ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Sunlenca 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

Sunlenca 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 SmPC).

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 only.

Sunlenca injections must only be administered subcutaneously into the abdomen (two injections, each at a separate site) by a healthcare professional (see section 6.6). Sunlenca injections must NOT be administered 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.

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 patients with HIV 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.

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. Sunlenca injections must only be administered subcutaneously (see section 4.2).

Slow or non-resolving injection site nodules and indurations
Administration of Sunlenca 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. In CAPELLA (see section 5.1), nodules associated with the first injections of Sunlenca had not resolved in 10% of participants after a median follow-up of 554 days, whereas all indurations had resolved (see section 4.8). The mechanism driving the persistence of injection site nodules in some participants 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.

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 is not recommended (see section 4.4).

Medicinal product by therapeutic areas	Effects on concentrations. Mean percent change in AUC, C_{max}	Recommendation concerning co-administration with Sunlenca
	Co-administration of rifabutin may decrease lenacapavir plasma concentrations, which may result in loss of therapeutic effect and development of resistance.	
ANTICONVULSANTS		
Carbamazepine Phenytoin	Interaction not studied.	Co-administration is contraindicated (see section 4.3).
Oxcarbazepine Phenobarbital	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 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, 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.

Medicinal product by therapeutic areas	Effects on concentrations. Mean percent change in AUC, C_{max}	Recommendation concerning co-administration with Sunlenca
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. 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)		
Cortisone/hydrocortisone Dexamethasone	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	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
	co-administered with lenacapavir.	
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 inhibitors 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 participants with HIV were ISRs (76%) and nausea (6%).

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 participants (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 from CAPELLA; and necrosis identified from post-marketing surveillance.

Description of selected adverse reactions

Immune Reconstitution Inflammatory Syndrome
In patients with HIV 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
Through Week 156 of treatment, most participants had mild (Grade 1, 54%) or moderate (Grade 2, 17%) ISRs. Six percent (4/72) of participants experienced a severe Grade 3 ISR with a median time to resolution of 15 (range: 1 to 71) days. No participants experienced a Grade 4 ISR. The median time to resolution of all ISRs, excluding nodules and indurations, was 5 days. The median time to resolution of nodules and indurations associated with the first injections of Sunlenca was 191 (Q1, Q3: 71, 366) and 113 (Q1, Q3: 29, 224) days, respectively. After a median follow-up of 554 days, nodules associated with the first injections of Sunlenca had not resolved in 10% (7/72) of the participants. All indurations associated with the first injections of Sunlenca had resolved.

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 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 WT 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’), 39% (28/72) of heavily treatment-experienced participants met the criteria for resistance analyses through Week 156 (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 19.0% (n = 14) of participants. The M66I CA mutation was observed in 8.3% (n = 6) of participants, alone or in combination with other Sunlenca-associated capsid mutations including Q67Q/H/K/N, K70K/N/R/S, N74D/H, A105T and T107T/A/C. Four participants had emergence of Q67H + K70R in CA with or without A105T and/or T107N. One participant had emergence of K70N + N74K + T107T/N, one participant had emergence of N74D alone, one participant had emergence of Q67Q/H alone, and one participant had emergence of Q67K + K70H. Eight participants with virologic failure had emergent resistance substitutions to components of the OBR.

Phenotypic analyses indicated that the M66I and Q67K + K70H mutation patterns were associated with a decrease in lenacapavir susceptibility of 234-fold (median) and 167-fold, respectively, in comparison to WT. The Q67H + K70R + A105T or T107N resistance pattern was associated with an average 195-fold decrease in lenacapavir susceptibility compared to WT, and Q67H + K70R alone was associated with a 15-fold decrease in lenacapavir susceptibility compared to WT. The presence of mutations K70N + N74K was associated with a 289-fold decrease in lenacapavir susceptibility

compared to WT, and the Q67Q/H mutation was associated with a 5.9-fold decrease in lenacapavir susceptibility compared to WT.

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 heavily treatment-experienced participants with multidrug resistant HIV-1 is based on 156-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 participants with multiclass resistant HIV-1. Participants 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. Participants 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. Participants 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. Participants 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, participants in Cohort 1 were randomised in a 2:1 ratio in a blinded fashion, to receive either Sunlenca or placebo, while continuing their failing regimen. After the functional monotherapy period, participants who had received Sunlenca continued on Sunlenca along with an OBR; Participants who had received placebo during this period initiated Sunlenca along with an OBR.

The majority of participants 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 participants had no fully active agents within their initial failing regimen.

Participants in Cohort 2 initiated Sunlenca and an OBR on Day 1.

The majority of participants 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 participants 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 participants 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 participants achieving a ≥ 0.5 $\log_{10}$ decrease in viral load (Cohort 1)

	Sunlenca (n = 24)	**Placebo (n = 12)**
Proportion of participants 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, 52 and 156 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], 52[b] and 156[c] with Sunlenca plus OBR in the CAPELLA trial (Cohort 1)

	Sunlenca plus OBR		
	Week 26 n = 36	**Week 52 n = 36**	**Week 156 n = 34[d]**
HIV-1 RNA < 50 copies/mL	81%	83%	65%[e]
HIV-1 RNA < 200 copies/mL	89%	86%	68%[f]
HIV-1 RNA ≥ 50 copies/mL[g]	19%	14%	18%
HIV-1 RNA ≥ 200 copies/mL[g]	11%	11%	15%
No virologic data in week 26, 52 or 156 Window	0	3%	18%
Discontinued study drug due to AE or death [h]	0	0	3%
Discontinued study drug due to other reasons [i] and last available HIV-1 RNA < 50 copies/mL or < 200 copies/mL	0	3%	9%
Missing data during window but on study drug	0	0	6%

a Week 26 window was between Days 184 and 232 (inclusive).
b Week 52 window was between Days 324 and 414 (inclusive).
c Week 156 window was between Days 1052 and 1142 (inclusive).
d Two participants who completed the CAPELLA trial before Week 156 were excluded from the analysis.
e Based on missing = excluded analysis to impute missing values, 82% (23/28) of participants had HIV-1 RNA < 50 copies/mL at Week 156.
f Based on missing = excluded analysis to impute missing values, 86% (24/28) of participants had HIV-1 RNA < 200 copies/mL at Week 156.
g Includes participants who had ≥ 50 copies/mL or ≥ 200 copies/mL, respectively, in the Week 26, 52 or 156 window; participants who discontinued early due to lack or loss of efficacy; participants 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.
h Includes participants 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.
i Includes participants 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], 52[b] and 156[c] with Sunlenca plus OBR in the CAPELLA trial (Cohort 1)

	Sunlenca plus OBR		
	Week 26 n = 36	**Week 52 n = 36**	**Week 156 n = 34**
Baseline plasma viral load (copies/mL)			
≤ 100,000	86% (25/29)	86% (25/29)	67% (18/27)
> 100,000	57% (4/7)	71% (5/7)	57% (4/7)

	Sunlenca plus OBR		
	Week 26 n = 36	**Week 52 n = 36**	**Week 156 n = 34**
Baseline CD4+ (cells/mm^3)			
< 200	78% (21/27)	78% (21/27)	58% (15/26)
≥ 200	89% (8/9)	100% (9/9)	88% (7/8)
Baseline INSTI resistance profile			
With INSTI resistance	85% (23/27)	81% (22/27)	62% (16/26)
Without INSTI resistance	63% (5/8)	88% (7/8)	71% (5/7)
Number of fully active ARV agents in the OBR			
0	67% (4/6)	67% (4/6)	67% (4/6)
1	86% (12/14)	79% (11/14)	58% (7/12)
≥ 2	81% (13/16)	94% (15/16)	69% (11/16)
Use of DTG and/or DRV in the OBR			
With DTG and DRV	83% (10/12)	83% (10/12)	58% (7/12)
With DTG, without DRV	83% (5/6)	83% (5/6)	60% (3/5)
Without DTG, with DRV	78% (7/9)	89% (8/9)	67% (6/9)
Without DTG or DRV	78% (7/9)	78% (7/9)	75% (6/8)

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).
c Week 156 window was between Days 1052 and 1142 (inclusive).

In Cohort 1, at Weeks 26, 52 and 156, the mean change from baseline in CD4+ cell count was 81 cells/mm^3 (range: -101 to 522), 82 cells/mm^3 (range: -194 to 467), and 157 cells/mm^3 (range: -93 to 659), respectively.

In Cohort 2, at Weeks 26, 52 and 156, 81% (29/36), 72% (26/36), and 58% (21/36) of participants achieved HIV-1 RNA < 50 copies/mL, respectively, and the mean change from baseline in CD4+ cell count was 98 cells/mm^3 (range: -103 to 459), 113 cells/mm^3 (range: -124 to 405), and 173 cells/mm^3 (range: -168 to 455), respectively.

Paediatric population

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

5.2 Pharmacokinetic properties

Lenacapavir exposures (AUC_{tau}, C_{max} and C_{trough}) were 29% to 84% higher in heavily treatment experienced participants with HIV-1 infection as compared to participants 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 participants 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 participants 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 participants, 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 participants 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 participants (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 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 participants 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 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 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 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

4 years

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. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1671/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 August 2022

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.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Sunlenca 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

Sunlenca tablet, 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, for oral loading prior to administration of long-acting lenacapavir injection (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.

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.

Posology

Initiation of treatment with lenacapavir requires Sunlenca film-coated tablets to be taken as oral loading prior to administration of Sunlenca injection.

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.

Table 1: Recommended treatment regimen for Sunlenca: initiation

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])

a Two injections, each at a separate site in the abdomen.

Missed dose
If the Day 2 (600 mg) oral dose is missed by:
- less than 6 days, the patient should take 600 mg as soon as possible, and 300 mg on Day 8.
- 6 days or more, the patient should take 600 mg as soon as possible, and 300 mg on Day 15.

If the Day 8 (300 mg) oral dose is missed by:
- less than 6 days, the patient should take 300 mg as soon as possible.
- 6 days or more, the patient should take 300 mg on Day 15.

Regardless of when the Day 2 or Day 8 oral dose is being taken, subcutaneous injection should be administered on Day 15 as described in Table 1.

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

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 oral use.

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

4.3 Contraindications

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

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

Immune Reconstitution Inflammatory Syndrome

In patients with HIV 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 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, 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.
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).

Medicinal product by therapeutic areas	Effects on concentrations. Mean percent change in AUC, C_{max}	Recommendation concerning co-administration with Sunlenca
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. 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 Sunlenca
CORTICOSTEROIDS (systemic)		
Cortisone/hydrocortisone Dexamethasone	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.
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)	Interaction not studied.	Due to potential bleeding risk, dose adjustment of DOAC may be

Medicinal product by therapeutic areas	Effects on concentrations. Mean percent change in AUC, C_{max}	Recommendation concerning co-administration with Sunlenca
Rivaroxaban Dabigatran Edoxaban	Plasma concentration of DOAC may be increased when co-administered with lenacapavir.	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,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 reaction in heavily treatment experienced adult participants with HIV was nausea (6%).

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

a Frequency based on all participants (Cohorts 1 and 2) in CAPELLA (see section 5.1).

Description of selected adverse reactions

Immune Reconstitution Inflammatory Syndrome
In patients with HIV 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).

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 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 WT 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'), 39% (28/72) of heavily treatment-experienced participants met the criteria for resistance analyses through Week 156 (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 19.0% (n = 14) of participants. The M66I CA mutation was observed in 8.3% (n = 6) of participants, alone or in combination with other Sunlenca-associated capsid mutations including, Q67Q/H/K/N, K70K/N/R/S, N74D/H, A105T and T107T/A/C. Four participants had emergence of Q67H + K70R in CA with or without A105T and/or T107N. One participant had emergence of K70N + N74K + T107T/N, one participant had emergence of N74D alone, one participant had emergence of Q67Q/H alone, and one participant had emergence of Q67K + K70H. Eight participants with virologic failure had emergent resistance substitutions to components of the OBR.

Phenotypic analyses indicated that the M66I and Q67K + K70H mutation patterns were associated with a decrease in lenacapavir susceptibility of 234-fold (median) and 167-fold, respectively, in comparison to WT. The Q67H + K70R + A105T or T107N resistance pattern was associated with an average 195-fold decrease in lenacapavir susceptibility compared to WT, and Q67H + K70R alone was associated with a 15-fold decrease in lenacapavir susceptibility compared to WT. The presence of mutations K70N + N74K was associated with a 289-fold decrease in lenacapavir susceptibility compared to WT, and the Q67Q/H mutation was associated with a 5.9-fold decrease in lenacapavir susceptibility compared to WT.

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 heavily treatment-experienced participants with multidrug resistant HIV-1 is based on 156-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 participants with multiclass resistant HIV-1. Participants 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. Participants 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. Participants 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. Participants 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, participants 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, participants who had received Sunlenca continued on Sunlenca along with an OBR; participants who had received placebo during this period initiated Sunlenca along with an OBR.

The majority of participants 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 participants had no fully active agents within their initial failing regimen.

Participants in Cohort 2 initiated Sunlenca and an OBR on Day 1.

The majority of participants 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 participants 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 participants 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 participants achieving a ≥ 0.5 log_{10} decrease in viral load (Cohort 1)

	Sunlenca (n = 24)	**Placebo (n = 12)**
Proportion of participants 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, 52 and 156 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], 52[b] and 156[c] with Sunlenca plus OBR in the CAPELLA trial (Cohort 1)

	Sunlenca plus OBR		
	Week 26 n = 36	**Week 52 n = 36**	**Week 156 n = 34[d]**
HIV-1 RNA < 50 copies/mL	81%	83%	65%[e]
HIV-1 RNA < 200 copies/mL	89%	86%	68%[f]
HIV-1 RNA ≥ 50 copies/mL[g]	19%	14%	18%
HIV-1 RNA ≥ 200 copies/mL[g]	11%	11%	15%
No virologic data in week 26, 52 or 156 Window	0	3%	18%
Discontinued study drug due to AE or death [h]	0	0	3%
Discontinued study drug due to other reasons [i] and last available HIV-1 RNA < 50 copies/mL or < 200 copies/mL	0	3%	9%
Missing data during window but on study drug	0	0	6%

a Week 26 window was between Days 184 and 232 (inclusive).
b Week 52 window was between Days 324 and 414 (inclusive).
c Week 156 window was between Days 1052 and 1142 (inclusive).
d Two participants who completed the CAPELLA trial before Week 156 were excluded from the analysis.
e Based on missing = excluded analysis to impute missing values, 82% (23/28) of participants had HIV-1 RNA < 50 copies/mL at Week 156.
f Based on missing = excluded analysis to impute missing values, 86% (24/28) of participants had HIV-1 RNA < 200 copies/mL at Week 156.
g Includes participants who had ≥ 50 copies/mL or ≥ 200 copies/mL, respectively, in the Week 26 or 52 window; participants who discontinued early due to lack or loss of efficacy; participants 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.
h Includes participants 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.
i Includes participants 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], 52[b] and 156[c] with Sunlenca plus OBR in the CAPELLA trial (Cohort 1)

	Sunlenca plus OBR		
	Week 26 n = 36	**Week 52 n = 36**	**Week 156 n = 34**
Baseline plasma viral load (copies/mL)			
≤ 100,000	86% (25/29)	86% (25/29)	67% (18/27)
> 100,000	57% (4/7)	71% (5/7)	57% (4/7)
Baseline CD4+ (cells/mm^3)			
< 200	78% (21/27)	78% (21/27)	58% (15/26)
≥ 200	89% (8/9)	100% (9/9)	88% (7/8)
Baseline INSTI resistance profile			
With INSTI resistance	85% (23/27)	81% (22/27)	62% (16/26)
Without INSTI resistance	63% (5/8)	88% (7/8)	71% (5/7)
Number of fully active ARV agents in the OBR			
0	67% (4/6)	67% (4/6)	67% (4/6)
1	86% (12/14)	79% (11/14)	58% (7/12)
≥ 2	81% (13/16)	94% (15/16)	69% (11/16)
Use of DTG and/or DRV in the OBR			
With DTG and DRV	83% (10/12)	83% (10/12)	58% (7/12)
With DTG, without DRV	83% (5/6)	83% (5/6)	60% (3/5)
Without DTG, with DRV	78% (7/9)	89% (8/9)	67% (6/9)
Without DTG or DRV	78% (7/9)	78% (7/9)	75% (6/8)

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).
c Week 156 window was between Days 1052 and 1142 (inclusive).

In Cohort 1, at Weeks 26, 52, and 156, the mean change from baseline in CD4+ cell count was 81 cells/mm^3 (range: -101 to 522), 82 cells/mm^3 (range: -194 to 467), and157 cells/mm^3 (range: -93 to 659), respectively.

In Cohort 2, at Weeks 26, 52, and 156, 81% (29/36), 72% (26/36), and 58% (21/36) of participants achieved HIV-1 RNA < 50 copies/mL, respectively, and the mean change from baseline in CD4+ cell count was 98 cells/mm^3 (range: -103 to 459), 113 cells/mm^3 (range: -124 to 405), and 173 cells/mm^3 (range: -168 to 455), respectively.

Paediatric population

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

5.2 Pharmacokinetic properties

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

Absorption

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.

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.

Pharmacokinetic parameters
Simulated steady state exposures of lenacapavir following recommended dosing regimen in heavily treatment experienced participants 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 participants 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 participants, 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 participants 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 participants (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 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 participants 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 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 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 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

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

4 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Sunlenca tablets are packaged in child-resistant clear PVC/aluminium/paperboard blister. The blister is packaged with silica gel desiccant in a flexible laminated pouch. Pack size of 5 tablets.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1671/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 August 2022

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 MARKETING AUTHORISATION

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

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 MARKETING AUTHORISATION

- **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 marketing authorisation holder (MAH) 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 marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation 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

Sunlenca 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 vial access devices
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 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 MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1671/002

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

Sunlenca 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

BACKING CARD-For Healthcare Professionals Only
INSTRUCTIONS FOR USE (SOLUTION FOR INJECTION)

1. NAME OF THE MEDICINAL PRODUCT

Sunlenca 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

VIAL x2



VIAL ACCESS DEVICE x2



SYRINGE x2



22G, 13mm INJECTION NEEDLE x2



NOTE: all components are for single use

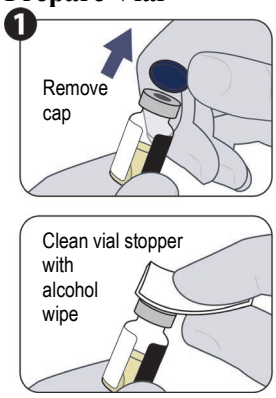
5. METHOD AND ROUTE(S) OF ADMINISTRATION

For Healthcare Professionals Only
INSTRUCTIONS FOR USE

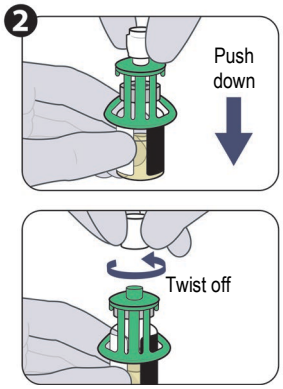
ATTENTION!
- **TWO 1.5 mL injections** are required to complete dose
- Use of **VIAL ACCESS DEVICE** is required

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

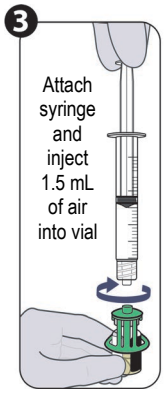
Prepare Vial

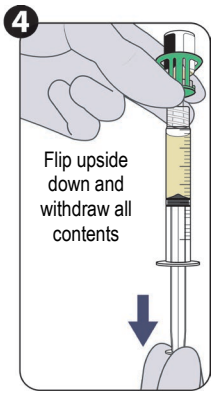


Prepare Vial Access Device

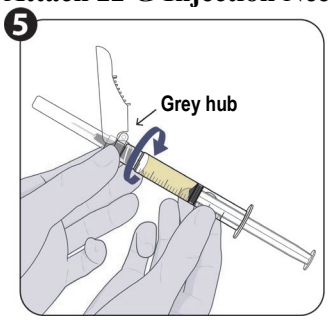


Attach and Fill Syringe

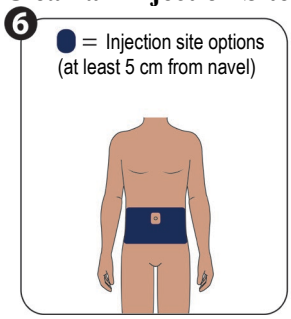




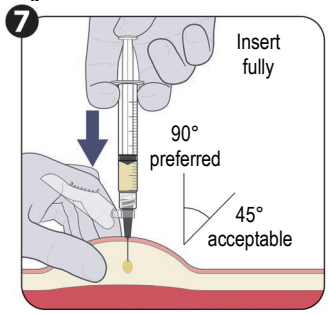
Attach 22 G Injection Needle to Syringe, Expel Air Bubbles, and Prime to 1.5 mL



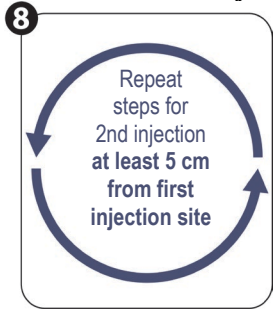
Clean an Injection Site on Patient's Abdomen



Inject 1.5 mL of Sunlenca Subcutaneously



Administer 2nd Injection



PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON AND POUCH (FILM-COATED TABLET)

1. NAME OF THE MEDICINAL PRODUCT

Sunlenca 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

5 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.
Tear or use scissors to cut at the dotted line. [Pouch only]

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 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 MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1671/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sunlenca [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]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER (5 tablets blister pack)

1. NAME OF THE MEDICINAL PRODUCT

Sunlenca 300 mg film-coated tablets
lenacapavir

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Day 1 Take two tablets
Date: _/ /_
Day 2 Take two tablets
Date: _/ /_
Day 8 Take one tablet
Date: _/ /_

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Sunlenca 464 mg solution for injection
lenacapavir

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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 or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Sunlenca is and what it is used for
2. What you need to know before you are given Sunlenca
3. How Sunlenca is given
4. Possible side effects
5. How to store Sunlenca
6. Contents of the pack and other information

1. What Sunlenca is and what it is used for

Sunlenca contains the active substance lenacapavir. This is an antiretroviral medicine known as a capsid inhibitor.

Sunlenca is a long acting medicine and **is used in combination with other antiretroviral medicines** to treat type 1 human immunodeficiency virus (HIV), the virus that cause acquired immunodeficiency syndrome (AIDS).

It is used to treat HIV infection in adults with limited treatment options (for example when other antiretroviral medicines are not sufficiently effective or are not suitable).

Treatment with Sunlenca in combination with other antiretrovirals reduces the amount of HIV in your body. This will improve the function of your immune system (the body's natural defences) and reduce the risk of developing illnesses linked to HIV infection.

2. What you need to know before you are given Sunlenca

Do not receive Sunlenca

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

- 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 Sunlenca and tell your doctor immediately** if you think this applies to you**.**

Warnings and precautions

Talk to your doctor before using Sunlenca

- **Talk to your doctor or pharmacist if you have ever had severe liver disease, or if tests have shown problems with your liver.** Your doctor will carefully consider whether to treat you with Sunlenca.

While you are using Sunlenca

Once you start using Sunlenca, look out for:

- **Signs of inflammation** or **infection**.

→ **If you notice any of these symptoms, tell your doctor immediately**. For more information, see section 4, *Possible side effects*.

- **Reactions where Sunlenca 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*.

Regular appointments are important

It is important that you **attend your planned appointments** to receive your Sunlenca injection, to control your HIV infection, and to stop your illness from getting worse. Talk to your doctor if you are thinking about stopping treatment. If you are late receiving your Sunlenca injection, or if you stop receiving Sunlenca, your will need to take other medicines to treat your HIV infection and to reduce the risk of developing viral resistance.

Children and adolescents

Do not give this medicine to children under 18 years of age. The use of Sunlenca in patients aged under 18 has not yet been studied, so it is not known how safe and effective the medicine is in that age group.

Other medicines and Sunlenca

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

Medicines that must never be taken with Sunlenca:

- **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 Sunlenca injection and tell your doctor immediately**.

Talk to your doctor in particular if you are taking:

- antibiotics containing:
  - rifabutin
- anticonvulsants used to treat epilepsy and prevent seizures (fits**)**, containing:
  - oxcarbazepine or phenobarbital
- medicines used to treat HIV, containing:
  - atazanavir/cobicistat, efavirenz, nevirapine, tipranavir/ritonavir or etravirine
- medicines used to treat migraine headache, containing:
  - dihydroergotamine or ergotamine
- medicine 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 various illnesses involving inflammations 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 if you are taking any of these medicines** or if you start taking any of these medicines during treatment with Sunlenca. Do not stop any treatment without contacting your doctor.

Sunlenca is a long-acting medicine. If after talking to your doctor you decide to stop your treatment or switch to another, you should know low levels of lenacapavir (the active substance in Sunlenca) can remain in your system for many months after your last injection. These low remaining levels should not affect other antiretroviral medicines that you take afterwards to treat your HIV infection. Some other medicines however may be affected by the low levels of lenacapavir in your system if you take them within 9 months after your last Sunlenca injection. You should check with your doctor if such medicines are safe for you to take after you stop treatment with Sunlenca.

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 or pharmacist for advice before taking this medicine.

As a precautionary measure you should avoid the use of Sunlenca during pregnancy unless your doctor tells you otherwise.

Breast-feeding is not recommended in women living with HIV because HIV infection can be passed on to the baby through breast milk. If you are breast-feeding, or thinking about breast-feeding, **you should discuss it with your doctor as soon as possible.**

Driving and using machines

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

Sunlenca contains sodium

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

3. How Sunlenca is given

Sunlenca is **used in combination with other antiretroviral medicines** to treat HIV infection. Your doctor will advise which other medicines you need to take to treat your HIV infection, and when you need to take them.

Your treatment with Sunlenca starts with tablets you take by mouth, followed by injections given by your doctor or nurse, as described below.

Talk to your doctor before taking the tablets. You will be advised when to start your tablets and when your appointment for the first injections will be scheduled.

Day 1 of treatment:
- Two tablets taken by mouth. These can be taken with or without food.

Day 2 of treatment:
- Two tablets taken by mouth. These can be taken with or without food.

Day 8 of treatment:
- One tablet taken by mouth. This can be taken with or without food.

Day 15 of treatment:
- Two injections into your abdomen (tummy) given at the same time by your doctor or nurse.

Every 6 months:
- Two injections into your abdomen given at the same time by your doctor or nurse.

If you are given more Sunlenca 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, tell the doctor or a nurse.

If you miss a Sunlenca injection

- It is important that you **attend your planned appointments every 6 months** to receive your injections of Sunlenca. This will help to control your HIV infection and to stop your illness from getting worse.
- If you think you will not be able to attend your appointment for your injections, call your doctor as soon as possible to discuss your treatment options.

If you miss or vomit the tablets, refer to the package leaflet for Sunlenca tablets.

If you stop receiving Sunlenca

Do not stop receiving Sunlenca without talking to your doctor. Keep receiving Sunlenca injections for as long as your doctor recommends. Stopping Sunlenca can seriously affect how future HIV treatments work.

→ Talk to your doctor if you want to stop receiving Sunlenca injections.

4. Possible side effects

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

Possible serious side effects: tell a doctor immediately

- **Any signs of inflammation or infection.** In some patients with advanced HIV infection (AIDS) and a history of opportunistic infections (infections that occur in people with a weak immune system), signs and symptoms of inflammation from previous infections may occur soon after HIV treatment is started. It is thought that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.

- **Autoimmune disorders**, when the immune system attacks healthy body tissue, may also occur after you start taking medicines for HIV infection. Autoimmune disorders may occur many months after the start of treatment. Look out for any symptoms of infection or other symptoms such as:
  - muscle weakness
  - weakness beginning in the hands and feet and moving up towards the trunk of the body
  - palpitations, tremor or hyperactivity

→ If you notice these or any symptoms of inflammation or infection, **tell your doctor immediately.**

Very common side effects
(may affect more than 1 in 10 people)
- **Reactions where Sunlenca is injected.**
  Symptoms may include:
  - pain and discomfort
  - a hardened mass or lump, which may take longer to go away than other reactions at the injection site or may not go away
  - inflammatory reaction such as redness, itching, and swelling
  - open sore on the skin

Common side effects
(may affect up to 1 in 10 people)
- **Feeling sick** (nausea)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. 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 Sunlenca

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.

This medicine does not require any special temperature storage conditions. Store in the original package in order to protect from light.

6. Contents of the pack and other information

What Sunlenca 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 Sunlenca looks like and contents of the pack

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

Marketing Authorisation Holder
Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Gilead Sciences Belgium SRL-BV
Tél/Tel: + 32 (0) 24 01 35 50

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Тел.: + 353 (0) 1 686 1888

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Gilead Sciences Poland Sp. z o.o.
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Puh/Tel: + 46 (0) 8 5057 1849

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Tel: + 46 (0) 8 5057 1849

This leaflet was last revised in.

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

The following information is intended for healthcare professionals only:

Instructions for Use-Sunlenca 464 mg solution for injection

Your pack contains

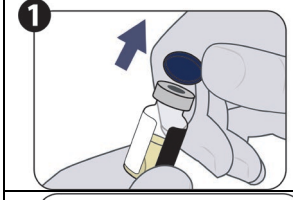
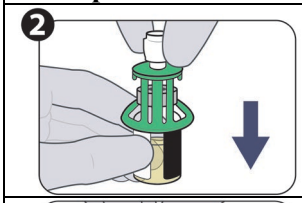
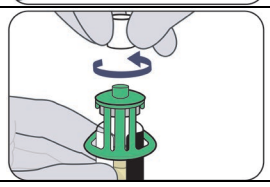
2 x vials	
2 x vials access devices	
2 x syringes	
2 x 22G, 13mm injection needles	

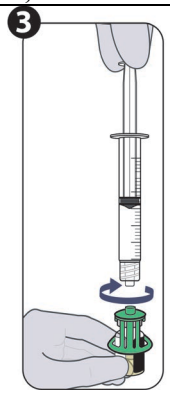
All the components are for single use.

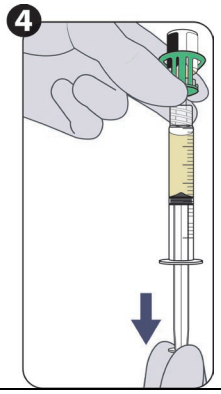
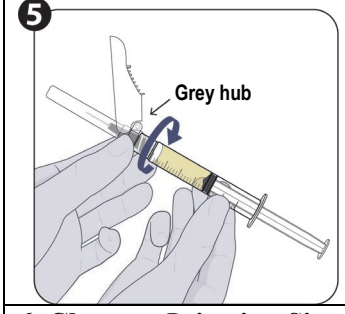
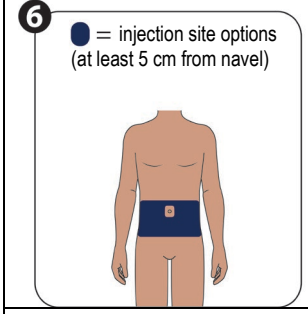
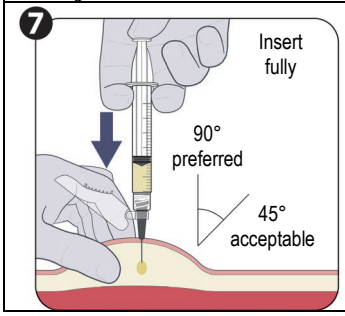
A complete dose requires **two 1.5 mL injections.** The use of **the vial access device** is required.

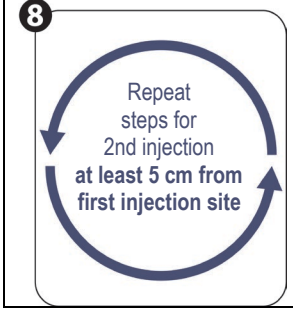
Make sure that:

- Vial and prepared syringe contain 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. Prepare Vial Access Device	
	Push Down.
	Twist off.

<table>
<tr><td colspan="2">3., 4. Attach and Fill Syringe</td></tr>
<tr><td>


</td><td>• Attach syringe and inject 1.5 mL of air into vial.
• Flip upside down and withdraw all contents.</td></tr>
<tr><td colspan="2">5. Attach 22G Injection Needle to Syringe, Expel Air Bubbles, and Prime to 1.5 mL</td></tr>
<tr><td>
</td><td></td></tr>
<tr><td colspan="2">6. Clean an Injection Site on Patient’s Abdomen</td></tr>
<tr><td>
</td><td>Injection site options (at least 5 cm from navel)</td></tr>
<tr><td colspan="2">7. Inject 1.5 mL of Sunlenca Subcutaneously</td></tr>
<tr><td>
</td><td></td></tr>
</table>

8. Administer 2nd Injection	
	

Package leaflet: Information for the patient

Sunlenca 300 mg film-coated tablets
lenacapavir

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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 or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Sunlenca is and what it is used for
2. What you need to know before you take Sunlenca
3. How to take Sunlenca
4. Possible side effects
5. How to store Sunlenca
6. Contents of the pack and other information

1. What Sunlenca is and what it is used for

Sunlenca contains the active substance lenacapavir. This is an antiretroviral medicine known as a capsid inhibitor.

Sunlenca **is used in combination with other antiretroviral medicines** to treat type 1 human immunodeficiency virus (HIV), the virus that cause acquired immunodeficiency syndrome (AIDS).

It is used to treat HIV infection in adults with limited treatment options (for example when other antiretroviral medicines are not sufficiently effective or are not suitable).

Treatment with Sunlenca in combination with other antiretrovirals reduces the amount of HIV in your body. This will improve the function of your immune system (the body's natural defences) and reduce the risk of developing illnesses linked to HIV infection.

Your doctor will advise you to take Sunlenca tablets before you are given Sunlenca injections for the first time.

2. What you need to know before you take Sunlenca

Do not take Sunlenca

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

- 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 Sunlenca and tell your doctor immediately** if you think this applies to you.

Warnings and precautions

Talk to your doctor before taking Sunlenca

- **Talk to your doctor or pharmacist if you have ever had severe liver disease, or if tests have shown problems with your liver.** Your doctor will carefully consider whether to treat you with Sunlenca.

While you are using Sunlenca

Once you start using Sunlenca, look out for:

- **Signs of inflammation** or **infection**.

→ **If you notice any of these symptoms, tell your doctor immediately.** For more information, see section 4, *Possible side effects*.

Children and adolescents

Do not give this medicine to children under 18 years of age. The use of Sunlenca in patients aged under 18 has not yet been studied, so it is not known how safe and effective the medicine is in this age group.

Other medicines and Sunlenca

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

Medicines that must never be taken with Sunlenca:

- **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 Sunlenca and tell your doctor immediately**.

Talk to your doctor in particular if you are taking:

- antibiotics containing:
  - rifabutin
- anticonvulsants used to treat epilepsy and prevent seizures (fits), containing:
  - oxcarbazepine or phenobarbital
- medicines used to treat HIV, containing:
  - atazanavir/cobicistat, efavirenz, nevirapine, tipranavir/ritonavir or etravirine
- medicines used to treat migraine headache, containing:
  - dihydroergotamine or ergotamine
- medicine 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 various illnesses involving inflammations 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 if you are taking any of these medicines** or if you start taking any of these medicines during treatment with Sunlenca. Do not stop any treatment without contacting your doctor.

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 or pharmacist for advice before taking this medicine.

As a precautionary measure you should avoid the use of Sunlenca during pregnancy unless your doctor tells you otherwise.

Breast-feeding is not recommended in women living with HIV because HIV infection can be passed on to the baby through breast milk. If you are breast-feeding, or thinking about breast-feeding, **you should discuss it with your doctor as soon as possible.**

Driving and using machines

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

Sunlenca 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 Sunlenca

Sunlenca is **used in combination with other antiretroviral medicines** to treat HIV infection. Your doctor will advise which other medicines you need to take to treat your HIV infection, and when you need to take them.

Your treatment with Sunlenca starts with tablets you take by mouth, followed by injections given by your doctor or nurse, as described below.

Talk to your doctor before taking the tablets. You will be advised when to start your tablets and when your appointment for the first injections will be scheduled.

Day 1 of treatment:
- Two tablets taken by mouth. These can be taken with or without food.

Day 2 of treatment:
- Two tablets taken by mouth. These can be taken with or without food.

Day 8 of treatment:
- One tablet taken by mouth. This can be taken with or without food.

Day 15 of treatment:
- Two injections into your abdomen (tummy) given at the same time by your doctor or nurse.

Every 6 months:
- Two injections into your abdomen given at the same time by your doctor or nurse.

If you take more Sunlenca than you should

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

It is important not to miss a dose of Sunlenca tablets.

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

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

If you miss a Sunlenca injection

- It is important that you attend **your planned appointments every 6 months** to receive your injections of Sunlenca. This will help to control your HIV infection and to stop your illness from getting worse.
- If you think you will not be able to attend your appointment for your injections, call your doctor as soon as possible to discuss your treatment options.

Do not stop taking Sunlenca

Do not stop taking Sunlenca tablets without talking to your doctor. Stopping Sunlenca can seriously affect how future HIV treatments work.

4. Possible side effects

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

Possible serious side effects: tell a doctor immediately

- **Any signs of inflammation or infection.** In some patients with advanced HIV infection (AIDS) and a history of opportunistic infections (infections that occur in people with a weak immune system), signs and symptoms of inflammation from previous infections may occur soon after HIV treatment is started. It is thought that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.

- **Autoimmune disorders**, when the immune system attacks healthy body tissue, may also occur after you start taking medicines for HIV infection. Autoimmune disorders may occur many months after the start of treatment. Look out for any symptoms of infection or other symptoms such as:
  - muscle weakness
  - weakness beginning in the hands and feet and moving up towards the trunk of the body
  - palpitations, tremor or hyperactivity

→ If you notice these or any symptoms of inflammation or infection, **tell your doctor immediately.**

Common side effects
(may affect up to 1 in 10 people)
- **Feeling sick** (nausea)

Reporting of side effects
If you get any side effects**,** talk to your doctor or pharmacist. 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 Sunlenca

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 blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions. 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 Sunlenca 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, *Sunlenca 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 Sunlenca looks like and contents of the pack

Sunlenca 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. Sunlenca comes in a blister of 5 tablets surrounded by a blister card. The blister is placed within a foil pouch. The foil pouch contains a silica gel desiccant that must be kept in the foil pouch to help protect your tablets. The silica gel is contained in a separate sachet or canister and is not to be swallowed.

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