mg once daily)	Lenacapavir: AUC: ↑ 128% C_{max}:↑ 110%	No dose adjustment of lenacapavir is required.
Darunavir/cobicistat[b,d,h] (800 mg/150 mg once daily)	Lenacapavir: AUC:↑ 94% C_{max}:↑ 130%	
Ritonavir	Interaction not studied. Co-administation of ritonavir may increase lenacapavir plasma concentrations.	
Tenofovir alafenamide[d,i,j] (25 mg)	Tenofovir alafenamide: AUC:↑ 32% C_{max}:↑ 24% Tenofovir[k]: 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 Sunlenca.
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.

Medicinal product by therapeutic areas	Effects on concentrations. Mean percent change in AUC, C_{max}	Recommendation concerning co-administration with Sunlenca
		Vardenafil: No more than 5 mg in a 24-hour period. Tadalafil: • For use as needed: no more than 10 mg every 72 hours • For once daily use: dose not to exceed 2.5 mg
CORTICOSTEROIDS (systemic)		
Dexamethasone Hydrocortisone/cortisone	Interaction not studied. Plasma concentrations of corticosteroids may be increased when co-administered with lenacapavir. Plasma concentrations of lenacapavir may decrease when co-administered with systemic dexamethasone, which may result in loss of therapeutic effect and development of resistance.	Co-administration of Sunlenca 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 Sunlenca, 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[d,i,l] (2 mg single dose; simultaneous or 3 days after lenacapavir)	Pitavastatin: AUC:↔ C_{max}:↔	No dose adjustment of pitavastatin and rosuvastatin is required.
Rosuvastatin[d,i,m] (5 mg single dose)	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 Sunlenca
SEDATIVES/HYPNOTICS		
Midazolam[d,i,n] (2.5 mg single dose; oral; simultaneous administration)	Midazolam: AUC: ↑ 259% C_{max}: ↑ 94% 1-hydroxymidazolam[o]: AUC: ↓ 24% C_{max}: ↓ 46%	Caution is warranted when midazolam or triazolam, is co-administered with Sunlenca.
Midazolam[d,i,n] (2.5 mg single dose; oral;1 day after lenacapavir)	Midazolam: AUC: ↑ 308% C_{max}: ↑ 116% 1-hydroxymidazolam[o]: 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 inhibitor and/or P-gp inhibitors.
ANTIFUNGALS		
Voriconazole[a,b,p,q] (400 mg twice daily/200 mg twice daily)	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 CONTRACEPTIVES		
Ethinylestradiol Progestins	Interaction not studied. Plasma concentrations of ethinylestradiol and progestins may be increased when co-administered with lenacapavir.	No dose adjustment of ethinylestradiol and progestins is required.
GENDER AFFIRMING HORMONES		
17β-estradiol Anti-androgens Progestogen Testosterone	Interaction not studied. Plasma concentrations of these medicinal products may be increased when co-administered with lenacapavir.	No dose adjustment of these gender affirming hormones is required.

a Fasted.

b This study was conducted using lenacapavir 300 mg single dose administered orally.

c Evaluated as a strong inducer of CYP3A, and an inducer of P-gp and UGT.
d Fed.
e Evaluated as a strong inhibitor of CYP3A, and an inhibitor UGT1A1 and P-gp.
f Evaluated as a moderate inducer of CYP3A and an inducer of P-gp.
g Evaluated as a strong inhibitor of CYP3A and an inhibitor of P-gp.
h Evaluated as a strong inhibitor of CYP3A, and an inhibitor and inducer of P-gp.
i This study was conducted using lenacapavir 600 mg single dose following a loading regimen of 600 mg twice daily for 2 days, single 600 mg doses of lenacapavir were administered with each co-administered medicinal product.
j Evaluated as a P-gp substrate.
k Tenofovir alafenamide is converted to tenofovir *in vivo*.
l Evaluated as an OATP substrate.
m Evaluated as an BCRP substrate.
n Evaluated as a CYP3A substrate.
o Major active metabolite of midazolam.
p Evaluated as a strong inhibitor of CYP3A.
q 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

Pregnancy

There are no or limited amount of data from the use of lenacapavir in pregnant women.

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

As a precautionary measure, it is preferable to avoid the use of Sunlenca during pregnancy unless the clinical condition of the women requires treatment with Sunlenca.

Breast-feeding

In order to avoid transmission of HIV to the infant it is recommended that women living with HIV do not breast-feed their infants.

It is unknown whether lenacapavir is excreted in human milk. After administration to rats during pregnancy and lactation, lenacapavir was detected at low levels in the plasma of nursing rat pups, without effects on these nursing pups.

Fertility

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

4.7 Effects on ability to drive and use machines

Sunlenca 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 reactions in heavily treatment experienced adult patients with HIV were injection site reactions (ISRs) (63%) and nausea (4%).

Tabulated list of adverse reactions

A tabulated list of adverse reactions is presented in Table 3. 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
Immune system disorders	
Not known	immune reconstitution inflammatory syndrome
Gastrointestinal disorders	
Common	nausea
General disorders and administration site conditions	
Very common	injection site reactions[b]

a Frequency based on all patients (Cohorts 1 and 2) in CAPELLA (see section 5.1).
b Includes injection site swelling, pain, nodule, erythema, induration, pruritus, extravasation, discomfort, mass, haematoma, oedema, and ulcer.

Description of selected adverse reactions

Immune Reconstitution Inflammatory Syndrome
In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

Local injection site reactions
Most patients had ISRs that were mild (Grade 1, 42%) or moderate (Grade 2, 18%). Three percent of patients experienced a severe (Grade 3) ISR that resolved within 1 to 8 days. No patients experienced a Grade 4 ISR. The median duration of all ISRs excluding nodules and indurations was 6 days. The median duration of nodules and indurations was 180 and 118 days, respectively.

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.

You can report any side effects to the Ministry of Health by clicking on the link "Report side effects due to medical treatment" that is located on the Ministry of Health homepage (www.health.gov.il) which redirects to the online form for reporting side effects or by clicking on the link: https://sideeffects.health.gov.il.

4.9 Overdose

If overdose occurs the patient must be monitored for signs or symptoms of adverse reactions (see section 4.8). Treatment of overdose with Sunlenca consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient. 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.

In a study of lenacapavir in combination with representatives from the main classes of antiretroviral agents (nucleoside reverse transcriptase inhibitors [NRTIs], non-nucleoside reverse transcriptase inhibitors [NNRTIs], integrase strand-transfer inhibitors [INSTIs], and protease inhibitors [PIs]), synergistic antiviral effects were observed. No antagonism was observed for these combinations.

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. HIV-1 variants with >10-fold reduction in susceptibility to lenacapavir compared to WT virus displayed diminished replication capacity in primary human CD4+ T lymphocytes and macrophages (0.03 – 28% and 1.9 – 72% of WT virus, respectively).

In GS-US-200-4625 (‘CAPELLA’), 29% (21/72) of heavily treatment experienced-patients met the criteria for resistance analyses through Week 52 (HIV-1 RNA ≥50 copies/mL at confirmed virologic failure [suboptimal virologic response at Week 4, virologic rebound, or viremia at last visit]) and were analysed for lenacapavir-associated mutation emergence. Lenacapavir-associated capsid mutations were found in 11.1% (n = 8) of these patients. The M66I CA mutation was observed in 8.3% (n = 6) of patients, alone or in combination with other Sunlenca-associated capsid mutations including N74D, Q67Q/H/K/N, K70K/N/R/S, T107T/C, and T107A. One patient had a K70H CA mutation emerging along with T107T/N, and one patient had emergence of both Q67H and K70R in CA.

Phenotypic analyses indicated that the M66I and K70H mutations were associated with an average decrease in lenacapavir susceptibility of 234-fold and 265-fold, respectively, when compared to WT. The Q67H + K70R CA resistance pattern was associated with a 15-fold decrease in lenacapavir susceptibility.

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 = 24), 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 (9-fold higher than the therapeutic exposures of Sunlenca), 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 Sunlenca in HIV-1 infected, heavily treatment experienced patients with multidrug resistance is based on 52-week data from a partially randomised, placebo-controlled, double-blind, multicentre study, GS-US-200-4625 ('CAPELLA').

CAPELLA was conducted in 72 heavily treatment-experienced patients with multiclass resistant HIV-1. Patients were required to have a viral load ≥ 400 copies/mL, documented resistance to at least two antiretroviral medicinal products from each of at least 3 of the 4 classes of antiretroviral medicinal products (NRTI, NNRTI, PI and INSTI), and no more than 2 fully active antiretroviral medicinal products from the 4 classes of antiretroviral medicinal products remaining at baseline due to resistance, intolerability, medicinal product access, contraindication, or other safety concerns.

The trial was composed of two cohorts. Patients were enrolled into the randomised cohort (Cohort 1, n = 36)) if they had a < 0.5 $\log_{10}$ HIV-1 RNA decline compared to the screening visit. Patients were enrolled into the non-randomised cohort (Cohort 2, n = 36) if they had a ≥ 0.5 $\log_{10}$ HIV-1 RNA decline compared to the screening visit or after Cohort 1 reached its planned sample size. Patients were administered 600 mg, 600 mg, and 300 mg lenacapavir orally on Days 1, 2, and 8, respectively, followed by 927 mg subcutaneously on Day 15 and 927 mg subcutaneously every 6 months thereafter (see section 5.2).

In the 14-day functional monotherapy period, patients in cohort 1 were randomised in a 2:1 ratio in a blinded fashion, to receive either lenacapavir or placebo, while continuing their failing regimen. After the functional monotherapy period, patients who had received Sunlenca continued on Sunlenca along with an OBR; patients who had received placebo during this period initiated Sunlenca along with an OBR.

The majority of patients in Cohort 1 were male (72%), White (46%) or Black (46%), and between 24 and 71 years of age (mean [SD]: 52 [11.2] years). At baseline, median viral load and CD4+ cell counts were 4.5 $\log_{10}$ copies/mL (range 2.33 to 5.40) and 127 cells/mm^3 (range 6 to 827), respectively. The majority (53%) of patients had no fully active agents within their initial failing regimen.

Patients in cohort 2 initiated Sunlenca and an OBR on Day 1.

The majority of patients in Cohort 2 were male (78%), White (36%), Black (31%) or Asian (33%), and between 23 and 78 years of age (mean [SD]: 48 [13.7] years). At baseline, median viral load and CD4+ cell counts were 4.5 $\log_{10}$ copies/mL (range 1.28 to 5.70) and 195 cells/mm^3 (range 3 to 1296), respectively. In cohort 2, 31% of patients had no fully active agents, 42% had 1 fully active agent, and 28% had 2 or more fully active agents within their initial failing regimen.

The primary efficacy endpoint was the proportion of patients in cohort 1 achieving ≥ 0.5 $\log_{10}$ copies/mL reduction from baseline in HIV-1 RNA at the end of the functional monotherapy period. The results of the primary endpoint analysis demonstrated the superiority of Sunlenca compared with placebo, as shown in Table 4.

Table 4: Proportion of patients achieving a ≥ 0.5 log_{10} decrease in viral load (Cohort 1)

	Sunlenca (n = 24)	**Placebo (n = 12)**
Proportion of patients achieving a ≥ 0.5 log_{10} decrease in viral load	87.5%	16.7%
Treatment difference (95% CI); p-value	70.8% (34.9% to 90.0%); p < 0.0001	

The results at Weeks 26 and 52 are provided in Table 5 and Table 6.

Table 5: Virologic outcomes (HIV-1 RNA < 50 copies/mL and < 200 copies/mL) at weeks 26[a] and 52[b] with Sunlenca plus OBR in the CAPELLA trial (Cohort 1)

	Sunlenca plus OBR (n= 36)	
	Week 26	**Week 52**
HIV-1 RNA < 50 copies/mL **HIV-1 RNA < 200 copies/mL**	81% 89%	83% 86%
HIV-1 RNA ≥ 50 copies/mL[c] **HIV-1 RNA ≥ 200 copies/mL[c]**	19% 11%	14% 11%
No virologic data in week 26 or week 52 Window	0	3%
Discontinued study drug due to AE or death [d]	0	0
Discontinued study drug due to other reasons [e] and last available HIV-1 RNA < 50 copies/mL or < 200 copies/mL	0	3%
Missing data during window but on study drug	0	0

a Week 26 window was between Days 184 and 232 (inclusive).
b Week 52 window was between Days 324 and 414 (inclusive).
c Includes patients who had ≥ 50 copies/mL or ≥ 200 copies/mL, respectively, in the Week 26 or 52 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL or ≥ 200 copies/mL, respectively.
d Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
e Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

Table 6: Virologic outcomes (HIV-1 RNA < 50 copies/mL) by baseline covariates at weeks 26[a] and 52[b] with Sunlenca plus OBR in the CAPELLA trial (Cohort 1)

	Sunlenca plus OBR (n = 36)	
	Week 26	**Week 52**
Baseline plasma viral load (copies/mL)		
≤ 100,000	86% (25/29)	86% (25/29)
> 100,000	57% (4/7)	71% (5/7)
Baseline CD4+ (cells/mm^3)		
< 200	78% (21/27)	78% (21/27)
≥ 200	89% (8/9)	100% (9/9)
Baseline INSTI resistance profile		
With INSTI resistance	85% (23/27)	81% (22/27)
Without INSTI resistance	63% (5/8)	88% (7/8)
Number of fully active ARV agents in the OBR		
0	67% (4/6)	67% (4/6)
1	86% (12/14)	79% (11/14)
≥ 2	81% (13/16)	94% (15/16)
Use of DTG and/or DRV in the OBR		
With DTG and DRV	83% (10/12)	83% (10/12)
With DTG, without DRV	83% (5/6)	83% (5/6)
Without DTG, with DRV	78% (7/9)	89% (8/9)

	Sunlenca plus OBR (n = 36)	
	Week 26	Week 52
Without DTG or DRV	78% (7/9)	78% (7/9)

ARV = antiretroviral; DRV = darunavir; DTG = dolutegravir; INSTI = integrase strand-transfer inhibitor; OBR = optimised background regimen

a Week 26 window was between Days 184 and 232 (inclusive).

b Week 52 window was between Day 324 and 414 (inclusive).

In cohort 1, at Weeks 26 and 52, the mean change from baseline in CD4+ cell count was 81 cells/mm^3 (range: -101 to 522) and 83 cells/mm^3 (range: -194 to 467).

In cohort 2, at Week 26, 81% (29/36) of patients achieved HIV-1 RNA < 50 copies/mL and the mean change from baseline in CD4+ cell count was 98 cells/mm^3 (range: -103 to 459).

5.2 Pharmacokinetic properties

Lenacapavir exposures (AUC_{tau}, C_{max} and C_{trough}) were 29% to 84% higher in heavily treatment experienced patients with HIV-1 infection as compared to subjects without HIV-1 infection based on population pharmacokinetics analysis.

Absorption

Subcutaneous administration
Lenacapavir is completely absorbed following subcutaneous administration. Due to slow release from the site of subcutaneous administration, the absorption profile of subcutaneously administered lenacapavir is complex with peak plasma concentrations occurring 84 days postdose.

Oral administration
Lenacapavir is absorbed following oral administration with peak plasma concentrations occurring approximately 4 hours after administration of Sunlenca. Absolute bioavailability following oral administration of lenacapavir is low (approximately 6 to 10%). 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
Simulated steady state exposures of lenacapavir following recommended dosing regimen in heavily treatment experienced patients with HIV are provided in Table 7.

Table 7: Pharmacokinetic parameters of lenacapavir following oral and subcutaneous administration

Parameter Mean (%CV)[a]	Day 1 and 2: 600 mg (oral), Day 8: 300 mg (oral), Day 15: 927 mg (SC)		
	Day 1 to Day 15	Day 15 to end of month 6	Steady state
C_{max} (ng/ mL)	69.6 (56)	87 (71.8)	97.2 (70.3)
AUC_{tau} (h•ng/mL)	15,600 (52.9)	250,000 (66.6)	300,000 (68.5)
C_{trough} (ng/mL)	35.9 (56.8)	32.7 (88)	36.2 (90.6)

CV = Coefficient of Variation; SC = subcutaneous

a Simulated exposures utilizing population PK analysis.

Distribution

Lenacapavir steady state volume of distribution was 976 litres in heavily treatment experienced patients with HIV-1 infection based on population pharmacokinetic analysis.

Lenacapavir is highly bound to plasma proteins (approximately 99.8%, based on *in vivo* data).

Biotransformation

Following a single intravenous dose of radiolabelled-lenacapavir to healthy subjects, 76% of the total radioactivity was recovered from feces and < 1% from urine. Unchanged lenacapavir was the predominant moiety in plasma (69%) and feces (33%). Metabolism played a lesser role in lenacapavir elimination. Lenacapavir was metabolized 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. Lenacapavir clearance was 3.62 L/h in heavily treatment experienced patients with HIV-1 infection 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, gender, and race
Population PK analyses using data from adult trials, including a limited number of elderly patients (n = 5; ≥ 65 to 78 years), did not identify any clinically relevant differences in the exposure of lenacapavir due to age, gender, 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 subjects 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 patients with moderate hepatic impairment (Child-Pugh B) compared to subjects 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 patients 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 subjects 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 subjects with severe renal impairment compared with subjects with normal renal function; however, the increase was not considered clinically relevant. The pharmacokinetics of lenacapavir have not been studied in patients 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.

5.3 Preclinical safety data

Non-clinical data reveal 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 60 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 8 times the human exposure at the (RHD. In rats and rabbits, embryofoetal development was not affected at exposures up to 21 and 172 times the human exposure, respectively, at the RHD. In rats, pre- and postnatal development was not affected at exposures up to 7 times the human exposure at the RHD.

Transfer of lenacapavir from maternal to neonatal rats was observed in a prenatal and postnatal development study, but it is not known whether the transport occurred via the placenta or the milk; therefore the potential for lenacapavir to pass into the placenta or be excreted into milk in humans is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol (E1521)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original outer carton in order to protect from light. 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.

6.5 Nature and contents of container

Sunlenca 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 aluminum overseal with flip off cap;
- 2 vial access devices, 2 disposable syringes, and 2 injection safety needles for subcutaneous injection (22-gauge, 12.7 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. Sunlenca injection is a yellow to brown solution. Do not use Sunlenca 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. Use of the vial access device is required. Two 1.5 mL injections are required for a complete dose.

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

7. MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

8. REGISTRATION HOLDER

Gilead Sciences Israel Ltd.
4 HaHarash Street
Hod Hasharon,
4524075
Israel

9. REGISTRATION NUMBER

34743

Revised in September 2024.
Reference: EU SmPC September 2024

IL-SEP24-EU-SEP24