▼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

APRETUDE (cabotegravir) film-coated tablets and prolonged-release suspension for injection

1 NAME OF THE MEDICINE

Film-coated tablets: Cabotegravir (as cabotegravir sodium)

Prolonged-release suspension for injection: Cabotegravir

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cabotegravir is a white to almost white solid.

Film-coated tablets

APRETUDE tablet contains 30 mg cabotegravir (as cabotegravir sodium).

Prolonged-release suspension for injection

APRETUDE injection contains 600 mg cabotegravir (as cabotegravir free acid) in 3 mL vial.

List of excipients with known effect

APRETUDE tablets contain lactose monohydrate.

APRETUDE injection: None

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Film-coated tablets

APRETUDE tablets are white, oval, film-coated, tablets, debossed with ‘SV CTV’ on one side.

Prolonged-release suspension for injection

APRETUDE injection is a white to light pink suspension.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

APRETUDE is indicated in at-risk adults and adolescents (at least 12 years of age) and weighing at least 35 kg for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection.

APRETUDE tablets may be used as an oral lead-in to assess tolerability of cabotegravir prior to administration of cabotegravir injections or as short-term oral PrEP in individuals who will miss planned dosing with cabotegravir injections.

Individuals must have a documented negative HIV-1 test prior to initiating APRETUDE for HIV-1 PrEP.

4.2 DOSE AND METHOD OF ADMINISTRATION

Individuals must have had a documented negative HIV-1 test, in accordance with applicable guidelines, prior to initiating APRETUDE.

Prior to starting APRETUDE, healthcare professionals should carefully select individuals who agree to the required injection dosing schedule and counsel individuals about the importance of adherence to scheduled dosing visits to help reduce the risk of acquiring HIV-1 infection (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Adults, adolescents weighing at least 35 kg

Following discussion with the individual, the physician may proceed directly to APRETUDE injection, (see Table 2 for dosing recommendations).

Alternatively, APRETUDE tablets may be used as an oral lead in prior to the initiation of APRETUDE injection to assess tolerability to cabotegravir (see Table 1).

Oral lead-in (Film-coated Tablets)

When used for oral lead-in, APRETUDE tablets are recommended for approximately one month (at least 28 days) prior to the initiation of APRETUDE injection to assess tolerability to cabotegravir.

Table 1 Oral Lead-in Dosing Schedule

	ORAL LEAD-IN
Drug	**For 1 month (at least 28 days), followed by the Initiation Injection**
Cabotegravir	30 mg once daily

Prolonged-release suspension for injection

Initiation Injections

The recommended initial APRETUDE injection dose is a single 3 mL (600 mg) intramuscular injection. If oral lead-in has been used, the first injection should be planned for the last day of oral lead-in or within 3 days thereafter.

One month later, a second 3 mL (600 mg) intramuscular injection should be administered. Individuals may be given the second 3 mL (600 mg) initiation injection up to 7 days before or after the scheduled dosing date.

Continuation Injections

After the second initiation injection, the recommended APRETUDE continuation injection dose is a single 3 mL (600 mg) intramuscular injection administered every 2 months. Individuals may be given injections up to 7 days before or after the scheduled dosing date.

Table 2 Recommended Intramuscular Dosing Schedule

	INITIATION INJECTIONS (one month apart)	**CONTINUATION INJECTIONS (two months apart)**
Medicinal product	**Direct to injection:** **months 1 and 2** **or** **Following oral lead-in: months 2 and 3**	**Two months after final initiation injection and every 2 months onwards**
Cabotegravir	3 mL (600 mg)	3 mL (600 mg)

Missed dose

Missed APRETUDE Film-coated Tablet

If the individual misses a dose of APRETUDE tablets, they should take the missed dose as soon as possible.

Missed APRETUDE Prolonged-release Suspension for Injection

Adherence to the injection dosing schedule is strongly recommended.

Individuals who miss a scheduled injection visit should be clinically reassessed and a HIV test performed to ensure resumption of PrEP remains appropriate. See Table 3 for dosing recommendations after a missed injection.

If a delay of more than 7 days from a scheduled injection visit cannot be avoided, APRETUDE tablets (30 mg) may be used once daily to replace one scheduled injection visit.

For oral APRETUDE PrEP durations greater than two months, an alternative regimen is recommended.

The first dose of oral PrEP should be taken two months (+/- 7 days) after the last injection dose of APRETUDE. Injection dosing should be planned to resume on the last day of oral PrEP or within 3 days, thereafter, as recommended in Table 3.

Table 3: Injection dosing recommendations after missed injections or following APREUDE tablets to replace an injection

Missed Doses	
Time since last injection	**Recommendation**
If second injection is missed and time since first injection is:	
≤2 months	Administer one 3 mL (600 mg) injection as soon as possible and continue with the every-2 month injection dosing schedule.
>2 months	Restart the individual on one 3 mL (600 mg) initiation injection, followed by a second 3 mL (600 mg) initiation injection one month later. Then follow the every-2 month injection dosing schedule.
If 3rd or subsequent injection is missed and time since prior injection is:	
≤3 months	Administer one 3 mL (600 mg) injection as soon as possible and continue with the every-2 month injection dosing schedule.
>3 months	Restart the individual on one 3 mL (600 mg) initiation injection, followed by a second 3 mL (600 mg) initiation injection one month later. Then follow the every-2 month injection dosing schedule.

Adolescents and Children

The safety and efficacy of APRETUDE in children < 12 years of age, and in adolescents weighing less than 35 kg have not been established.

Elderly

No dose adjustment is required in elderly individuals. There are limited data available on the use of APRETUDE in individuals aged 65 years and over (see section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations).

Renal impairment

No dosage adjustment is required in individuals with mild to severe renal impairment and who are not on dialysis (see section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations).

Hepatic impairment

No dosage adjustment is required in individuals with mild or moderate hepatic impairment (Child-Pugh score A or B). APRETUDE has not been studied in individuals with severe hepatic impairment (Child-Pugh score C) (see section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations).

Method of Administration

Film-coated Tablet

Oral use. APRETUDE tablets may be taken with or without food.

Prolonged-release Suspension for Injection

For gluteal intramuscular (IM) injection use only. Do not inject intravenously.

APRETUDE injection should be administered by a healthcare professional. For instructions on administration, see “Instructions for Use” attached. Carefully follow these instructions when preparing the suspension for injection to avoid leakage.

When administering APRETUDE injection, healthcare professionals should take into consideration the Body Mass Index (BMI) of the patient to ensure that the needle length is sufficient to reach the gluteus muscle.

4.3 CONTRAINDICATIONS

APRETUDE is contraindicated in individuals:

- with an unknown or a positive HIV-1 status
- with known hypersensitivity to cabotegravir or to any of the excipients in the tablets or the injection formulation.
- receiving rifampicin, rifapentine, phenytoin, phenobarbital, carbamazepine and oxcarbazepine.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Overall HIV-1 infection prevention strategy
APRETUDE is not always effective in preventing HIV-1 acquisition (see 5.1 Clinical trials). The time to onset of protection after commencing APRETUDE is unknown.

APRETUDE should be used for pre-exposure prophylaxis as part of an overall HIV-1 infection prevention strategy including the use of other HIV-1 prevention measures (e.g. knowledge of HIV-1 status, regular testing for other sexually transmitted infections, condom use).

APRETUDE should only be used to reduce the risk of acquiring HIV-1 in individuals confirmed to be HIV negative (see 4.3 CONTRAINDICATIONS). Individuals should be re-confirmed to be HIV-negative at frequent intervals (e.g. in line with local guidelines, but at no more than 3 month intervals) while taking APRETUDE for pre-exposure prophylaxis.

Adolescents may benefit from more frequent visits and counselling to support adherence to the dosing and testing schedule.

If clinical symptoms consistent with acute viral infection are present and recent (< 1 month) exposures to HIV-1 are suspected, HIV-1 status should be reconfirmed.

Potential risk of resistance
There is a potential risk of developing resistance to APRETUDE if an individual acquires HIV-1 either before or during administration of APRETUDE, or following discontinuation of APRETUDE, (see Prolonged-release properties of APRETUDE injection).

To minimise this risk, it is essential to clinically reassess individuals for risk of HIV acquisition and to frequently test to confirm HIV negative status. Individuals who are suspected or confirmed with HIV-1 should immediately begin antiretroviral treatment (ART).

Alternative forms of PrEP should be considered following discontinuation of APRETUDE for those individuals at continuing risk of HIV acquisition and initiated within 2 months of the final APRETUDE injection.

Prolonged-release properties of APRETUDE injection

Residual concentrations of cabotegravir injection may remain in the systemic circulation of individuals for prolonged periods (up to 12 months or longer), therefore, physicians should take the prolonged release characteristics of APRETUDE into consideration when the medicinal product is discontinued (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, 4.6 FERTILITY, PREGNANCY AND LACTATION, 4.9 OVERDOSE).

Importance of adherence

Individuals should be counselled periodically to strictly adhere to the recommended APRETUDE dosing schedule in order to reduce the risk of HIV-1 acquisition and the potential development of resistance.

Hypersensitivity reactions

Hypersensitivity reactions have been reported in association with integrase inhibitors. These reactions were characterised by rash, constitutional findings and sometimes organ dysfunction, including liver injury. Discontinue APRETUDE and other suspected agents immediately, should signs or symptoms of hypersensitivity develop (including, but not limited to, severe rash, or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia or angioedema). Clinical status, including liver aminotransferases should be monitored and appropriate therapy initiated. (see section 4.2 DOSAGE AND METHOD OF ADMINISTRATION, 4.3 CONTRAINDICATIONS, Prolonged release properties of APRETUDE injection, Clinical trials).

Hepatotoxicity

Hepatotoxicity has been reported in a limited number of individuals receiving APRETUDE with or without known pre-existing hepatic disease (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Clinical and laboratory monitoring should be considered and APRETUDE should be discontinued if hepatotoxicity is confirmed and individuals managed as clinically indicated (see Prolonged-release properties of APRETUDE injection).

Interactions with medicinal products

Caution should be given when prescribing APRETUDE with medicinal products that may reduce its exposure (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Use in hepatic impairment

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations.

Use in renal impairment

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations.

Use in the elderly

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations.

Paediatric use

The safety and efficacy of APRETUDE in children < 12 years of age, and in adolescents weighing less than 35 kg have not been established.

Effects on laboratory tests

In both HPTN 083 and HPTN 084, a similar proportion of participants in the cabotegravir and tenofovir disoproxil fumarate (TDF)/ emtricitabine (FTC) groups were observed to have elevated hepatic transaminases (ALT/AST) levels and maximum post baseline increases

were mostly Grades 1 and 2. In HPTN 083, the number of participants in the cabotegravir vs TDF/FTC groups who experienced maximum post baseline Grade 3 or 4 ALT levels were 40 (2%) vs 44 (2%) and Grade 3 or 4 AST levels were; 68 (3%) vs 79 (3%), respectively. In HPTN 084, the number of participants in the cabotegravir vs TDF/FTC groups who experienced maximum post baseline Grade 3 or 4 ALT levels were 12 (<1%) vs 18 (1%) and Grade 3 and 4 AST levels were; 15 (<1%) vs 14 (<1%), respectively.

A few participants in both the cabotegravir and TDF/FTC groups had adverse events of AST or ALT increased which resulted in discontinuation of study product. In HPTN 083, the number of participants in the cabotegravir vs TDF/FTC groups who discontinued due to ALT increased were: 29 (1%) vs 31 (1%) and due to AST increased were 7 (<1%) vs 8 (<1%), respectively. In HPTN 084, the number of participants in the cabotegravir vs TDF/FTC groups who discontinued due to ALT increased were 12 (<1%) vs 15 (<1%) and there were no discontinuations due to AST increased.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of other medicinal products on the pharmacokinetics of cabotegravir

Cabotegravir is primarily metabolised by uridine diphosphate glucuronosyl transferase (UGT) 1A1 with some contribution from UGT1A9. Medicinal products which are strong inducers of UGT1A1 or UGT1A9 are expected to decrease cabotegravir plasma concentrations leading to lack of efficacy (see section 4.3 CONTRAINDICATIONS).

Simulations using physiologically based pharmacokinetic (PBPK) modelling show that no clinically significant interaction is expected following co-administration of cabotegravir with drugs that inhibit UGT enzymes.

In vitro, cabotegravir was not a substrate of organic anion transporting polypeptide (OATP) 1B1, OATP1B3, OATP2B1 or organic cation transporter (OCT1).

Cabotegravir is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), however, because of its high permeability, no alteration in absorption is expected when co-administered with either P-gp or BCRP inhibitors.

Effect of cabotegravir on the pharmacokinetics of other medicinal products

In vivo, cabotegravir did not have an effect on midazolam, a cytochrome P450 (CYP) 3A4 probe. Cabotegravir is not a clinically relevant inhibitor of the following enzymes and transporters: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B4, UGT2B7, UGT2B15, and UGT2B17, P-gp, BCRP, Bile salt export pump (BSEP), OCT1, OCT2, OATP1B1, OATP1B3, multidrug and toxin extrusion transporter (MATE) 1, MATE 2-K, multidrug resistance protein (MRP) 2 or MRP4.

Cabotegravir inhibited the organic anion transporters (OAT) 1 (IC_{50}=0.81 µM) and OAT3 (IC_{50}=0.41 µM) *in vitro*, however, based on PBPK modelling no interaction with OAT substrates is expected at clinically relevant concentrations.

In vitro, cabotegravir did not induce CYP1A2, CYP2B6, or CYP3A4.

Based on these data and the results of drug interaction studies, cabotegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

Based on the *in vitro* and clinical drug interaction profile, cabotegravir is not expected to alter concentrations of other antiretroviral medications including protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, integrase inhibitors, entry inhibitors, and ibalizumab.

No drug interaction studies have been performed with cabotegravir injection. The drug interaction data provided in Table 4 is obtained from studies with oral cabotegravir.

Table 4 Drug Interactions

Concomitant Drug Class: Drug Name	**Effect on Concentration of Cabotegravir or Concomitant Drug**	**Clinical Comment**
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine	Cabotegravir ↔ AUC ↑ 1% C_{max} ↑ 4% C_T ↔ 0%	Etravirine did not significantly change cabotegravir plasma concentration. No dosage adjustment is required.
Non-nucleoside Reverse Transcriptase Inhibitor: Rilpivirine	Cabotegravir ↔ AUC ↑ 12% C_{max} ↑ 5% C_T ↑ 14% Rilpivirine ↔ AUC ↓1% C_{max} ↓ 4% C_T ↓8%	Rilpivirine did not significantly change cabotegravir plasma concentration or vice versa. No dose adjustment of APRETUDE or rilpivirine is necessary when co-administered.
Rifampicin	Cabotegravir ↓ AUC ↓ 59% Cmax ↓ 6%	Rifampicin significantly decreased cabotegravir plasma concentration, which is likely to result in loss of therapeutic effect. Co-administration of APRETUDE with rifampicin is contraindicated. Dosing recommendations for co-administration of APRETUDE (oral and injection) with rifampicin have not been established.
Rifapentine	Cabotegravir ↓	Rifapentine may significantly decrease cabotegravir plasma

		concentrations, concomitant use is contraindicated.
Rifabutin	Cabotegravir ↓ AUC ↓ 21% Cmax ↓ 17% C_T ↓ 8%	APRETUDE tablets: Rifabutin did not significantly change cabotegravir plasma concentration. No dose adjustment is required. APRETUDE injection: When rifabutin is started before or concomitantly with the first APRETUDE initiation injection the recommended APRETUDE dosing schedule is one 3 mL (600 mg) injection followed 2 weeks later by a second 3 mL (600 mg) initiation injection and monthly, thereafter, while on rifabutin. When rifabutin is started at the time of the second initiation injection or later, the recommended dosing schedule is 3 mL (600 mg), monthly, while on rifabutin. After stopping rifabutin, the recommended APRETUDE dosing schedule is 3 mL (600 mg) every 2 months.
Anticonvulsants: Carbamazepine Oxcarbazepine Phenytoin Phenobarbital	Cabotegravir ↓	Metabolic inducers may significantly decrease cabotegravir plasma concentrations. Concomitant use is contraindicated.
Antacids (e.g., magnesium, calcium or aluminium)	Cabotegravir ↓	APRETUDE tablets: Co-administration of antacid supplements has the potential to decrease oral cabotegravir absorption and has not been studied. Antacid products containing polyvalent cations are recommended to be administered at least 2 hours

		before or 4 hours after oral cabotegravir. APRETUDE injection: Interaction is not relevant following parenteral administration.
Oral contraceptives (Ethinyl estradiol (EE) and levonorgestrel	EE ↔ AUC ↑ 2% Cmax ↓ 8% C_T ↔ 0% LNG ↔	Cabotegravir did not significantly change ethinyl estradiol and levonorgestrel plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with APRETUDE.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effects of cabotegravir on human male or female fertility. Animal studies indicate no effects of cabotegravir on male or female fertility.

Cabotegravir when administered orally to male and female rats at 1,000 mg/kg/day (>30 times the exposure in humans at the Maximum Recommended Human Dose [MHRD] of 30 mg oral or 400 mg intramuscular (IM) dose) for up to 26 weeks did not cause adverse effects on male or female reproductive organs or spermatogenesis. No functional effects on male or female mating or fertility were observed in rats given cabotegravir at doses up to 1,000 mg/kg/day.

Use in pregnancy

(Pregnancy Category B1)

There are limited data for cabotegravir in pregnant women. The effect of APRETUDE on human pregnancy is unknown.

APRETUDE should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus.

Cabotegravir has been detected in systemic circulation for up to 12 months or longer after an injection, therefore, consideration should be given to the potential for foetal exposure during pregnancy (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Cabotegravir crossed the placenta in pregnant rats and could be detected in foetal tissues. Cabotegravir was not teratogenic in rats at oral doses up to 1000 mg/kg/day (>30 times the exposure in humans at the MRHD of 30 mg oral or 400 mg IM dose) but caused a delay in delivery that was associated with reduced survival and viability of rat offspring; there was no effect on survival at birth when foetuses were delivered by caesarean section. Exposures at the NOAEL were at least 11 times the exposure in humans at the MRHD of 30 mg oral or 400 mg IM dose. The relevance to human pregnancy is unknown

Use in lactation

It is expected that cabotegravir will be secreted into human milk based on animal data, although this has not been confirmed in humans. Cabotegravir may be present in human milk for up to 12 months or longer after the last cabotegravir injection.

It is recommended that women breast-feed only if the expected benefit justifies the potential risk to the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There have been no studies to investigate the effect of cabotegravir on driving performance or the ability to operate machinery. The clinical status of the individual and the adverse event profile of APRETUDE should be borne in mind when considering the individual's ability to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial data

The safety assessment of APRETUDE is based on two Phase III clinical studies; HPTN 083 and HPTN 084. In HPTN 083, the median time on blinded study product was 65 weeks and 2 days (1 day to 156 weeks and 1 day), with a total exposure on cabotegravir of 3270 person years. In HPTN 084, the median time on blinded study product was 64 weeks and 1 days (1 day to 153 weeks and 1 day), with a total exposure on cabotegravir of 1920 person years.

Adverse events

The most common adverse events reported in greater than 10% of participants in any treatment group from HPTN 083 or HPTN 083 are presented in Table 5.

Table 5 Most Common Adverse Events (Reported in ≥10% of Participants in Any Treatment Group from HPTN 083 or HPTN 084)[1] by Preferred Term

	HPTN 083		HPTN 084	
Preferred Term	**CAB (N=2281) n (%)**	**TDF/FTC (N=2285) n (%)**	**CAB (N=1614) n (%)**	**TDF/FTC (N=1610) n (%)**
Injection site pain	1713 (75)	688 (30)	522 (32)	147 (9)
Creatinine renal clearance decreased	1576 (69)	1661 (73)	1160 (72)	1192 (74)
Blood creatine phosphokinase increased	506 (22)	497 (22)	237 (15)	263 (16)
Nasopharyngitis	383 (17)	379 (17)	82 (5)	96 (6)
Blood creatinine increased	379 (17)	426 (19)	363 (22)	347 (22)
Headache	377 (17)	356 (16)	377 (23)	373 (23)
Diarrhoea	328 (14)	336 (15)	101 (6)	119 (7)
Anal chlamydia infection	264 (12)	297 (13)	-	-
Upper respiratory tract infection	264 (12)	271 (12)	268 (17)	293 (18)
Injection site nodule	263 (12)	13 (<1)	80 (5)	5 (<1)
Lipase increased	255 (11)	272 (12)	198 (12)	171 (11)
Injection site induration	255 (11)	8 (<1)	70 (4)	4 (<1)
Blood glucose increased	247 (11)	166 (7)	584 (36)	451 (28)
Pyrexia	232 (10)	112 (5)	22 (1)	21 (1)
Proctitis gonococcal	220 (10)	236 (10)	-	-
Aspartate aminotransferase increased	213 (9)	220 (10)	212 (13)	181 (11)
Alanine aminotransferase increased	186 (8)	220 (10)	232 (14)	228 (14)
Amylase increased	158 (7)	183 (8)	558 (35)	573 (36)
Blood glucose decreased	109 (5)	118 (5)	425 (26)	439 (27)
Blood phosphorus decreased	107 (5)	126 (6)	278 (17)	322 (20)
Urinary tract infection	32 (1)	23 (1)	225 (14)	210 (13)

	HPTN 083		HPTN 084	
Preferred Term	**CAB (N=2281) n (%)**	**TDF/FTC (N=2285) n (%)**	**CAB (N=1614) n (%)**	**TDF/FTC (N=1610) n (%)**
Dysfunctional uterine bleeding	-	-	161 (10)	161 (10)
Vulvovaginal candidiasis	-	-	139 (9)	162 (10)

[1] During the blinded oral and injection phase of the study

The PTs are in descending order of frequency, based on the HPTN 083 CAB arm.

Adverse drug reactions (ADR)

ADRs listed include those attributable to the oral or injectable formulations of APRETUDE. When frequencies differed between HPTN 083 and 084, the highest frequency category is quoted.

The most frequently reported ADRs in HPTN 083 were: Injection site reactions (ISR) (82%), headache (17%) and diarrhoea (14%).

The most frequently reported ADRs in HPTN 084 were: Injection site reactions (38%), headache (23%) and transaminase increased (19%).

The ADRs identified in these studies are listed below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000) and very rare (<1/10,000), including isolated reports.

Table 6 Adverse reactions[1]

MedDRA System Organ Class (SOC)	Frequency Category	Adverse Reactions
Psychiatric disorders	Common	Abnormal dreams Insomnia Depression
Nervous system disorders	Very Common	Headache
	Common	Dizziness
	Uncommon	Vasovagal reactions (in response to injections)
Gastrointestinal disorders	Very Common	Diarrhoea
	Common	Nausea Abdominal pain[2] Flatulence Vomiting
Hepatobiliary Disorders	Very Common	Transaminase increased
	Uncommon	Hepatotoxicity
Skin and subcutaneous tissue disorders	Common	Rash[3]
Musculoskeletal and connective tissue disorders	Common	Myalgia
General disorders and administrative site conditions	Very Common	Pyrexia[4] Injection site reactions[5] (pain and tenderness, nodule, induration)
	Common	Injection site reaction[5] (swelling, bruising, erythema, warmth, pruritus, anaesthesia) Fatigue Malaise

	Uncommon	Injection site reactions[5] (haematoma, discolouration, abscess)
Investigations	Uncommon	Weight increased

[1]The frequency of the identified adverse reactions are based on all reported occurrences of the events and are not limited to those considered at least possibly related by the investigator.
[2]Abdominal pain includes the following grouped MedDRA preferred terms: upper abdominal pain and abdominal pain.
[3]Rash includes the following grouped MedDRA preferred terms: rash, rash erythematous, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic.
[4]Pyrexia includes the following grouped MedDRA preferred terms: pyrexia and feeling hot. The majority of pyrexia events were reported within one week of injections.
[5]ISRs listed in the table have been seen in 2 participants or more.

Local Injection Site Reactions

In HPTN 083, 2% of participants discontinued APRETUDE because of Injection site reactions (ISRs).

Out of 20286 injections, 8900 ISRs were reported.

A total of 2117 participants received at least one injection. Of the 1740 (82%) participants who experienced at least one ISR, the maximum severity of ISRs reported was mild (Grade 1, 34% of participants), moderate (Grade 2, 46% of participants) or severe (Grade 3, 3% of participants). No participants experienced Grade 4 ISRs. The median duration of overall ISR events was 4 days. The proportion of participants reporting ISRs at each visit and the severity of the ISRs decreased over time.

In HPTN 084, no participants discontinued APRETUDE because of ISRs.

Out of 13068 injections, 1171 ISRs were reported.

A total of 1519 participants received at least one injection. Of the 578 (38%) participants who experienced at last one ISR, the maximum severity of ISRs reported was mild (Grade 1, 25% of participants), moderate (Grade 2, 13% of participants) or severe (Grade 3, <1% of participants). No participants experienced Grade 4 ISRs. The median duration of overall ISR events was 8 days. The proportion of participants reporting ISRs at each visit and the severity of the ISRs generally decreased over time.

Weight increased

At the Week 41 and 97 timepoints in HPTN 083, participants who received APRETUDE gained a median of 1.2 kg (IQR -1.0, 3.5; n=1623) and 2.1 kg (IQR; -0.9, 5.9 n=601) in weight from baseline, respectively; those in the tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) group gained a median of 0.0 kg (IQR -2.1, 2.4, n=1611) and 1.0 kg (IQR; -1.9, 4.0 n=598) in weight from baseline, respectively.

At the Week 41 and 97 timepoints in HPTN 084, participants who received APRETUDE gained a median of 2.0 kg (IQR 0.0, 5.0; n=1151) and 4.0 kg (IQR; 0.0, 8.0, n=216) in weight from baseline, respectively; those in the tenofovir disoproxil fumarate (TDF)/emtricitabine

(FTC) group gained a median of 1.0 kg (IQR -1.0, 4.0, n=1131) and 3.0 kg (IQR; -1.0, 6.0 n=218) in weight from baseline, respectively.

Clinical Trials Experience in Adolescents
In adolescents receiving APRETUDE for HIV-1 PrEP, the safety data were comparable to the safety data reported in adults receiving APRETUDE for HIV-1 PrEP (see section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

Post-marketing data
Table 7 Adverse reactions based on post-marketing experience

MedDRA System Organ Class (SOC)	Frequency Category	Adverse Reactions
Immune system disorders	Uncommon	Hypersensitivity (including angioedema, urticaria)
Psychiatric disorders	Uncommon	Suicidal ideation*, suicide attempt* *particularly in patients with a pre-existing history of depression or psychiatric illness

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

Symptoms and signs
There is currently no experience of overdose with APRETUDE.

Treatment
There is no specific treatment for overdose with APRETUDE. If overdose occurs, the individual should be treated supportively with appropriate monitoring as necessary. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

APRETUDE is known to be highly protein bound in plasma; therefore, dialysis is unlikely to be helpful in removal of drug from the body. Management of overdose with APRETUDE injection should take into consideration the prolonged exposure to drug following an injection (see section 4.4 Warnings and Precautions FOR USE).

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

Cabotegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle.

Pharmacodynamic effects

Antiviral Activity in cell culture

Cabotegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean concentration of cabotegravir necessary to reduce viral replication by 50 percent (EC_{50}) values of 0.22 nM in peripheral blood mononuclear cells (PBMCs), 0.74 nM in 293T cells and 0.57 nM in MT4 cells. Cabotegravir demonstrated antiviral activity in cell culture against a panel of 24 HIV-1 clinical isolates (three in each group of M clades A, B, C, D, E, F, and G, and 3 in group O) with EC_{50} values ranging from 0.02 nM to 1.06 nM for HIV-1. Cabotegravir EC_{50} values against three HIV-2 clinical isolates ranged from 0.10 nM to 0.14 nM. No clinical data is available in patients with HIV-2.

Antiviral Activity in combination with other antiviral agents

In *in vitro* combination studies, cabotegravir had weak synergistic antiviral effects with nucleoside reverse transcriptase inhibitors (lamivudine, tenofovir disoproxil fumarate, emtricitabine) and additive effects with the non-nucleoside reverse transcriptase inhibitor, rilpivirine.

Effect of Human Serum and Serum Proteins

In vitro studies suggested a 408-fold shift in IC_{50} of cabotegravir in the presence of 100% human serum (by method of extrapolation), and the protein adjusted IC_{50} (PA-IC_{50}) was estimated to be 102 nM in MT4 cells.

Resistance in vitro

Isolation from wild-type HIV-1 and activity against resistant strains: Viruses with >10-fold increase in cabotegravir EC_{50} were not observed during the 112-day passage of strain IIIB. The following integrase (IN) mutations emerged after passaging wild type HIV-1 (with T124A polymorphism) in the presence of cabotegravir: Q146L (fold-change range 1.3-4.6), S153Y (fold-change range 2.8-8.4) and I162M (fold-change = 2.8). As noted above, the detection of T124A is selection of a pre-existing minority variant that does not have differential susceptibility to cabotegravir. No amino acid substitutions in the integrase region were selected when passaging the wild-type HIV-1 NL-432 in the presence of 6.4 nM of cabotegravir through Day 56.

Among the known integrase resistant mutants tested, mild resistance (≥ 5-fold but <10-fold resistance) was seen with E92Q/N155H, G118R, G140S/Q148H, Y143H/N155H, Q148K, Q148R, T66K/L74M and G140S/Q148K. High resistance (≥10-fold resistance) was seen with E138K/Q148K, V72I/E138K/Q148K, E138K/Q148R, E138K/G140S/Q148R, L74M/V75A/G140S/Q148H, G140C/Q148R, Q148R/N155H and G140S/Q148R.

Resistance in vivo

HPTN 083

In the primary analysis of the HPTN 083 study, there were 13 incident infections on the cabotegravir arm and 39 incident infections on the tenofovir disoproxil fumarate

(TDF)/emtricitabine (FTC) arm. In the cabotegravir arm, 5 incident infections occurred when receiving cabotegravir PrEP injections, of which 4 participants received on-time injections and 1 participant had one injection off-schedule. Five incident infections occurred ≥6 months after the last dose of cabotegravir PrEP. Three incident infections occurred during the oral lead-in period.

HIV genotyping and phenotyping were attempted at the first visit where HIV viral load was >500 copies/mL. Of the 13 incident infections in the cabotegravir arm, 4 participants had INSTI resistance mutations. In the TDF/FTC arm, the 4 participants with NRTI resistance (including 3 who had multi-class resistance) included 3 with M184V/I and one with K65R.

None of the 5 participants who were infected after prolonged interruption from cabotegravir administration had INSTI resistance mutations. Neither genotype nor phenotype could be generated for one of the 5 participants, with just 770 copies/mL HIV-1 RNA. Integrase phenotype could not be generated for one of the remaining 4 participants. The remaining 3 participants retained susceptibility to all INSTIs.

Three participants became infected during the oral lead-in phase, prior to receiving cabotegravir injections. One participant with undetectable plasma cabotegravir levels had no INSTI resistance mutations and was susceptible to all INSTIs. Two participants with detectable plasma cabotegravir concentrations had INSTI resistance mutations. The first participant had INSTI resistant mutations E138E/K, G140G/S, Q148R and E157Q. Integrase phenotype could not be generated. The second participant had INSTI resistance mutations E138A and Q148R. This virus was resistant to cabotegravir (fold-change =5.92) but susceptible to dolutegravir (fold-change=1.69).

Five participants acquired HIV-1, despite on time cabotegravir injections for 4 participants and one off-schedule injection for one participant. Two participants had viral loads too low to analyse. The third participant had no INSTI resistance mutations at the first viraemic visit (Week 17) but had R263K at 112 and 117 days later. While phenotype could not be determined 112 days later, day 117 phenotype showed this virus to be susceptible to both cabotegravir (fold-change= 2.32) and dolutegravir (fold-change=2.29). The fourth participant had INSTI resistance mutations G140A and Q148R. Phenotype showed resistance to cabotegravir (fold-change=13) but susceptibility to dolutegravir (fold-change=2.09). The fifth participant had no INSTI resistance mutations.

In addition to the 13 incident infections, one further participant was HIV-1 infected at enrolment and had no INSTI resistance mutations at that time, however, 60 days later, INSTI resistance mutation E138K and Q148K were detected. Phenotype could not be generated.

Following the primary analysis, extended retrospective virologic testing was performed to better characterise the timing of HIV infections. As a result, one of the 13 incident infections in a participant receiving on time cabotegravir injections was determined to be a prevalent infection.

HPTN 084

In the primary analysis of the HPTN 084 study, there were 4 incident infections on the cabotegravir arm and 36 incident infections on the TDF/FTC arm.

In the cabotegravir arm, 2 incident infections occurred while receiving injections; one participant had 3 delayed cabotegravir injections and both had been non-adherent to oral cabotegravir.

Two incident infections occurred after the last dose of oral cabotegravir; both participants were non-adherent to oral cabotegravir. The first HIV positive visit occurred approx. 11 weeks after enrolment for one participant and 57 weeks after enrolment for the other.

HIV genotyping was attempted at the first visit where HIV viral load was >500 c/mL (first viraemic visit). HIV genotyping results were available for 3 of the 4 cabotegravir arm participants. No major INSTI resistance mutations were detected.

HIV genotyping results were available for 33 of the 36 incident infections in the TDF/FTC group. One participant had a major NRTI mutation (M184V); this participant also had NNRTI resistance with the mutation K103N. Nine other participants had NNRTI resistance (7 had K103N, alone or with E138A or P225H; 1 had K101E alone; 1 had E138K alone).

Following the primary analysis, extended retrospective virologic testing was performed to better characterize the timing of HIV-1 infections. As a result, 1 of the 4 HIV-1 incident infections in participants receiving cabotegravir was determined to be a prevalent infection.

Effects on Electrocardiogram

In a randomised, placebo-controlled, three-period cross-over trial, 42 healthy subjects were randomized into 6 random sequences and received three doses of oral administration of placebo, cabotegravir 150 mg every 12 hours (mean steady-state C_{max} was approximately 2.8-fold and 5.6-fold above the 30 mg oral once-daily dose and the 600 mg cabotegravir injection every 2 month dose, respectively), or single dose of moxifloxacin 400 mg (active control). After baseline and placebo adjustment, the maximum time-matched mean QTc change based on Fridericia's correction method (QTcF) for cabotegravir was 2.62 msec (1-side 90% upper CI:5.26 msec). Cabotegravir did not prolong the QTc interval over 24 hours post-dose.

Clinical Trials

Clinical efficacy

The efficacy of APRETUDE to reduce the risk of acquiring HIV-1 infection has been evaluated in two randomised (1:1), double blind, multi-site, two-arm, controlled studies, HPTN 083 in HIV-1 uninfected men and transgender women who have sex with men and have evidence of high-risk behaviour for HIV-1 infection and HPTN 084 in HIV-1 uninfected cisgender women at risk of acquiring HIV-1. The efficacy of APRETUDE was compared with daily oral tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC).

Participants randomised to receive APRETUDE initiated oral lead-in dosing with one APRETUDE 30 mg tablet and a placebo daily, for up to 5 weeks, followed by APRETUDE intramuscular (IM) injection (single 600 mg [3 mL] injection, at months 1, 2 and every 2 months thereafter and a daily placebo tablet. Participants randomised to receive TDF/FTC initiated oral TDF 300 mg/FTC 200 mg and placebo for up to 5 weeks, followed by oral TDF 300 mg/FTC 200 mg daily and placebo (IM) injection (3 mL, 20% lipid injectable emulsion at months 1, 2 and every 2 months thereafter).

HPTN 083

In HPTN 083, a non-inferiority study, 4566 cisgender men and transgender women who have sex with men, were randomised 1:1 and received either cabotegravir (n=2281) or TDF/FTC (n=2285) as blinded study medication up to Week 153.

At baseline, the median age of participants was 26 years, 12% were transgender women, 72% were non-white and 67% were < 30 years.

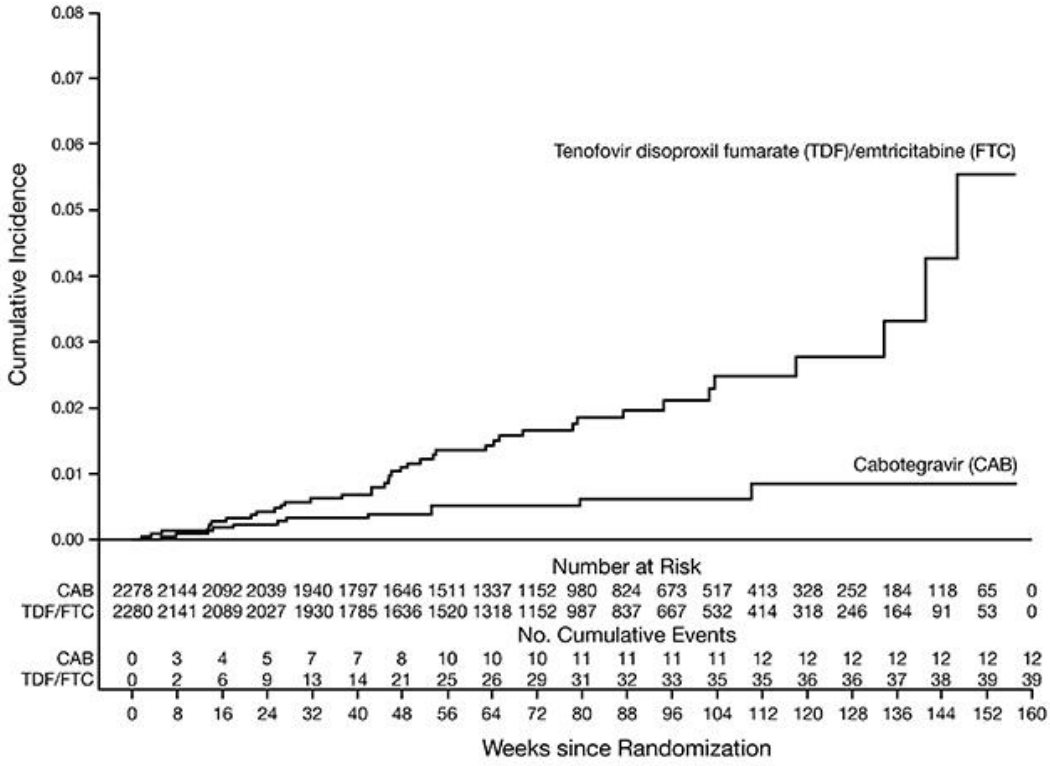
The primary endpoint was the rate of incident HIV infections among participants randomised to APRETUDE tablets and APRETUDE injections compared to oral TDF/FTC (corrected for early stopping). The primary analysis demonstrated the superiority of APRETUDE compared to TDF/FTC with a 66% reduction in the risk of acquiring incident HIV infection, hazard ratio (95% CI) 0.34 (0.18, 0.62); further testing revealed one of the infections on cabotegravir to be prevalent then yielding a 69% reduction in the risk of incident infection relative to TDF/FTC (see Table 8).

Table 8 Primary Efficacy Endpoint: Comparison of Rates of Incident HIV Infections during Randomised Phase in HPTN 083 (mITT, extended retrospective virologic testing)

	Cabotegravir (N = 2,278)	**TDF/FDC (N = 2,281)**	**Superiority *P* Value**
Person-years	3,211	3,193	
HIV-1 infections (incidence rate per 100 person-years)	12[a] (0.37)	39 (1.22)	
Hazard ratio (95% CI)	0.31 (0.16, 0.58)		*P* = 0.0003

[a] Following the primary analysis, extended retrospective virologic testing was performed to better characterize the timing of HIV-1 infections. As a result, 1 of the 13 HIV-1 incident infections in participants receiving APRETUDE was determined to be a prevalent infection. The original hazard ratio (95% CI) from the primary analysis is 0.34 (0.18, 0.62).

Figure 1. Cumulative Incidence of HIV Infections in HPTN 083



Results from all subgroup analyses were consistent with the overall protective effect, with a lower rate of incident HIV-1 infections observed for participants randomised to APRETUDE compared with participants randomised to TDF/FTC (see Table 9).

Table 9. Rate of incident HIV-1 infection by subgroup in HPTN 083 (mITT, extended retrospective virologic testing)

Subgroup	Cabotegravir incidence per 100 person years	Cabotegravir person years	TDF/FTC incidence per 100 person years	TDF/FTC person years)	HR (95% CI)
Age					
<30 years	0.47	2110	1.66	1987	0.29 (0.15, 0.59)
≥30 years	0.18	1101	0.50	1206	0.39 (0.08, 1.84)
Gender					
MSM	0.35	2836	1.14	2803	0.32 (0.16, 0.64)
TGW	0.54	371	1.80	389	0.34 (0.08, 1.56)
Race (US)					
Black	0.58	691	2.28	703	0.26 (0.09, 0.76)
Non-Black	0.00	836	0.50	801	0.11 (0.00, 2.80)
Region					
US	0.26	1528	1.33	1504	0.21 (0.07, 0.60)
Latin America	0.49	1020	1.09	1011	0.47 (0.17, 1.35)
Asia	0.35	570	1.03	581	0.39 (0.08, 1.82)
Africa	1.08	93	2.07	97	0.63 (0.06, 6.50)

MSM=Cisgender men who have sex with men.
TGW=Transgender women who have sex with men.

HPTN 084

In HPTN 084, a superiority study, 3224 cisgender women were randomised 1:1 and received either cabotegravir (n=1614) or TDF/FTC (n=1610) as blinded study medication up to Week 153.

At baseline, the median age of participants was 25 years, >99% were non-white, >99% were cisgender women and 49% were <25 years of age.

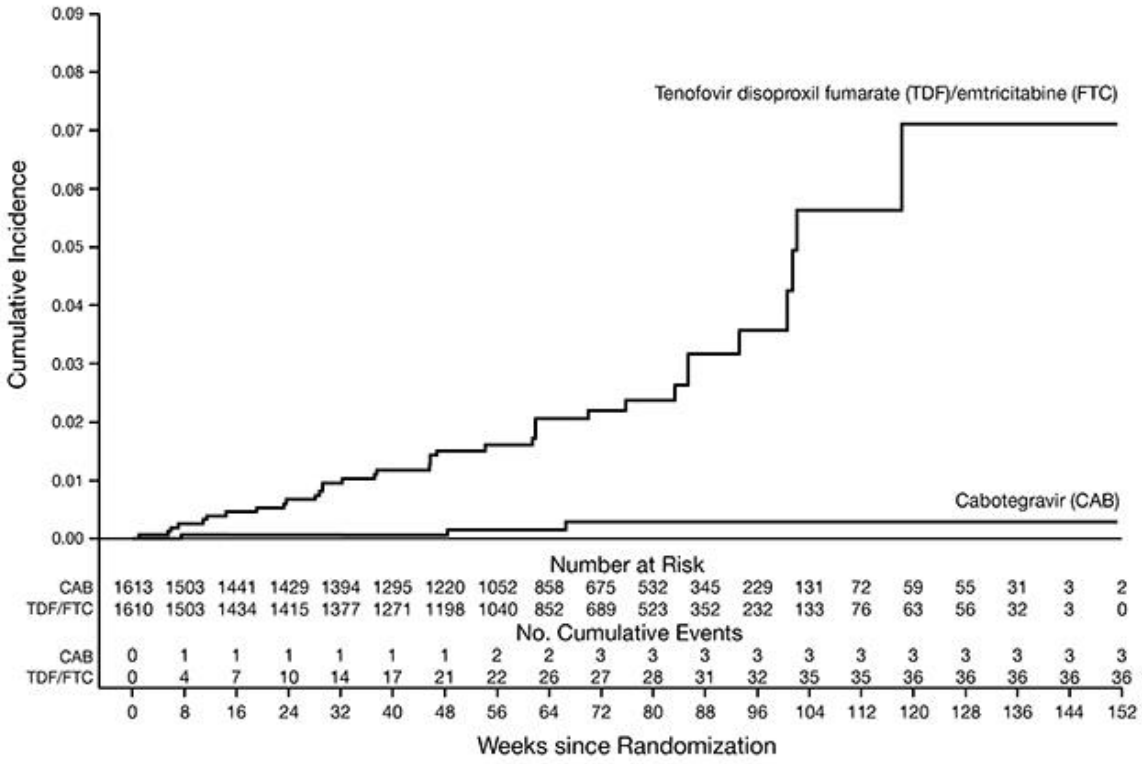
The primary endpoint was the rate of incident HIV infections among participants randomised to APRETUDE tablets and APRETUDE injections compared to oral TDF/FTC (corrected for early stopping). The primary analysis demonstrated the superiority of APRETUDE compared to TDF/FTC with an 88% reduction in the risk of acquiring incident HIV-1 infection hazard ratio (95% CI) 0.12 (0.05, 0.31); further testing revealed 1 of the infections on APRETUDE to be prevalent then yielding a 90% reduction in the risk of HIV-1 incident infection relative to TDF/FTC (see Table 10).

Table 10 Primary Efficacy Endpoint in HPTN 084: Comparison of Rates of Incident HIV Infections during Randomised Phase (mITT, extended retrospective virologic testing)

	Cabotegravir (N=1613)	TDF/FDC (N=1610)	Superiority P-Value
Person years	1960	1946	
HIV-1 incident infections (incidence rate per 100 person years)	3[a](0.15)	36 (1.85)	
Hazard ratio (95% CI)	0.10 (0.04, 0.27)		P<0.0001

[a] Following the primary analysis, extended retrospective virologic testing was performed to better characterize the timing of HIV-1 infections. As a result, 1 of the 4 HIV-1 incident infections in participants receiving APRETUDE was determined to be a prevalent infection. The original hazard ratio corrected for early stopping (95% CI) from the primary analysis is 0.12 (0.05, 0.31).

Figure 2. Cumulative Incidence of HIV Infections in HPTN 084



Results from pre-planned subgroup analyses were consistent with the overall protective effect, with a lower rate of incident HIV-1 infections observed for participants randomised to APRETUDE compared with participants randomised to TDF/FTC (see Table 11).

Table 11 Rate of incident HIV-1 infection by subgroup in HPTN 084 (mITT, extended retrospective virologic testing)

Subgroup	Cabotegravir Incidence per 100 Person-Years	Cabotegravir Person-Years	TDF/FTC Incidence per 100 Person-Years	TDF/FTC Person-Years	Hazard Ratio (95% CI)
Age					
<25 years	0.23	868	2.34	853	0.12 (0.03, 0.46)
≥25 years	0.09	1,093	1.46	1,093	0.09 (0.02, 0.49)
Body Mass Index					
<30	0.22	1,385	1.88	1,435	0.12 (0.04, 0.38)
≥30	0.00	575	1.76	511	0.04 (0.00, 0.93)

Adolescents

The safety and effectiveness of APRETUDE for HIV-1 PrEP in at-risk adolescents aged 12 years and older and weighing at least 35 kg is supported by data from 2 adequate and well-controlled trials of APRETUDE for HIV-1 PrEP in adults with additional safety and pharmacokinetic data from studies in HIV-1 infected adults who were administered CABENUVA (cabotegravir and rilpivirine prolonged release suspensions for injection), and in HIV-1 infected paediatric subjects who were administered separate components of CABENUVA in addition to their current antiretroviral therapy (see section 4.2 DOSE AND METHOD OF ADMINISTRATION, section 4.8 ADVERSE EFFECTS, section 5.2 PHARMACOKINETIC PROPERTIES).

5.2 PHARMACOKINETIC PROPERTIES

Film-coated tablets

Cabotegravir pharmacokinetics is similar between healthy and HIV-infected subjects. The PK variability of cabotegravir is moderate to high. In Phase I studies in healthy subjects, between-subject CVb% for AUC, Cmax, and Ctau ranged from 34 to 91% across healthy subject studies. Within-subject variability (CVw%) is lower than between-subject variability

Prolonged-release suspension for injection

Cabotegravir pharmacokinetics is similar between healthy and HIV-infected subjects. The PK variability of cabotegravir is moderate to high. In HIV-infected subjects participating in Phase III studies, between-subject CVb% for C_{tau} ranged from 39 to 48%. Higher between-subject variability ranging from 65 to 76% was observed with single dose administration of long-acting cabotegravir injection.

Table 12. Pharmacokinetic parameters following cabotegravir orally once daily, and initiation and every 2 month continuation intramuscular injections

Dosing Phase	Dosage Regimen	Geometric Mean (5th, 95th Percentile)[a]		
		$AUC_{(0\text{-}tau)}$[b] (µg•h/mL)	**C_{max} (µg/mL)**	**C_{tau} (µg/mL)**
Oral lead-in[c]	30 mg once daily	145 (93.5, 224)	8.0 (5.3, 11.9)	4.6 (2.8, 7.5)
Initial injection[d]	600 mg IM Initial Dose	1591 (714, 3245)	8.0 (5.3, 11.9)	1.5 (0.65, 2.9)
Every 2-month injection[e]	600 mg IM Every 2-month	3764 (2431, 5857)	4.0 (2.3, 6.8)	1.6 (0.8, 3.0)

[a] Pharmacokinetic (PK) parameter values were based on individual post-hoc estimates from population PK models for patients in Phase III treatment studies of HIV treatment studies.
[b] tau is dosing interval: 24 hours for oral administration; 1 month for the initial injection and 2 months for every 2 months for IM injections of extended-release injectable suspension.
[c] Oral lead-in pharmacokinetic parameter values represent steady-state.
[d] Initial injection C_{max} values primarily reflect oral dosing because the initial injection was administered on the same day as the last oral dose; however, the $AUC_{(0\text{-}tau)}$ and C_{tau} values reflect the initial injection. When administered without oral lead-in to HIV infected recipients (n = 110), the observed cabotegravir geometric mean (5th, 95th percentile) C_{max} (1 week post-initial injection) was 1.89 µg/mL (0.438, 5.69) and C_{tau} was 1.43 µg/mL (0.403, 3.90).
[e] Pharmacokinetic parameter values represent steady state.

Absorption

Film-coated tablets

Cabotegravir is rapidly absorbed following oral administration, with median T_{max} at 3 hours post dose for tablet formulation. The linearity of cabotegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablet formulations, cabotegravir pharmacokinetics was dose-proportional to slightly less than proportional to dose from 5 mg to 60 mg. With once daily dosing, pharmacokinetic steady-state is achieved by 7 days.

Cabotegravir may be administered with or without food. Food increased the extent of absorption of cabotegravir. Bioavailability of cabotegravir is independent of meal content: high fat meals increased cabotegravir $AUC_{(0\text{-}\infty)}$ by 14% and increased C_{max} by 14% relative to fasted conditions. These increases are not clinically significant.

The absolute bioavailability of cabotegravir has not been established.

Prolonged-release suspension for injection

Cabotegravir injection exhibits absorption-limited pharmacokinetics because cabotegravir is slowly absorbed into the systemic circulation from the gluteal muscle resulting in sustained plasma concentrations. Following a single 600 mg intramuscular dose, plasma cabotegravir concentrations are detectable on the first day with median cabotegravir concentrations at 4 hours post dose of 0.290 mg/mL, which is above *in-vitro* PA-IC_{90} of 0.166 mg/mL, and reach maximum plasma concentration with a median T_{max} of 7 days. Target concentrations are achieved following the initial IM injection (see Table 11). Cabotegravir has been detected in plasma up to 52 weeks or longer after administration of a single injection.
Plasma CAB exposure increases in proportion or slightly less than in proportion to dose following single and repeat IM injection of doses ranging from 100 to 800 mg.

Distribution

Cabotegravir is highly bound (approximately >99%) to human plasma proteins, based on *in vitro* data. Following administration of oral tablets, the mean apparent oral volume of distribution (Vz/F) in plasma was 12.3 L. In humans, the estimate of plasma cabotegravir Vc/F was 5.27 L and Vp/F was 2.43 L. These volume estimates, along with the assumption of high F, suggest some distribution of cabotegravir to the extracellular space.

Cabotegravir is present in the female and male genital tract, following a single 3 mL (600 mg) IM injection, as observed in a study in healthy participants (n=15). Median cabotegravir concentrations at Day 3 (the earliest tissue PK sample) were 0.49 mg/mL in cervical tissue, 0.29 mg/mL in cervicovaginal fluid, 0.37 mg/mL in vaginal tissue, 0.32 mg/mL in rectal tissue, and 0.69 mg/mL in rectal fluid, which are above the *in vitro* PA-IC_{90}.

Metabolism

Cabotegravir is primarily metabolised by UGT1A1 with a minor UGT1A9 component. Cabotegravir is the predominant circulating compound in plasma, representing > 90% of plasma total radiocarbon. Following oral administration in humans, cabotegravir is primarily eliminated through metabolism; renal elimination of unchanged cabotegravir is low (<1% of the dose). Forty-seven percent of the total oral dose is excreted as unchanged cabotegravir in the faeces. It is unknown if all or part of this is due to unabsorbed drug or biliary excretion of the glucuronidate conjugate, which can be further degraded to form the parent compound in the gut lumen. Cabotegravir was observed to be present in duodenal bile samples. The glucuronic acid metabolite was also present in some but not all of the duodenal bile samples. Twenty-seven percent of the total oral dose is excreted in the urine, primarily as a glucuronide metabolite (75% of urine radioactivity, 20% of total dose).

Excretion

Film-coated tablets

Cabotegravir has a mean terminal half-life of 41 h and an apparent clearance (CL/F) of 0.21 L per hour observed following oral administration in healthy subjects.

Prolonged-release suspension for injection
Cabotegravir mean apparent terminal phase half-life is absorption-rate limited and is estimated to be 5.6 to 11.5 weeks after a single dose IM injection. The significantly longer apparent half-life compared to oral administration reflects absorption from the injection site into the systemic circulation. The apparent CL/F was 0.151 L/h.

Special patient populations

Gender

Population pharmacokinetic analyses revealed no clinically relevant effect of gender on the exposure of cabotegravir. In addition, no clinically relevant differences in plasma cabotegravir concentrations were observed in the HPTN 083 study by gender, including in cisgender men and transgender women with or without cross-sex hormone therapy use. Therefore, no dose adjustment is required on the basis of gender.

Race

Population pharmacokinetic analyses revealed no clinically relevant effect of race on the exposure of cabotegravir, therefore no dosage adjustment is required on the basis of race.

BMI

Population pharmacokinetic analyses revealed no clinically relevant effect of BMI on the exposure of cabotegravir, therefore no dose adjustment is required on the basis of BMI.

Adolescents (aged > 12 years to <18 years)

Population pharmacokinetic analyses revealed no clinically relevant differences in exposure between the HIV-1 infected adolescent and HIV-1 infected and uninfected adult participants from the cabotegravir development programme, therefore, no dosage adjustment is needed for adolescents weighing ≥35 kg.

Table 13. Predicted pharmacokinetic parameters following cabotegravir orally once daily, and initiation and every 2 month continuation intramuscular injections in Adolescent Participants aged 12 to less than 18 years (≥35 kg)

Dosing Phase	Dosage Regimen	Geometric Mean (5th, 95th Percentile)[a]		
		$AUC_{(0\text{-}tau)}$[b] (µg•h/mL)	C_{max} (µg/mL)	C_{tau} (µg/mL)
Oral lead-in[c]	30 mg once daily	193 (106, 346)	14.4 (8.02,25.5)	5.79 (2.48,12.6)
Initial injection[d]	600 mg IM Initial Dose	2123 (881, 4938)	11.2 (5.63,21.5)	1.84 (0.64,4.52)
Every 2-month injection[e]	600 mg IM Every 2-month	4871 (2827, 8232)	7.23 (3.76,14.1)	2.01 (0.64,4.73)

[a] Pharmacokinetic (PK) parameter values were based on population PK model simulations in a virtual HIV-1 infected adolescent population weighing 35-156 kg.
[b] tau is dosing interval: 24 hours for oral administration; 1 month for the initial injection, 2 months for every 2 months for IM injections of extended-release injectable suspension.
[c] Oral lead-in pharmacokinetic parameter values represent steady-state.
[d] Initial injection C_{max} values primarily reflect oral dosing because the initial injection was administered on the same day as the last oral dose; however, the $AUC_{(0\text{-}tau)}$ and C_{tau} values reflect the initial injection.
[e] Pharmacokinetic parameter values represent steady state.

Children

The pharmacokinetics and dosing recommendations of cabotegravir in children less than 12 years of age or 35 kg or less have not been established.

Elderly

Population pharmacokinetic analysis of cabotegravir revealed no clinically relevant effect of age on cabotegravir exposure.

Pharmacokinetic data for cabotegravir in subjects of >65 years old are limited.

Renal impairment

No clinically important pharmacokinetic differences between subjects with severe renal impairment (CrCL <30 mL/min and not on dialysis) and matching healthy subjects were observed. No dosage adjustment is necessary for individuals with mild to severe renal impairment (not on dialysis). Cabotegravir has not been studied in individuals on dialysis.

Hepatic impairment

No clinically important pharmacokinetic differences between subjects with moderate hepatic impairment and matching healthy subjects were observed. No dosage adjustment is necessary for individuals with mild to moderate hepatic impairment (Child-Pugh Score A or B). The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of cabotegravir has not been studied.

HBV and HCV Infected Individuals

There are no data for the use of cabotegravir in subjects with HBV and HCV infection in PrEP studies.

Polymorphisms in Drug Metabolising Enzymes

In a meta-analysis of healthy and HIV-infected subjects, HIV-infected subjects with UGT1A1 genotypes conferring poor cabotegravir metabolism had a 1.2-fold increase in mean steady-state cabotegravir AUC, C_{max}, and C_{tau} following cabotegravir injection vs. 1.38-fold mean increase following oral cabotegravir administration. This was similar to 1.3- to 1.5-fold mean increase in steady-state cabotegravir, cabotegravir AUC, C_{max}, and C_{tau} observed following oral cabotegravir in healthy and HIV infected subjects combined. These differences are not considered clinically relevant. Polymorphisms in UGT1A9 were not associated with differences in the pharmacokinetics of cabotegravir, therefore, no dose adjustment is required in subjects with either UGT1A1 or UGT1A9 polymorphisms.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Cabotegravir was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay.

Carcinogenicity

Cabotegravir was not carcinogenic in long term oral studies in the mouse and rat at doses resulting in up to 7–8 and 26 times, respectively (75 mg/kg/day in male mice and rats and 35 mg/kg/day in female mice), the maximum AUC in patients.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Film-coated tablets

Lactose monohydrate
Microcrystalline cellulose
Hypromellose
Sodium starch glycolate Type A
Magnesium stearate
Titanium dioxide
Macrogol

Cabotegravir prolonged-release suspension for injection

Mannitol
Polysorbate 20
Macrogol 3350
Water for injections

6.2 INCOMPATIBILITIES

In the absence of compatibility studies cabotegravir injection must not be mixed with other medicinal products

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.

In use shelf life:

Once the suspension has been drawn into the syringe, the injection should be used as soon as possible, but may be stored for up to 2 hours at room temperature. If 2 hours are exceeded, the medication, syringe and needle must be discarded.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

Film-coated tablets

APRETUDE tablets are supplied in HDPE (high density polyethylene) bottles with a polypropylene child-resistant closure and a polyethylene faced induction heat seal-liner. Each bottle contains 30 tablets.

Prolonged-release suspension for injection

APRETUDE injection is supplied in a Type I clear glass vial, sealed with bromobutyl rubber stopper and an aluminum overseal with a removeable plastic cap. Supplied as a single 3 mL vial or 25 x 3 mL vials.

Not all pack sizes may be distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

Full instructions for use and handling of APRETUDE prolonged-release suspension for injection is provided in the Instructions for Use included as a package insert.

6.7 PHYSICOCHEMICAL PROPERTIES

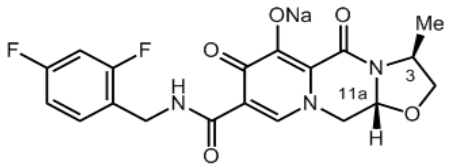
Cabotegravir sodium

Chemical name: sodium (3S,11aR)-N-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido [1,2-d]pyrazine-8-carboxamide

Molecular formula: $C_{19}H_{16}F_2N_3NaO_5$

Molecular weight: 427.33 g/mol

Chemical structure



CAS number: 1051375-13-3

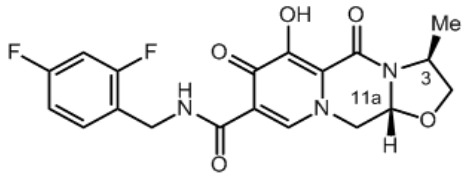
Cabotegravir

Chemical name: (3S,11aR)-N-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide

Molecular formula: $C_{19}H_{17}F_2N_3O_5$

Molecular weight: 405.35 g/mol

Chemical structure



CAS number: 1051375-10-0

Cabotegravir is a white to almost white solid.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

ViiV Healthcare Pty Ltd
Level 4, 436 Johnston Street,
Abbotsford, Victoria, 3067

9 DATE OF FIRST APPROVAL

11 August 2022

10 DATE OF REVISION

15 September 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	Additional warning added to avoid leakage of prepared suspension
4.8	Hypersensitivity adverse effect moved to post-marketing data
4.8	Post-marketing psychological adverse reactions included
All	Minor editorial corrections

Version 3.0