▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION
SUNLENCA (LENACAPAVIR (AS SODIUM)) INJECTION, TABLETS

1 NAME OF THE MEDICINE

Lenacapavir sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each tablet contains lenacapavir sodium equivalent to 300 mg of lenacapavir.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear, yellow to brown solution with an apparent pH of 9.0 to 10.2 and a viscosity not more than 300 cP.

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, in combination with other antiretrovirals, 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

SUNLENCA should be prescribed by physicians experienced in the treatment of HIV. Prior to starting SUNLENCA, the healthcare professional should carefully select patients who agree to the required injection schedule.

To help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance associated with missed doses, the healthcare professional should also counsel patients about the importance of adherence to both the scheduled dosing visits and the optimised background regimen.

The recommended SUNLENCA treatment regimen in adults consists of an initiation dosing period (oral tablets and subcutaneous injections) and once every 6-months maintenance dosing (subcutaneous injections). SUNLENCA oral tablets may be taken with or without food.

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).

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.

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).

Table 1 Recommended Treatment Regimen for SUNLENCA Initiation and Maintenance

Treatment Time	
Dosage 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

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.

Elderly

No dose adjustment of SUNLENCA is required for elderly patients.

Renal Impairment

No dose adjustment of SUNLENCA is required in patients with mild, moderate, or severe renal impairment (CrCl ≥15 mL/min). SUNLENCA has not been studied in patients with end stage renal disease (ESRD).

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).

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

Injection

For subcutaneous use.

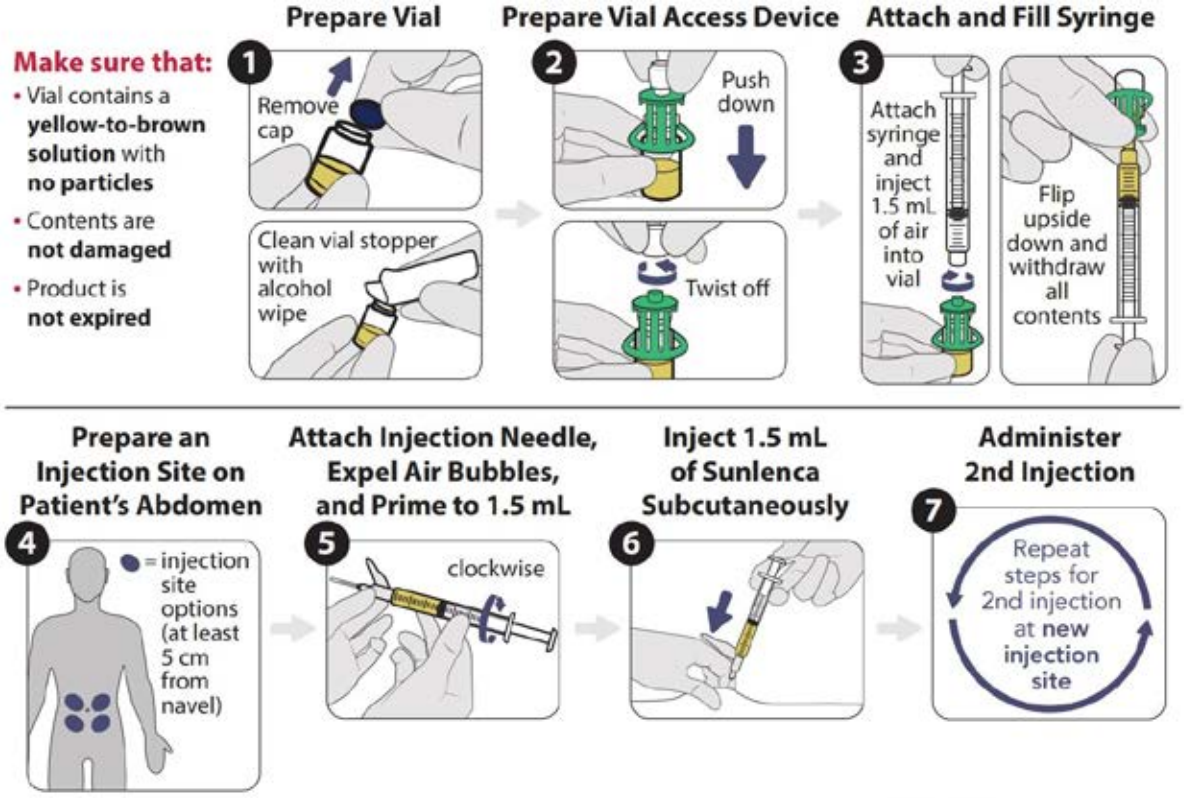
SUNLENCA injections should be administered into the abdomen by a healthcare professional.
Use aseptic technique. Visually inspect the solution in the vials for particulate matter and discoloration prior to administration. SUNLENCA injection is a yellow to brown solution. Do not use SUNLENCA injection if the solution contains particulate matter or discoloration. Once the solution is withdrawn from the vials, the subcutaneous injections should be administered as soon as possible (see section 6.4).

Refer to Figure 1 to identify the components for use in the administration steps. The administration steps are provided in Figure 2.

SUNLENCA is for single use in one patient only. Discard any residue. Use of a vial access device is required. Two 1.5 mL injections are required for a complete dose.

Figure 1 SUNLENCA Injection Kit Components

Figure 2 SUNLENCA Injection Steps



Tablets

For oral use.

SUNLENCA should be taken orally with or without food. The film-coated tablet should not be chewed, crushed, or split.

4.3 CONTRAINDICATIONS

Co-administration with strong inducers of CYP3A, P-gp, and UGT1A1, such as rifampicin, carbamazepine, phenytoin, or St. John's wort is contraindicated (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 Syndrome

In HIV-infected patients treated with combination antiretroviral therapy, immune reconstitution syndrome has been reported. In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy, 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 antiretroviral therapy. 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 reconstitution; 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).

Use in hepatic impairment

See Section 4.2 Dose and Method of Administration and Section 5.2 Pharmacokinetic Properties, Pharmacokinetics in special populations.

Use in renal impairment

See Section 4.2 Dose and Method of Administration and Section 5.2 Pharmacokinetic Properties, Pharmacokinetics in special populations.

Use in the elderly

See Section 4.2 Dose and Method of Administration, Elderly.

Paediatric use

The safety and efficacy of SUNLENCA in children aged less than 18 years has not been established. No data are available.

Effects on laboratory tests

See Section 4.8 Adverse Effects, Laboratory abnormalities.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of other medicinal products on the pharmacokinetics of SUNLENCA

Lenacapavir is a substrate of CYP3A, P-gp and UGT1A1. Drugs that are strong inducers of CYP3A, P-gp and UGT1A1 (e.g., rifampicin), or that are moderate inducers of CYP3A and P-gp (e.g., efavirenz), may significantly decrease plasma concentrations of lenacapavir, which may result in loss of therapeutic effect of SUNLENCA and development of resistance.

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

Effect of SUNLENCA on the pharmacokinetics of other medicinal products

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

Use of other medicinal products drugs after discontinuation of SUNLENCA

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 drugs (i.e. sensitive CYP3A substrates) that are initiated within 9 months after the last subcutaneous dose of SUNLENCA. These concentrations are not expected to affect the exposures of other antiretroviral agents that are initiated after discontinuation of SUNLENCA.

Established and other potentially significant drug interactions

Drug interaction information for SUNLENCA with potential concomitant drugs is summarised in Table 2. The drug interactions described are based on the results of the studies conducted with SUNLENCA, or are potential drug interactions that may occur with SUNLENCA.

Table 2 Drug Interactions for SUNLENCA

Medicinal product by therapeutic areas	**Effects on concentrations. Mean percent change in AUC, C_{max}**	**Recommendation concerning co-administration with SUNLENCA**
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.
ANTICOAGULANTS		
Direct Oral Anticoagulants (DOACs) Rivaroxaban Dabigatran	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 Product Information of the DOAC for further information on use in combination with combined moderate CYP3A and P-gp inhibitors.
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. Alternative anticonvulsants should be considered.
ANTIFUNGALS		
Voriconazole[a,b,c,d] (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	

Medicinal product by therapeutic areas	**Effects on concentrations. Mean percent change in AUC, C_{max}**	**Recommendation concerning co-administration with SUNLENCA**
	co-administered with itraconazole or ketoconazole.	
ANTIMYCOBACTERIALS		
Rifampicin[a,b,e] (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.
ANTIRETROVIRAL AGENTS		
Atazanavir/cobicistat[b,f,g] (300 mg/150 mg once daily)	Lenacapavir: AUC: ↑ 321% C_{max}: ↑ 560%	Co-administration is not recommended.
Efavirenz[b,f,h] (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,f,i] (150 mg once daily)	Lenacapavir: AUC: ↑ 128% C_{max}: ↑ 110%	No dose adjustment of lenacapavir is required.
Darunavir/cobicistat[b,f,j] (800 mg/150 mg once daily)	Lenacapavir: AUC: ↑ 94% C_{max}: ↑ 130%	
Ritonavir	Interaction not studied. Co-administration of ritonavir may increase lenacapavir plasma concentrations.	
Tenofovir alafenamide[f,k,l] (25 mg)	Tenofovir alafenamide: AUC: ↑ 32% C_{max}: ↑ 24%	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**
	Tenofovir[m]: AUC: ↑ 47% C_{max}: ↑ 23%	
CORTICOSTEROIDS (SYSTEMIC)		
Dexamethasone Hydrocortisone/cortisone	Interaction not studied. Plasma concentrations of corticosteroids may be increased when co-administered with lenacapavir.	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.
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.
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.
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.
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).
HMG-CoA REDUCTASE INHIBITORS		
Lovastatin	Interaction not studied.	Initiate lovastatin and simvastatin with the lowest

Medicinal product by therapeutic areas	**Effects on concentrations. Mean percent change in AUC, C_{max}**	**Recommendation concerning co-administration with SUNLENCA**
Simvastatin	Plasma concentrations of these medicinal products may be increased when co-administered with lenacapavir.	starting dose and titrate carefully while monitoring for safety (e.g. myopathy).
Atorvastatin		No dose adjustment of atorvastatin is required.
Pitavastatin[f,k,n] (2 mg single dose; simultaneous or 3 days after lenacapavir)	Pitavastatin: AUC: ↔ C_{max}: ↔	No dose adjustment of pitavastatin and rosuvastatin is required.
Rosuvastatin[f,k,o] (5 mg single dose)	Rosuvastatin: AUC: ↑ 31% C_{max}: ↑ 57%	
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.
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
SEDATIVES/HYPNOTICS		
Midazolam[f,k,p] (2.5 mg single dose; oral; simultaneous administration)	Midazolam: AUC: ↑ 259% C_{max}: ↑ 94% 1-hydroxymidazolam[q]: AUC: ↓ 24%	Caution is warranted when midazolam or triazolam, is co-administered with SUNLENCA.

Medicinal product by therapeutic areas	**Effects on concentrations. Mean percent change in AUC, C_{max}**	**Recommendation concerning co-administration with SUNLENCA**
	C_{max}: ↓ 46%	
Midazolam[f,k,p] (2.5 mg single dose; oral;1 day after lenacapavir)	Midazolam: AUC: ↑ 308% C_{max}: ↑ 116% 1-hydroxymidazolam[q]: AUC: ↓ 16% C_{max}: ↓ 48%	
Triazolam	Interaction not studied. Plasma concentration of triazolam may be increased when co-administered with lenacapavir.	

a Fasted.
b This study was conducted using lenacapavir 300 mg single dose administered orally.
c Evaluated as a strong inhibitor of CYP3A.
d This study was conducted using voriconazole 400 mg loading dose twice daily for a day, followed by 200 mg maintenance dose twice daily.
e Evaluated as a strong inducer of CYP3A, and an inducer of P-gp and UGT.
f Fed.
g Evaluated as a strong inhibitor of CYP3A, and an inhibitor UGT1A1 and P-gp.
h Evaluated as a moderate inducer of CYP3A and an inducer of P-gp.
i Evaluated as a strong inhibitor of CYP3A and an inhibitor of P-gp.
j Evaluated as a strong inhibitor of CYP3A, and an inhibitor and inducer of P-gp.
k 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.
l Evaluated as a P-gp substrate.
m Tenofovir alafenamide is converted to tenofovir *in vivo*.
n Evaluated as an OATP substrate.
o Evaluated as an BCRP substrate.
p Evaluated as a CYP3A substrate.
q Major active metabolite of midazolam.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effects of lenacapavir on human male or female fertility. In rats, subcutaneous administration of lenacapavir (6 weeks prior to mating in males and 4 weeks prior to mating in females) had no adverse effects on fertility at doses up to 100 mg/kg (7.5 and 5.3 times the human clinical exposure based on AUC in males and females, respectively).

Use in pregnancy – Pregnancy Category B1

There are no adequate and well-controlled studies of SUNLENCA in pregnant women. Because animal reproductive studies are not always predictive of human response, SUNLENCA should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.
Studies in animals have shown no evidence of teratogenicity or an effect on reproductive function. No adverse effects on embryofetal development were seen in rats receiving ≤30 mg/kg/day PO from gestation day (GD) 6-17 (17 times the predicted human exposure at the

recommended clinical dose). In rabbits, doses of up to 20 mg/kg/day IV from GD7-19 caused no adverse effects on embryofetal development (at 135 times the predicted human exposure).

Use in lactation

It is unknown whether lenacapavir is excreted in human milk. After a single subcutaneous dose of 300 mg/kg on gestation day 6 to rats, lenacapavir was detected at low levels in the plasma of nursing rat pups, without effects on these nursing pups, at 5.3 times the predicted human exposure.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Experience from Clinical Studies

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The primary safety assessment of SUNLENCA was based on data from heavily treatment experienced adult subjects with HIV who received SUNLENCA in a Phase 2/3 trial (CAPELLA; N=72) through Week 52 (median duration on study of 54 weeks) *[see Clinical Studies (14)]*, as well as supportive data in treatment-naïve adult subjects with HIV who received SUNLENCA in a Phase 2 trial (CALIBRATE; N=157) through Week 54 (median duration of exposure of 66 weeks).

The most common adverse reactions (all Grades) reported in at least 3% of subjects in CAPELLA were nausea and injection site reactions.
Table 3 displays the frequency of adverse reactions (all Grades) greater than or equal to 3% in the SUNLENCA group.

Table 3 Adverse Reactions (All Grades) Reported in ≥ 3%[a] of Heavily Treatment Experienced Adults with HIV-1 Receiving SUNLENCA in CAPELLA (Week 52 Analysis)

Adverse Reactions	**SUNLENCA + Background Regimen** (N=72)
GASTROINTESTINAL DISORDERS Nausea	4%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS Injection Site Reactions [b]	63%

a Frequencies of adverse reactions are based on all adverse events attributed to trial drug by the investigator, based on all subjects (cohorts 1 and 2) in CAPELLA.

b Includes injection site swelling (31%), pain (31%), erythema (25%), nodule (24%), induration (15%), pruritus (4%), extravasation (3%), discomfort (1%), mass (1%), haematoma (1%), oedema (1%) and ulcer (1%). Median (Q1, Q3) duration of injection site reactions was 8 (3, 67) days.

The majority (97%) of all adverse reactions associated with SUNLENCA were mild or moderate in severity.

During the functional monotherapy period of CAPELLA, the only adverse event reported in more than one subject receiving SUNLENCA was nausea (Table 4).

Table 4 Treatment-Emergent Adverse Events for Cohort 1 Reported in > 5% of Participants Receiving SUNLENCA during the Functional Monotherapy Period in CAPELLA

Adverse Event	**SUNLENCA (tablet) (N= 24)**	**Placebo (N = 12)**
GASTROINTESTINAL DISORDERS Nausea	12%	0

Laboratory Abnormalities

The frequency of laboratory abnormalities (Grades 3 to 4) occurring in at least 2% of subjects in CAPELLA are presented in Table 5. A causal association between SUNLENCA and these laboratory abnormalities has not been established.

Table 5 Selected Laboratory Abnormalities (Grades 3 to 4) Reported in ≥ 2% of Subjects Receiving SUNLENCA in CAPELLA (Week 52 Analysis)

Laboratory Parameter Abnormality	**SUNLENCA + Background Regimen** (N=72)[a]
Creatinine (>1.8 x ULN or ≥1.5 x baseline)	13%
Glycosuria (>2+) [b]	6%
Hyperglycemia (fasting) (>13.9 mmol/L)	5%
Proteinuria (>2+) [b]	3%
ALT (≥5 x ULN) [b]	3%
AST (≥5 x ULN)	3%
Direct Bilirubin (>ULN) [b]	3%

ALT= alanine aminotransferase; AST= aspartate aminotransferase; ULN = upper limit of normal

a Frequencies are based on treatment-emergent laboratory abnormalities in all subjects (cohorts 1 and 2) in CAPELLA. Percentages were calculated based on the number of subjects with post-baseline toxicity grades for each laboratory parameter (n=72 for all parameters except hyperglycaemia fasting n=55).

b Grade 3 only (no Grade 4 values reported).

Description of selected adverse reactions

Immune Reconstitution Inflammatory Syndrome

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

Local injection site reactions

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

If overdose occurs, the patient must be monitored for evidence of toxicity. 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 (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 virions with malformed capsids and reduced infectivity).

Lenacapavir has activity that is specific to human immunodeficiency virus (HIV-1 and HIV-2).

Antiviral Activity

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 HIV-1 virus. The protein binding-adjusted EC_{95} for lenacapavir was 4 nM (3.87 ng per mL) in the MT-4 T-cell line for wild-type HIV-1 virus.

In a study of lenacapavir in combination with representatives from the main classes of antiretroviral agents (NRTIs, NNRTIs, INSTIs, and 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. Another mutation conferring resistance to lenacapavir was N57H. Phenotypic susceptibility to lenacapavir was reduced 4- to >5000-fold, relative to wild-type virus.

In Heavily Treatment Experienced Patients

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

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

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 nonoverlapping 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 lenacapavir), the predicted mean (upper 90% confidence interval) increase in QTcF interval was 2.6 (4.8) msec, and there was no association (p=0.36) between observed lenacapavir plasma concentrations and change in QTcF.

Clinical trials

The efficacy and safety of SUNLENCA in HIV-1 infected, heavily treatment experienced patients with multidrug resistance is based on 52-week data from a partially randomised, placebo-controlled, double-blind, multicentre study, GS-US-200-4625 (“CAPELLA”).

CAPELLA was conducted in 72 heavily treatment-experienced patients with multiclass resistant HIV-1. Patients were required to have a viral load ≥ 400 copies/mL, documented resistance to at least two antiretroviral medications from each of at least 3 of the 4 classes of antiretroviral medications (nucleoside reverse transcriptase inhibitors [NRTI], non-nucleoside reverse transcriptase inhibitors [NNRTI], protease inhibitors [PI] and integrase strand-transfer

inhibitors [INSTI]), and ≤ 2 fully active antiretroviral medications from the 4 classes of antiretroviral medications remaining at baseline due to resistance, intolerability, drug access, contraindication, or other safety concerns.

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

Cohort 1 (N=36, randomised): In the 14-day functional monotherapy period, patients in cohort 1 were randomised in a 2:1 ratio in a blinded fashion, to receive either SUNLENCA or placebo, while continuing their failing regimen. This period was to establish the virologic activity of SUNLENCA. After the functional monotherapy period, patients who had received SUNLENCA continued on SUNLENCA along with an optimised background regimen (OBR); patients who had received placebo during this period initiated SUNLENCA along with an OBR.

Patients in cohort 1 had a mean age of 52 years (range: 24 to 71), 72% were male, 46% were White, 46% were Black, and 9% were Asian. 29% percent of patients identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.3 log_{10} copies/mL (range: 2.3 to 5.4). 19% of patients had baseline viral loads greater than 100,000 copies/mL. The mean baseline CD4+ cell count was 161 cells/mm^3 (range: 6 to 827). 75% of patients had CD4+ cell counts below 200 cells/ mm^3. The mean number of years since patients first started HIV treatment was 24 years (range: 7 to 33); the mean number of antiretroviral agents in failing regimens at baseline was 4 (range: 1 to 7). The percentage of patients in the randomised cohort with known resistance to at least 2 agents from the NRTI, NNRTI, PI and INSTI classes was 97%, 94%, 78% and 75%, respectively. In cohort 1, 53% of patients had no fully active agents, 31% had 1 fully active agent, and 17% had 2 or more fully active agents within their initial failing regimen, including 6% of patients who were receiving fostemsavir, which was an investigational agent at the start of the CAPELLA trial.

Cohort 2 (N=36, non-randomised): Patients in cohort 2 initiated SUNLENCA and an OBR on Day 1.

Patients in cohort 2 had a mean age of 48 years (range: 23 to 78), 78% were male, 36% were White, 31% were Black, 33% were Asian, and 14% of patients identified as Hispanic/Latino. The mean baseline plasma HIV-1 RNA was 4.1 log_{10} copies/mL (range: 1.3 to 5.7). 19% of patients had baseline viral loads greater than 100,000 copies/mL. The mean baseline CD4+ cell count was 258 cells/mm^3 (range: 3 to 1296). 53% of patients had CD4+ cell counts below 200 cells/ mm^3. The mean number of years since patients first started HIV treatment was 19 years (range: 3 to 35); the mean number of antiretroviral agents in failing regimens at baseline was 4 (range: 2 to 7). The percentage of patients in the non-randomised cohort with known resistance to at least 2 agents from the NRTI, NNRTI, PI and INSTI classes was 100%, 100%, 83% and 64%, respectively. In cohort 2, 31% of patients had no fully active agents, 42% had 1 fully active agent, and 28% had 2 or more fully active agents within their

initial failing regimen, including 6% of patients who were receiving fostemsavir, which was an investigational agent at the start of the CAPELLA trial.

The primary efficacy endpoint was the proportion of patients in cohort 1 achieving ≥ 0.5 log_{10} copies/mL reduction from baseline in HIV-1 RNA at the end of the functional monotherapy period. The results of the primary endpoint analysis demonstrated the superiority of SUNLENCA compared with placebo, as shown in Table 6.

Table 6 Proportion of Patients Achieving a ≥ 0.5 log_{10} Decrease in Viral Load (Cohort 1)

	SUNLENCA (N = 24)	**Placebo (N = 12)**
Proportion of Patients Achieving a ≥ 0.5 log_{10} Decrease in Viral Load	87.5%	16.7%
Treatment Difference (95% CI); p-value	70.8% (34.9% to 90.0%); p < 0.0001	

The results at Weeks 26 and 52 are provided in Table 7 and Table 8.

Table 7 Virologic Outcomes (HIV-1 RNA < 50 copies/mL and < 200 copies/mL) at Weeks 26[a] and 52[b] with SUNLENCA plus OBR in the CAPELLA trial (Cohort 1)

	SUNLENCA plus OBR (N=36)	
	Week 26	**Week 52**
HIV-1 RNA < 50 copies/mL HIV-1 RNA < 200 copies/mL	81% 89%	83% 86%
HIV-1 RNA ≥ 50 copies/mL[b] HIV-1 RNA ≥ 200 copies/mL[b]	19% 11%	14% 11%
No virologic data in Week 26 Window	0	3%
Discontinued Study Drug Due to AE or Death [c]	0	0
Discontinued Study Drug Due to Other Reasons [d] and Last Available HIV-1 RNA < 50 copies/mL or < 200 copies/mL	0	3%
Missing Data During Window but on Study Drug	0	0

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

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

c Includes patients who had ≥ 50 copies/mL or ≥ 200 copies/mL, respectively, in the Week 26 or 52 window; patients who discontinued early due to lack or loss of efficacy; patients who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL or ≥ 200 copies/mL, respectively.

d Includes patients who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

e Includes patients who discontinued for reasons other than an AE, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

Table 8 Virologic Outcomes (HIV-1 RNA < 50 copies/mL) by Baseline Covariates at Weeks 26 [a] and 52[b] with SUNLENCA plus OBR in the CAPELLA trial (Cohort 1)

	SUNLENCA plus OBR (N=36)	
	Week 26	**Week 52**
Age (Years)		
< 50	100% (9/9)	89% (8/9)
≥ 50	74% (20/27)	81% (22/27)
Gender		
Male	77% (20/26)	77% (20/26)
Female	90% (9/10)	100% (10/10)
Race		
Black	81% (13/16)	75% (12/16)
Non-Black	84% (16/19)	89% (17/19)
Baseline plasma viral load (copies/mL)		
≤ 100,000	86% (25/29)	86% (25/29)
> 100,000	57% (4/7)	71% (5/7)
Baseline CD4+ (cells/mm^3)		
< 200	78% (21/27)	78% (21/27)
≥ 200	89% (8/9)	100% (9/9)
Baseline INSTI resistance profile		
With INSTI resistance	85% (23/27)	81% (22/27)
Without INSTI resistance	63% (5/8)	88% (7/8)
Number of fully active ARV agents in the OBR		
0	67% (4/6)	67% (4/6)
1	86% (12/14)	79% (11/14)
≥ 2	81% (13/16)	94% (15/16)
Use of DTG and/or DRV in the OBR		
With DTG and DRV	83% (10/12)	83% (10/12)
With DTG, without DRV	83% (5/6)	83% (5/6)
Without DTG, with DRV	78% (7/9)	89% (8/9)
Without DTG or DRV	78% (7/9)	78% (7/9)

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

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

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

In cohort 1, at Weeks 26 and 52, the mean change from baseline in CD4+ cell count was 81 cells/mm^3 (range: -101 to 522) and 83 cells/mm^3 (range: -194 to 467), respectively.
In cohort 2, at Week 26, 81% (29/36) of patients achieved HIV-1 RNA < 50 copies/mL and the mean change from baseline in CD4+ cell count was 98 cells/mm^3 (range: -103 to 459).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Oral Administration

Lenacapavir is absorbed following oral administration with peak plasma concentrations occurring 4 hours after administration of SUNLENCA. Absolute bioavailability following oral administration of lenacapavir is low (approximately 6‑10%). 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 77 to 84 days postdose.

Pharmacokinetic Parameters

Simulated steady state exposures of lenacapavir following recommended dosing regimen in heavily treatment experienced patients with HIV are provided in Table 9.

Table 9 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)		
	Days 1 – 15	Day 15 – 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.

Lenacapavir exposures (AUC_{tau}, C_{max} and C_{trough}) were 28.5% to 84.1% higher in HIV-1 infected, heavily treatment experienced patients as compared to participants without HIV-1 infection based on population PK analysis.

Distribution

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

Lenacapavir is highly bound to plasma proteins (> 98.5%).

Biotransformation

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

Elimination

The median half-life following oral and subcutaneous administration ranged from 10 to 12 days, and 8 to 12 weeks, respectively. Lenacapavir clearance was 3.62 L/h in heavily treatment experienced patients with HIV 1 infection based on population pharmacokinetic analysis.

Linearity/Non-linearity

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

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

Pharmacokinetics in Special Populations

Age, Gender and Race

Population PK analyses using data from adult trials 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 study in subjects with moderate hepatic impairment (Child-Pugh Class B). Lenacapavir mean exposures were increased (47% and 161% for AUC_{inf} and C_{max}, respectively) in patients with moderate hepatic impairment (Child-Pugh B) compared to subjects with normal hepatic function; however, the increase was not considered clinically

relevant. The pharmacokinetics of lenacapavir have not been studied in patients with severe hepatic impairment (Child-Pugh C).

Renal Impairment

The pharmacokinetics of a single 300 mg oral dose of lenacapavir were evaluated in a dedicated study in subjects with severe renal impairment (estimated creatinine clearance ≥ 15 and < 30 mL/minute). Lenacapavir exposures were increased (84% and 162% for AUC_{inf} and C_{max}, respectively) in subjects with severe renal impairment compared with subjects with normal renal function; however, the increase was not considered clinically relevant. The pharmacokinetics of lenacapavir have not been studied in patients with end-stage renal disease, including those on dialysis. As lenacapavir is > 98.5% protein bound, dialysis is not expected to alter exposures of lenacapavir.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Lenacapavir was not mutagenic in bacteria or clastogenic in cultured mammalian cells *in vitro* or an *in vivo* rat micronucleus assay.

Carcinogenicity

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 of approximately 71 times the exposure in humans at the recommended human dose. A 2-year carcinogenicity study is ongoing.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

SUNLENCA injection: Macrogol 300, Water for Injection

SUNLENCA tablets:

Tablet Core
Mannitol
Microcrystalline Cellulose
Croscarmellose Sodium
Copovidone
Magnesium Stearate
Poloxamer 407

Film Coat
Polyvinyl Alcohol
Titanium Dioxide
Macrogol 3350
Purified Talc
Iron Oxide Yellow
Iron Oxide Black

Iron Oxide Red

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

SUNLENCA injection: Store in the original package. Store below 30 °C. Keep the vials in the original carton until just prior to preparation of the injections in order to protect them from light. Once the solution has been drawn into the syringes, the injections should be administered as soon as possible.

SUNLENCA tablets: Store in the original package. Store below 30 °C.

6.5 NATURE AND CONTENTS OF CONTAINER

SUNLENCA injection is packaged in a dosing kit containing:

- 2 single-use clear glass vials of SUNLENCA, each containing sufficient volume to allow withdrawal of 1.5 mL/463.5 mg (309 mg/mL) of lenacapavir. Vials are sealed with an elastomeric closure and aluminium overseal with flip-off cap;
- 2 vial access devices, 2 disposable syringes, and 2 injection safety needles for subcutaneous injection (22-gauge, ½ inch).

SUNLENCA tablets are packaged in a blister pack containing:

- 5 tablets of SUNLENCA, each containing 300 mg of lenacapavir, in a clear blister film sealed to a foil lidding material. The blister card, which is fitted between child-resistant sealed paperboard cards, is packaged with silica gel desiccant in a sealed flexible laminated pouch.

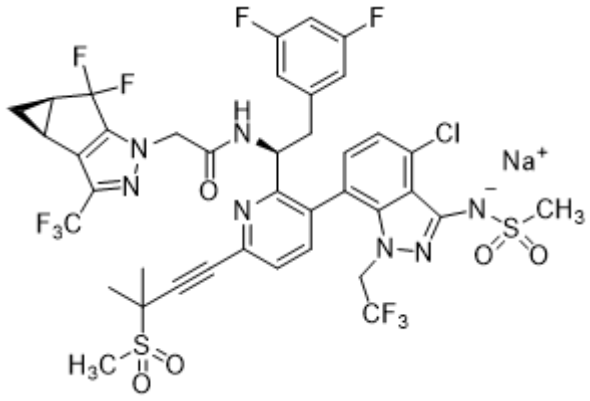
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name of lenacapavir is (4-chloro-7-(2-((S)-1-(2-((3bS,4aR)-5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)-6-(3-methyl-3-(methylsulfonyl)but-1-yn-1-yl)pyridin-3-yl)-1-(2,2,2-trifluoroethyl)-1H-indazol-3-yl)(methylsulfonyl)amide



CAS number

2283356-12-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

27 March 2023

10 DATE OF REVISION

27 March 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information