PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**APRETUDE**

Cabotegravir Tablets

30 mg cabotegravir (as cabotegravir sodium)

and

Cabotegravir Extended Release Injectable Suspension

200 mg cabotegravir/mL (600 mg/3mL)

Antiretroviral Agent

ViiV Healthcare ULC

75 Queen Street, Suite 1400

Montreal, Quebec

Canada

H3C 2N6

Date of Initial Authorization:
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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

APRETUDE is indicated for at-risk adults and adolescents aged 12 years and older and weighing at least 35 kg for PrEP to reduce the risk of sexually acquired HIV-1 infection.

1.1 Pediatrics

Pediatrics (≥ 12 and < 18 years of age): The use of APRETUDE in adolescent individuals ≥ 12 years of age and weighing ≥ 35 kg is supported by the interim safety and pharmacokinetic data of an ongoing phase 1/2 open-label, non-comparative study in which oral and injectable cabotegravir or oral and injectable rilpivirine, each as a single agent, was administered in combination with other antiretroviral agents to HIV-1 infected adolescents. The pharmacokinetic data from two open-label Phase 2b safety studies of adolescent individuals ≥ 12 years of age and weighing ≥ 35 kg receiving APRETUDE was consistent with that study. Additionally, the safety and pharmacokinetics were consistent with the two Phase 3 studies in adults, which showed the safety and efficacy of APRETUDE (see 8 ADVERSE REACTIONS, 10 CLINICAL PHARMACOLOGY, and 14 CLINICAL TRIALS).

Pediatrics (< 12 years of age): The safety and efficacy of APRETUDE in pediatric individuals < 12 years of age or weighing < 35 kg have not been established.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): 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 10.3 Pharmacokinetics).

2 CONTRAINDICATIONS

APRETUDE tablets and injection are contraindicated in individuals:

- who are hypersensitive to cabotegravir or to any ingredient in the formulations, including any non-medicinal ingredient, or component of the containers. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- with an unknown or positive HIV-1 status.

APRETUDE tablets and injection are contraindicated with strong inducers of UGT1A1 or UGT1A9, including the following (see 9 DRUG INTERACTIONS):

- Anticonvulsants: Carbamazepine, oxcarbazepine, phenobarbital, and phenytoin
- Antimycobacterials: Rifampin, rifapentine

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions
• RISK OF DRUG RESISTANCE WITH USE OF APRETUDE IN UNDIAGNOSED HIV-1 INFECTION Individuals must be tested for HIV-1 infection prior to initiating APRETUDE, and should be tested for HIV-1 infection with each subsequent injection of APRETUDE. APRETUDE must not be prescribed until confirmation of negative HIV-1 infection status. Drug-resistant HIV-1 variants

have been identified with use of APRETUDE by individuals with undiagnosed HIV-1 infection. Do not initiate APRETUDE if signs or symptoms of acute HIV-1 infection are present unless negative infection status is confirmed. Individuals who become infected with HIV-1 while receiving APRETUDE must transition to a complete HIV-1 treatment regimen (see 4 DOSAGE AND ADMINISTRATION, 7 WARNINGS AND PRECAUTIONS and 15 MICROBIOLOGY).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Individuals must have had a documented negative HIV-1 test, in accordance with applicable guidelines, prior to initiating APRETUDE.
- APRETUDE should be prescribed by a healthcare professional knowledgeable in the management of HIV PrEP.
- APRETUDE must be administered by a healthcare professional by gluteal intramuscular injection.
- Prior to starting APRETUDE, healthcare professionals should carefully select individuals who agree to the required 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 7 WARNINGS AND PRECAUTIONS).
- Prior to starting APRETUDE, the healthcare professional should discuss safer sex practices so as to reduce the risk of developing HIV-1. This may include being tested for other sexually transmitted infections, if appropriate.
- 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).
- Alternatively, the healthcare professional and individual may proceed directly to injection therapy with APRETUDE injection (see Table 2).
- Clinical and laboratory monitoring should be considered and APRETUDE should not be administered if hepatotoxicity is suspected. If hepatotoxicity is confirmed, APRETUDE should be discontinued and the individuals managed as clinically indicated.

4.2 Recommended Dose and Dosage Adjustment

Adults, adolescents weighing ≥ 35 kg

When an oral lead-in is used, dosing for APRETUDE consists of 3 distinct phases:

- An oral lead-in with APRETUDE tablets,
- Initiation injections of APRETUDE injection (3 mL), and
- Continuation injections with APRETUDE injection (3 mL every 2 months).

APRETUDE injection may also be initiated without an oral lead-in. No safety and efficacy data are available for use of APRETUDE without an oral lead-in (see 8 ADVERSE REACTIONS and 14 CLINICAL TRIALS). However, in HIV-1 treatment clinical trials, data show that an oral lead-in is not needed to ensure adequate plasma cabotegravir exposure upon initiation of injections and that the safety and efficacy results of CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine

extended-release injectable suspension) were similar when administered with and without an oral lead-in.

Refer to the recommended dosing section below (see Table 2).

Oral lead-in

The recommended dose of APRETUDE tablets is one 30 mg tablet orally once daily with or without food.

APRETUDE tablets is recommended to be administered for approximately one month (at least 28 days) prior to the initiation of APRETUDE injection to assess tolerability of the individual to cabotegravir. See Table 1 for recommended oral dosing schedule.

Intramuscular Injection Dosing

Initiation Injections

Initiation injections should be administered on the last day of oral lead-in if used or within 3 days thereafter (see Table 1). The recommended initial dose of APRETUDE injection is a single 3 mL (600 mg) intramuscular injection. 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 injection visit (see Table 1 or Table 2, as applicable).

Continuation Injections

After the second initiation injection, the recommended continuation dose of APRETUDE injection is a single 3 mL (600 mg) intramuscular injection administered every 2 months. Individuals may be given APRETUDE injection up to 7 days before or after the scheduled injection visit (see Table 1 or Table 2, as applicable).

Table 1 Recommended Dosing Schedule when using an Oral Lead-in

ORAL LEAD-IN	I.M. INITIATION INJECTIONS	I.M. CONTINUATION INJECTIONS
Month Prior to Starting Injections[a]	Month 1[b] and Month 2[c]	Month 4 and Every 2 Months Onwards[c]
APRETUDE Tablets 30 mg cabotegravir tablet once daily	APRETUDE Injection 3 mL (600 mg) cabotegravir injection	APRETUDE Injection 3 mL (600 mg) cabotegravir injection

I.M. = Intramuscular injection

[a]At least 28 days

[b]Should be administered on the last day of oral lead-in or within 3 days thereafter.

[c]Individuals may be given APRETUDE injection up to 7 days before or after the date the individual is scheduled to receive the injections.

Table 2 Recommended Dosing schedule when starting APRETUDE Injection directly

I.M. INITIATION INJECTIONS		I.M. CONTINUATION INJECTIONS
Month 1 and Month 2[a]		Month 4 and Every 2 Months Onwards[a]
APRETUDE Injection 3 mL (600 mg) cabotegravir injection		APRETUDE Injection 3 mL (600 mg) cabotegravir injection

I.M. = Intramuscular injection

[a]Individuals may be given APRETUDE injection up to 7 days before or after the date the individual is scheduled to receive the injections.

Pediatrics (<12 years of age)

The safety and efficacy of APRETUDE has not been established in pediatric individuals < 12 years of age or weighing < 35 kg.

Geriatrics

No dose adjustment is required in elderly individuals. There are limited data available on the use of APRETUDE in individuals ≥ 65 years of age (see 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics).

Hepatic Insufficiency

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 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency).

Renal Insufficiency

No dosage adjustment is required in individuals with mild to severe renal impairment and not on dialysis (see 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).

4.4 Administration

Intramuscular Injections of APRETUDE

Injections must be administered by a healthcare professional. Refer to the Instructions for Use for complete administration instructions with illustrations. Carefully follow these instructions when preparing the injection to avoid leakage.

The body mass index (BMI) of the individual should be taken into consideration to ensure that the needle length is sufficient to reach the gluteus muscle.

4.5 Missed Dose

Missed Tablet

If the individual misses a dose of APRETUDE tablets, they should take the missed dose as soon as they remember if it is more than 12 hours until the next dose. If the next dose is due within 12 hours, the individual should skip the missed dose and resume the usual dosing schedule.

Missed Injection

Adherence to the injection dosing schedule is strongly recommended. Individuals who miss a scheduled injection visit should be clinically reassessed and an HIV test performed to ensure resumption of PrEP remains appropriate. APRETUDE tablets may be used as short-term oral PrEP in individuals who will

miss planned dosing with APRETUDE injections. See Table 3 and Table 4 for dosing recommendations after a missed injection.

Table 3 Recommendation for Missed 2nd Initiation Injection

Time Since Last Injection	Recommendations for Oral Bridging
Less than or equal to 1 Month + 7 days	Continue with 3 mL (600 mg) APRETUDE injection
Greater than 1 Month + 7 days	It is strongly recommended that individuals begin the every-2-month dosing regimen only if they are able to attend both initiation injections visits. If the individual plans to miss the second initiation injection visit by more than 7 days, the individual should be initiated on APRETUDE Tablets once daily approximately 1 month after the initial initiation injection for up to two months. Injections are to be resumed on the same day as the last day of oral APRETUDE or within 3 days thereafter. For oral APRETUDE durations greater than two months, an alternate oral regimen is recommended. If oral dosing has not been taken, individuals should be clinically reassessed to determine if resumption of injections remains appropriate.
Time Since Last Injection	**Recommendations for Resumption of Injections**
Less than or equal to 2 Months	If clinically appropriate, resume with 3 mL (600 mg) APRETUDE injection as soon as possible. Then follow with the every-2-month injection dosing schedule.
Greater than 2 Months	If clinically appropriate, reinitiate the individual on 3 mL (600 mg) APRETUDE injection, followed one month later by a second dose of 3 ml (600 mg) cabotegravir injection. Then follow the every-2-month injection dosing schedule.

Table 4 Recommendation for Missed Continuation Injections

Time Since Last Injection	Recommendations for Oral Bridging
Less than or equal to 2 Months + 7 days	Continue with 3 mL (600 mg) APRETUDE Injection
Greater than 2 Months + 7 days	Planned Missed Injections If an individual plans to miss a scheduled injection visit by more than 7 days, APRETUDE tablets may be used once daily for a duration of up to 2 months to replace 1 missed injection. The first dose of oral APRETUDE should be taken approximately 2 months (+/- 7 days) after the last injection dose of APRETUDE injection. Injection dosing should be planned to resume on the last day of oral APRETUDEor within 3 days, thereafter. For oral APRETUDE durations greater than two months, an alternative regimen is recommended.

Time Since Last Injection	Recommendations for Oral Bridging
Greater than 2 Months + 7 days	Unplanned Missed Injections If a scheduled injection visit is missed or delayed by more than 7 days and oral dosing has not been taken in the interim, individuals should be clinically reassessed to determine if resumption of injections remains appropriate (see 7 WARNINGS AND PRECAUTIONS, Importance of adherence).
Time Since Last Injection	**Recommendation for Resumption of Injections**
Less than or equal to 3 Months	If clinically appropriate, resume with 3 mL (600 mg) APRETUDE injection as soon as possible. If the individual was on oral APRETUDE, injections are to be resumed on the same day as the last day of oral therapy dosing or within 3 days thereafter. Continue with the every-2-month injection dosing schedule.
Greater than 3 Months	If clinically appropriate, reinitiate the individual on 3 mL (600 mg) APRETUDE injection, followed one month later by the second initiation dose of 3 mL (600 mg) APRETUDE injection. If the individual was on oral APRETUDE, injections are to be resumed on the same day as the last day of oral APRETUDE or within 3 days thereafter. Continue with the every-2-month injection dosing schedule.

5 OVERDOSAGE

Symptoms and Signs

There is currently no experience of overdose with cabotegravir.

Treatment

There is no specific treatment for overdose with cabotegravir. 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.

Cabotegravir 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 cabotegravir injection should take into consideration the prolonged exposure to drug following an injection (see 7 WARNINGS AND PRECAUTIONS, Long acting properties of APRETUDE injection).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 5 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet / 30 mg cabotegravir (as cabotegravir sodium)	hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular	Extended Release Injectable Suspension/ 600 mg cabotegravir / 3 mL	mannitol, polysorbate 20, polyethylene glycol (PEG) 3350, water for injection

Dosage Forms

APRETUDE Tablets are white, film-coated, oval tablets debossed with "SV CTV" on one side. Each film-coated tablet contains 31.62 mg of cabotegravir sodium (equivalent to 30 mg of cabotegravir).

APRETUDE Injection is a white to light pink, free-flowing extended-release injectable suspension containing 200 mg/mL of cabotegravir.

Packaging

APRETUDE Tablets are supplied in white HDPE (high density polyethylene) bottles with child-resistant closures. Each bottle contains 30 film-coated tablets.

APRETUDE Injection is supplied as a kit containing one 3 mL single-dose vial, with an orange flip-off cap, of cabotegravir extended release injectable suspension containing 600 mg of cabotegravir. The kit also contains 1 syringe, 1 syringe adaptor, and 1 needle for intramuscular injection (23-gauge, 1½ inch). The vial stoppers are not made with natural latex rubber.

7 WARNINGS AND PRECAUTIONS

General

APRETUDE is not always effective in preventing HIV-1 acquisition (see 14 CLINICAL TRIALS). The time to onset of protection after commencing cabotegravir is unknown.

APRETUDE should only be used to reduce the risk of acquiring HIV-1 in individuals confirmed to be HIV negative (see 2 CONTRAINDICATIONS). Therefore, individuals must be confirmed to be HIV-1 negative prior to initiation of APRETUDE and re-confirmed to be HIV-negative at frequent intervals (e.g. at every dosing interval) while taking APRETUDE. HIV-1 resistance substitutions may emerge in individuals with undiagnosed HIV-1 infection who are taking APRETUDE. Counsel uninfected individuals to strictly adhere to the recommended dosing and testing schedule for APRETUDE to reduce the risk of HIV-1 acquisition and the potential development of resistance (see 4 DOSAGE AND ADMINISTRATION and 15 MICROBIOLOGY).

APRETUDE should be used as part of an overall HIV-1 infection prevention strategy including the use of other HIV-1 prevention measures. Individuals should be counselled periodically to strictly adhere to the recommended dosing schedule in order to reduce the risk of HIV-1 acquisition and the potential development of resistance. Risk for HIV-1 acquisition includes behavioral, biological, and epidemiologic factors including, but not limited to, condomless sex, past or current STIs, self-identified HIV risk, having sexual partners of unknown HIV-1 viremic status, or sexual activity in a high prevalence area or network. Individuals should be informed regarding the use of other prevention measures (e.g., consistent and correct condom use; knowledge of partner(s)' HIV-1 status, including viral suppression status; and regular testing for STIs) (see 4 DOSAGE AND ADMINISTRATION). 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.

Hepatic/Biliary/Pancreatic

Hepatotoxicity:

Cases of hepatotoxicity, presenting as serum transaminase elevations, have been reported in individuals receiving APRETUDE with or without known pre-existing hepatic disease or other identifiable risk factors (see 8 ADVERSE REACTIONS).

Individuals with marked elevations in transaminases prior to treatment or with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations. Clinical and laboratory monitoring should be considered and APRETUDE should not be administered if hepatotoxicity is suspected. If hepatotoxicity is confirmed, APRETUDE should be discontinued and the individuals managed as clinically indicated (see 4 DOSAGE AND ADMINISTRATION).

Importance of adherence

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

Risk of reduced drug concentration of APRETUDE due to drug interactions

The concomitant use of APRETUDE and other drugs may result in reduced drug concentration of APRETUDE (see 2 CONTRAINDICATIONS; 9 DRUG INTERACTIONS). Caution should be given when prescribing APRETUDE with other drugs that may reduce its exposure. See 9.4 Drug-Drug Interactions**,** Table 9 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with APRETUDE; review concomitant medications during therapy with APRETUDE.

Long-acting 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, healthcare professionals should take the prolonged release characteristics of cabotegravir into consideration when the medicinal product is discontinued. (see 5 OVERDOSAGE, 7.1.1 Pregnant Women, and 9 DRUG INTERACTIONS).

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.

To minimize this, it is essential to clinically reassess individuals for risk of HIV-1 acquisition and to frequently test to confirm HIV-1 negative status. Individuals who are suspected or confirmed with HIV-1 should immediately begin antiretroviral therapy. Alternative forms of PrEP should be considered following discontinuation of APRETUDE for those individuals at continued risk of HIV-1 acquisition and initiated within 2 months of the final APRETUDE injection.

Seroconversion while on APRETUDE is considered an adverse event and should be reported to the Canadian Vigilance Program by:

• Visiting the Web page on Adverse Reaction Reporting: www.canada.ca/en/healthcanada/services/drugs-health-products/medeffect-canada for information on how to report online, by mail or by fax; or

• Calling 1-866-234-2345 (toll-free).

Hypersensitivity Reactions

Hypersensitivity reactions have been reported in association with integrase inhibitors (INSTIs) and could occur with APRETUDE. Administration of cabotegravir oral lead-in dosing was used in clinical studies to help identify participants who may be at risk of a hypersensitivity reaction. These reactions were characterized by rash, constitutional findings and sometimes organ dysfunction, including liver injury. Discontinue APRETUDE immediately should signs or symptoms of hypersensitivity develop.

Discontinue APRETUDE immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash, or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, mucosal involvement [oral blisters or lesions], conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, or difficulty breathing). Clinical status, including laboratory parameters with liver aminotransferases, should be monitored and appropriate therapy initiated (see 2 CONTRAINDICATIONS; 4 DOSAGE AND ADMINISTRATION).

Psychiatric

Depressive Disorders:

Depressive disorders (including depression, depressed mood, major depression, suicidal ideation, suicide attempt) have been reported with APRETUDE (see 8 ADVERSE REACTIONS). Promptly evaluate individuals with depressive symptoms to assess whether the symptoms are related to APRETUDE and to determine whether the benefits of treatment are outweighed by the risks.

Reproductive Health: Female and Male Potential

- **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 exposure (AUC) greater than 20 times the exposure at the Maximum Recommended Human Dose (MRHD) of 30 mg dosed orally or 400 mg IM injection did not cause adverse effects on male or female reproductive organs or spermatogenesis, and no functional effects on mating or fertility were observed.

7.1 Special Populations

7.1.1 Pregnant Women

APRETUDE should be used in pregnant women only if the potential benefits outweigh the potential risks to the fetus. Healthcare professionals should discuss the benefit-risk of using APRETUDE with individuals of childbearing potential or during pregnancy. There are insufficient human data on the use of APRETUDE during pregnancy to adequately assess a drug-associated risk of birth defects and miscarriage. While there are insufficient human data to assess the risk of neural tube defects (NTDs)

with exposure to APRETUDE during pregnancy, NTDs were reported with dolutegravir, another integrase inhibitor.

Reproductive toxicity studies in pregnant rats showed that cabotegravir crosses the placenta and can be detected in fetal tissue. Cabotegravir was not teratogenic when studied in pregnant rats and rabbits but in rats caused decreased fetal weight, a delay in the onset of parturition and increased stillbirths and neonatal deaths at exposures higher than for therapeutic doses. The relevancy to human pregnancy is unknown.

In an embryo-fetal development study, there were no adverse developmental outcomes following oral administration of cabotegravir to pregnant rabbits at doses with exposures up to 0.66 times the exposure at the MRHD of 30 mg. In rats, alterations in fetal growth (decreased body weights) were observed at exposures that were 28 times the exposure at the MRHD.

In the rat pre- and post-natal studies at exposures 28 times the exposures at the MRHD of 30 mg oral or 400 mg IM dose, cabotegravir was associated with delayed onset of parturition, and increased number of stillbirths and neonatal mortalities immediately after birth. In a cross-fostering study, similar incidences of stillbirths and early postnatal deaths were observed when rat pups born to cabotegravir-treated mothers were nursed from birth by control mothers. There was no effect on neonatal survival of control pups nursed from birth by cabotegravir-treated mothers. A lower dose of cabotegravir (at exposures >10 times the exposure at the MRHD of 30 mg oral or 400 mg IM dose) was not associated with delayed parturition or neonatal mortality in rats. In rabbit and rat studies there was no effect on survival when fetuses were delivered by caesarean section.

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 fetal exposure during pregnancy (see 7 WARNINGS AND PRECAUTIONS, Long acting properties of APRETUDE injection).

Antiretroviral Pregnancy Registry (APR): To monitor pregnancy outcomes in women exposed to APRETUDE during pregnancy, an Antiretroviral Pregnancy Registry has been established. Healthcare Professionals are encouraged to register individuals:

http://www.apregistry.com

Telephone: (800) 258-4263

Fax: (800) 800-1052

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

Pediatrics (< 12 years of age): The safety and efficacy of APRETUDE in pediatric individuals < 12 years of age or weighing < 35 kg has not been established.

Adolescents (≥ 12 years to < 18 years): Although clinical studies did not show an increased incidence of psychiatric illness in adolescents compared to adult participants, suicidal ideation and suicide attempt

have been reported with cabotegravir, particularly in those with pre-existing psychiatric illness (see 7 WARNINGS AND PRECAUTIONS, Psychiatric). Given the vulnerability of the adolescent population, adolescents should be counselled before prescribing, and periodically while receiving APRETUDE, and managed as clinically indicated.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): 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 10.3 Pharmacokinetics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following adverse drug reactions are discussed in the 7 WARNINGS AND PRECAUTIONS section:

- Hepatotoxicity
- Hypersensitivity reactions
- Depressive disorders

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety assessment of APRETUDE is based on the analysis of data from 2 international, multicenter, double-blind trials, HPTN 083 and HPTN 084 (see 14 CLINICAL TRIALS).

Adverse reactions were reported while on blinded study product following exposure to APRETUDE extended-release injectable suspension and APRETUDE tablets as oral lead-in. The median time on blinded study product in HPTN 083 was 65 weeks and 2 days (range: 1 day to 156 weeks and 1 day), with a total exposure on cabotegravir of 3,231 person-years. The median time on blinded study product in HPTN 084 was 64 weeks and 1 day (range: 1 day to 153 weeks and 1 day), with a total exposure on cabotegravir of 2,009 person-years.

The most common adverse reactions regardless of severity reported in at least 1% of participants in HPTN 083 or HPTN 084 are presented in Table 6.

In HPTN 083, 6% of participants in the group receiving APRETUDE intramuscular injection every 2 months and 4% of participants receiving oral TRUVADA [emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF)] once daily discontinued due to adverse events (all causality). Adverse events (all causality) leading to discontinuation and occurring in ≥1% of participants were increased alanine aminotransferase with APRETUDE and TRUVADA, and injection site pain with APRETUDE.

In HPTN 084, 1% of participants receiving APRETUDE and 1% of participants receiving TRUVADA discontinued due to adverse events. The most commonly reported adverse event (all causality) leading to discontinuation was increased alanine aminotransferase (<1%) with APRETUDE and TRUVADA.

Table 6 Adverse Drug Reactions[a] (All Grades) Reported in at Least 1% of Participants Receiving APRETUDE in Either HPTN 083 or HPTN 084

Adverse Reactions	HPTN 083		HPTN 084	
	APRETUDE Every 2 Months (n = 2,281)	TRUVADA Once Daily (n = 2,285)	APRETUDE Every 2 Months (n = 1,614)	TRUVADA Once Daily (n = 1,610)
Injection site reactions[b]	82%	35%	38%	11%
Diarrhea	4%	5%	4%	4%
Headache	4%	3%	12%	13%
Pyrexia[c]	4%	<1%	<1%	<1%
Fatigue[d]	4%	2%	3%	3%
Sleep disorders[e]	3%	3%	1%	1%
Nausea	3%	5%	4%	8%
Dizziness	2%	3%	4%	6%
Flatulence	1%	1%	<1%	<1%
Abdominal pain[f]	1%	1%	2%	2%
Vomiting	<1%	1%	2%	5%
Myalgia	<1%	<1%	2%	1%
Rash[g]	<1%	<1%	2%	1%
Decreased appetite	<1%	<1%	2%	4%
Somnolence	<1%	<1%	2%	2%
Back pain	<1%	<1%	1%	<1%
Upper respiratory tract infection	0	<1%	4%	4%

[a] Adverse reactions defined as "treatment-related" as assessed by the investigator, with exception of injection site reactions, where all injection site reactions were reported regardless of causality.

[b] Participants who received injection: HPTN 083, APRETUDE (n = 2,117) and TRUVADA (n = 2,081); HPTN 084, APRETUDE (n = 1,519) and TRUVADA (n = 1,516). See Injection-Associated Adverse Reactions for additional information.

[c] Pyrexia includes pyrexia, feeling hot, chills, influenza-like illness. The majority of pyrexia events were reported within one week of injections.

[d] Fatigue includes fatigue, malaise.

[e] Sleep disorders includes insomnia, abnormal dreams.

[f] Abdominal pain includes abdominal pain, upper abdominal pain.

[g] Rash includes rash, erythema, pruritis, macular, papular, maculopapular.

Injection-Associated Adverse Reactions: Local Injection Site Reactions (ISRs)

The most frequent adverse reactions associated with the intramuscular administration of APRETUDE in HPTN 083 were ISRs. After 20,286 injections, 8,900 ISRs were reported. Of the 2,117 participants who received at least one injection of APRETUDE, 1,740 (82%) participants experienced at least one ISR, of which a total of 3% of participants discontinued APRETUDE because of ISRs. Among the participants who received APRETUDE and experienced at least one ISR, the maximum severity of reactions was mild (Grade 1) in 41% of participants, moderate (Grade 2) in 56% of participants, and severe (Grade 3) in 3% of participants. 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. The most commonly reported ISRs (all causality and grades) in at least 1% of participants who received APRETUDE and experienced at least one ISR from HPTN 083 are presented in Table 7.

The most frequent adverse reactions associated with the intramuscular administration of APRETUDE in HPTN 084 were ISRs. After 13,068 injections, 1,171 ISRs were reported. Of the 1,519 participants who received at least one injection of APRETUDE, 578 (38%) participants experienced at least one ISR. No participants discontinued APRETUDE because of ISRs. Among the participants who received APRETUDE and experienced at least one ISR, the maximum severity of reactions was mild (Grade 1) in 66% of participants, moderate (Grade 2) in 34% of participants, and severe (Grade 3) in less than 1% of participants. 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. The most commonly reported ISRs (all causality and grades) in at least 1% of participants who received APRETUDE and experienced at least one ISR from HPTN 084 are presented in Table 7.

Table 7 Injection Site Reactions (All Grades) Reported in at Least 1% of Participants who Experienced at Least One Injection Site Reaction (All Causality) with APRETUDE in Either HPTN 083 or HPTN 084

	HPTN 083		HPTN 084	
Injection Site Reactions	**APRETUDE (n = 1,740)**	**TRUVADA[a] (n = 724)**	**APRETUDE (n = 578)**	**TRUVADA[a] (n = 166)**
Pain/tenderness	98%	95%	90%	87%
Nodules	15%	2%	14%	2%
Induration	15%	<1%	12%	2%
Swelling	12%	1%	18%	3%
Bruising	4%	4%	1%	0
Erythema	4%	2%	5%	2%
Pruritus	3%	3%	6%	11%
Warmth	3%	1%	<1%	0
Anesthesia	1%	2%	1%	2%
Abscess	<1%	0	2%	3%
Discoloration	<1%	0	1%	0

[a] Placebo injectable suspension: intralipid 20% fat emulsion.

Other Injection-Associated Adverse Reactions: In the HPTN 083 clinical trial, an increased incidence of pyrexia (including pyrexia, feeling hot, chills, influenza-like illness) (4%) was reported by participants receiving APRETUDE compared with participants receiving TRUVADA (<1%). There were no differences reported in the incidence of pyrexia between groups in HPTN 084.

Vasovagal or pre-syncopal reactions considered treatment related were reported in <1% of participants after injection with APRETUDE in HPTN 083. None were reported as treatment related by the investigators in HPTN 084.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Based on data from the Week 16 analysis of the MOCHA study in 23 HIV-infected adolescents (aged at least 12 years and weighing 35 kg or more) receiving background antiretroviral therapy, no new safety concerns were identified in adolescents with the addition of oral cabotegravir followed by injectable cabotegravir (n=8) when compared with the safety profile established with cabotegravir in adults (see 14 CLINICAL TRIALS).

In 64 adolescents who received APRETUDE in the two Phase 2b clinical trials (HPTN 083-01 and HPTN 084-01), the safety data were comparable to the safety data reported in adults receiving APRETUDE.

8.3 Less Common Clinical Trial Adverse Reactions

Select adverse reactions of all Grades that occurred in <1% of participants receiving APRETUDE in HPTN 083 or HPTN 084 are presented below.

Hepatobiliary Disorders: Hepatotoxicity

Investigations: Weight increase (see below)

Psychiatric Disorders: Anxiety, depression, suicidal ideation*, suicide attempt* (*particularity in individuals with a pre-existing history of depression or psychiatric illness)

Weight Increase: At the Week 41 and Week 97 timepoints in HPTN 083, participants who received APRETUDE gained a median of 1.2 kg (Interquartile Range [IQR]; -1.0, 3.5; n = 1,623) and 2.1 kg (IQR; -0.9, 5.9; n = 601) in weight from baseline, respectively. Those who received TRUVADA gained a median of 0.0 kg (IQR; -2.1, 2.4; n = 1,611) 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 = 1,151) and 4.0 kg (IQR; 0.0, 8.0; n = 216) in weight from baseline, respectively. Those who received TRUVADA gained a median of 1.0 kg (IQR; -1.0, 4.0; n = 1,131) and 3.0 kg (IQR; -1.0, 6.0; n = 218) in weight from baseline, respectively.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Grade 3 or 4 post-baseline maximum toxicity laboratory abnormalities for HPTN 083 or HPTN 084 are summarized in Table 8.

A few participants in both the APRETUDE and TRUVADA 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 APRETUDE vs TRUVADA 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 APRETUDE vs TRUVADA groups who discontinued due to ALT increased were 12 (<1%) vs 15 (<1%) and there were no discontinuations due to AST increased.

Table 8 Laboratory Abnormalities (Grades 3 to 4) in ≥1% of Participants in Either HPTN 083 or HPTN 084

Laboratory Parameter	HPTN 083		HPTN 084	
	APRETUDE Every 2 Months (n = 2,281)	TRUVADA Once Daily (n = 2,285)	APRETUDE Every 2 Months (n = 1,614)	TRUVADA Once Daily (n = 1,610)
ALT (≥5.0 x ULN)	2%	2%	<1%	1%
AST (≥5.0 x ULN)	3%	3%	<1%	<1%
Creatine phosphokinase (≥10.0 x ULN)	15%	14%	2%	2%
Lipase (≥3.0 x ULN)	3%	3%	<1%	<1%
Creatinine (>1.8 x ULN) or increase to ≥1.5 x baseline)	3%	3%	5%	4%

ALT = Alanine transaminase, ULN = upper limit of normal, AST = Aspartate aminotransferase.

8.5 Post-Market Adverse Reactions

These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection to cabotegravir-containing regimens, or a combination of these factors. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Immune System Disorders: Hypersensitivity reactions (including angioedema and urticaria)

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

APRETUDE is a single antiretroviral agent for the pre-exposure prophylaxis of HIV-1 in uninfected individuals. If an individual develops HIV-1, APRETUDE should be discontinued and a complete antiretroviral regimen should be initiated. Cabotegravir is detectable in the plasma for an extended period of time (up to a year or longer). At this time, there are no limitations on the use of other antiretroviral medications for the treatment of HIV-1 infection if APRETUDE is discontinued (see 9.4 Drug-Drug Interactions, Established or Potential Drug Interactions).

9.4 Drug-Drug Interactions

Effect of Cabotegravir on the Pharmacokinetics of Other Agents

In vitro, cabotegravir did not inhibit (IC_{50} >50 micromolar) the enzymes and transporters: cytochrome P450 (CYP)1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4; uridine diphosphate glucuronosyl transferase (UGT) 1A1, 1A3, 1A4, 1A6, 1A9, 2B4, 2B7, 2B15, and 2B17; P-glycoprotein (P-gp); breast cancer resistance protein (BCRP); Bile salt export pump (BSEP); organic cation transporter (OCT)1, OCT2;

organic anion transporter polypeptide (OATP) 1B1, OATP1B3; multidrug and toxin extrusion transporter (MATE) 1, MATE 2-K; multidrug resistance protein (MRP) 2 or MRP4.

In vitro, cabotegravir is a metabolism dependent inhibitor of CYP3A4; however, no clinical drug interaction was observed with repeat administration of cabotegravir once daily with the CYP3A4 substrates midazolam or rilpivirine (see Table 10).

In vitro, cabotegravir inhibited the basolateral renal transporters, organic anion transporters (OAT) 1 (IC_{50}=0.81 micromolar) and OAT3 (IC50=0.41 micromolar). However, based on physiologically based pharmacokinetics (PBPK) modelling no interaction with OAT substrates is expected at clinically relevant concentrations. Therefore, caution is advised when co-dosing APRETUDE with narrow therapeutic index OAT 1/3 substrate drugs (e.g. methotrexate).

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 anti-retroviral medications including protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, integrase inhibitors, entry inhibitors, and ibalizumab.

Effect of Other Agents on the Pharmacokinetics of Cabotegravir

Cabotegravir is metabolized by UGT1A1 with some contribution from UGT1A9. Drugs which are strong inducers of UGT1A1 or 1A9 are expected to decrease cabotegravir plasma concentrations and may result in loss of virologic response; therefore, co-administration with these drugs is contraindicated (see 2 CONTRAINDICATIONS). Simulations using PBPK modeling show that no clinically significant interaction is expected with co-administration of cabotegravir with drugs that inhibit these enzymes. *In vitro*, cabotegravir is not a substrate of OATP1B1, OATP1B3, OATP2B1, or OCT1 therefore drugs that solely modulate these transporters are not expected to affect cabotegravir plasma concentration. *In vitro,* cabotegravir is a substrate of BCRP and P-gp, however, because of its high permeability, no alteration in cabotegravir absorption is expected when co-administered with BCRP or P-gp inhibitors. Antacid products containing polyvalent cations (e.g. Aluminum or magnesium hydroxide, calcium carbonate) are recommended to be administered at least 2 hours before or 4 hours after taking APRETUDE tablets.

No drug interaction studies have been performed with cabotegravir injection. The drug interaction data provided in Table 9 is obtained from studies with oral cabotegravir.

Established or Potential Drug Interactions

Established and theoretical interactions with selected medicinal products are listed in Table 9. The drugs listed in this table are not all-inclusive. Recommendations are based on either drug interaction studies, or potential or predicted interactions due to the expected magnitude of interaction and/or potential for serious adverse events or loss of efficacy.

Table 9 Established or Potential Drug-Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical comment
Antacids containing polyvalent cations (e.g., Aluminum or magnesium hydroxide, calcium carbonate)	↓Cabotegravir (tablets)	Administer antacid products at least 2 hours before or 4 hours after taking APRETUDE tablets.
Anticonvulsants: Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	↓Cabotegravir	Co-administration is contraindicated with APRETUDE.
Antimycobacterials: Rifampin[a] Rifapentine	↓Cabotegravir	Co-administration is contraindicated with APRETUDE
Antimycobacterial: Rifabutin[a]	↓Cabotegravir ↔Rifabutin	APRETUDE tablets: No dose adjustment is required. APRETUDE injection: When rifabutin is started before or concomitantly with the first initiation injection of APRETUDE, the recommended dosing of APRETUDE 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 of APRETUDE is 3 mL (600 mg), monthly, while on rifabutin. After stopping rifabutin, the recommended dosing schedule of APRETUDE is 3 mL (600 mg) every 2 months.

Legend: ↓ = Decrease, ↔ = No change.
[a]See Table 11 for magnitude of interaction.

Drugs without Clinically Significant Interactions

Cabotegravir

Based on drug interaction study results, the following drugs can be co-administered with cabotegravir without a dose adjustment: etravirine, midazolam, oral contraceptives containing levonorgestrel and ethinyl estradiol, and rilpivirine (see **Table 10** and **Table 11**).

The effects of cabotegravir on the exposure of co-administered drugs are shown in **Table 10.** The effects of co-administered drugs on the exposure of cabotegravir are shown in **Table 11**.

Table 10 Effect of Cabotegravir on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug(s) and Dose(s)	Dose of Cabotegravir	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Cabotegravir No Effect = 1.00		
			C_{max}	AUC	C_τ or C_{24}
Ethinyl estradiol 0.03 mg once daily	30 mg once daily	19	0.92 [0.83, 1.03]	1.02 [0.97, 1.08]	1.00 [0.92, 1.10]
Levonorgestrel 0.15 mg once daily	30 mg once daily	19	1.05 [0.96, 1.15]	1.12 [1.07, 1.18]	1.07 [1.01, 1.15]
Midazolam 3 mg	30 mg once daily	12	1.09 [0.94, 1.26]	1.10 [0.95, 1.26]	NA
Rilpivirine 25 mg once daily	30 mg once daily	11	0.96 [0.85, 1.09]	0.99 [0.89, 1.09]	0.92 [0.79, 1.07]

CI = Confidence Interval; n = Maximum number of participants with data; NA = Not available.

Table 11 Effect of Co-administered Drugs on the Pharmacokinetics of Cabotegravir

Co-administered Drug(s) and Dose(s)	Dose of Cabotegravir	n	Geometric Mean Ratio (90% CI) of Cabotegravir Pharmacokinetic Parameters with/without Co-administered Drugs No Effect = 1.00		
			C_{max}	AUC	C_τ or C_{24}
Etravirine 200 mg twice daily	30 mg once daily	12	1.04 [0.99, 1.09]	1.01 [0.96, 1.06]	1.00 [0.94, 1.06]
Rifabutin 300 mg once daily	30 mg once daily	12	0.83 [0.76, 0.90]	0.79 [0.74, 0.83]	0.74 [0.70, 0.78]
Rifampin 600 mg once daily	30 mg single dose	15	0.94 [0.87, 1.02]	0.41 [0.36, 0.46]	NA
Rilpivirine 25 mg once daily	30 mg once daily	11	1.05 [0.96, 1.15]	1.12 [1.05, 1.19]	1.14 [1.04, 1.24]

CI = Confidence Interval; n = Maximum number of participants with data; NA = Not available.

9.5 Drug-Food Interactions

APRETUDE tablets may be taken without regard to food. (see 10 CLINICAL PHARMACOLOGY).

9.6 Drug-Herb interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 Pharmacodynamics

Effects on Electrocardiogram

In a randomized, placebo-controlled, 3-period cross-over trial, 42 healthy participants were randomized into 6 random sequences and received 3 oral doses 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.

10.3 Pharmacokinetics

The pharmacokinetic (PK) properties of the components of APRETUDE tablets and APRETUDE injection are provided in Table 12. The multiple-dose pharmacokinetic parameters are provided in Table 13 and Table 14.

Table 12 Pharmacokinetic Properties of APRETUDE (Cabotegravir Tablets and Injection)

	Cabotegravir Tablets	**Cabotegravir Injection**
Absorption		
T_{max}, median	3 hours	7 days
Effect of high-fat meal (relative to fasting): AUC_T ratio[a]	1.14 (1.02, 1.28)	NA
Distribution		
Bound to human plasma proteins	>99.8%	>99.8%
Blood-to-plasma ratio	0.5	0.5
CSF-to-plasma concentration ratio[b]	0.003 (0.002 to 0.004)	0.003 (0.002 to 0.004)
Metabolism		
Metabolic pathways	UGT1A1	UGT1A1

	Cabotegravir Tablets	Cabotegravir Injection
	UGT1A9 (minor)	UGT1A9 (minor)
Elimination		
$t_{1/2}$, mean	41 (h)	5.6 to 11.5 (weeks)[c]
Major route of elimination	Metabolism	Metabolism
% Dose excreted as total ^{14}C (unchanged drug) in urine[d]	27 (0)	ND
% Dose excreted as total ^{14}C (unchanged drug) in feces[d]	59 (47)	ND

[a]Geometric mean ratio (fed/fasted) in pharmacokinetic parameters and 90% confidence interval. High calorie/high-fat meal = 870 kcal, 53% fat

[b] Median (range). The clinical relevance of CSF-to-plasma concentration ratios is unknown. Concentrations were measured at steady-state 1 week after intramuscular administration of cabotegravir extended-release injectable suspensions given monthly or every 2 months.

[c]$t_{1/2}$ absorption rate limited

[d]Dosing in mass balance studies: single-dose oral administration of [^{14}C] cabotegravir

Table 13 Multiple-Dose Pharmacokinetic Parameters of APRETUDE Tablets

Parameter	Geometric Mean (5^{th}, 95^{th} percentile)[a]
C_{max} (mcg/mL)	8.0 (5.3, 11.9)
AUC_{tau} (mcg.h/mL)	145 (93.5, 224)
C_{tau} (mcg/mL)	4.6 (2.8, 7.5)

[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.

Table 14 Multiple-Dose Pharmacokinetic Parameters following Initiation and Every 2 Month Continuation IM Injections of APRETUDE Injection

Dose	Geometric Mean (5^{th}, 95^{th} percentile)[a]		
	AUC_{tau}[b] (mcg•h/mL)	C_{max} (mcg/mL)	C_{tau}(mcg/mL)
600-mg Initial IM injection[c]	1591 (714, 3245)	8.0 (5.3, 11.9)	1.5 (0.65, 2.9)
600-mg Every 2 month IM Injection	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-month dosing schedule for IM injections of extended-release injectable suspension.

[c] 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).

Absorption

Oral Cabotegravir

Cabotegravir is rapidly absorbed following oral administration of the tablet formulation, with median T_{max} at 3 hours. The linearity of cabotegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of the tablet formulation, cabotegravir pharmacokinetics was dose-proportional to slightly less than proportional to dose from 10 mg to 60 mg. With once daily dosing, pharmacokinetic steady-state is achieved by 7 days.

The absolute bioavailability of cabotegravir has not been established.

Effects of Food on Oral Absorption

Food increased the extent of absorption of cabotegravir: high fat meals increased cabotegravir $AUC_{(0-\infty)}$ by 14% and increased C_{max} by 14% relative to fasted conditions. These increases are not clinically significant.

Cabotegravir Injection

Cabotegravir injection exhibits absorption-limited (flip-flop) kinetics resulting from slow absorption from the gluteal muscle into the systemic circulation 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 μg/mL, which is above *in-vitro* PA-IC90 of 0.166 μg/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 15). Cabotegravir has been detected in plasma up to 52 weeks or longer after administration of a single injection.

Plasma cabotegravir 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 μg/mL in cervical tissue, 0.29 μg/mL in cervicovaginal fluid, 0.37 μg/mL in vaginal tissue, 0.32 μg/mL in rectal tissue, and 0.69 μg/mL in rectal fluid, which are above the *in vitro* PA-IC90. Median tissue cabotegravir concentrations remained approximately equal to or above the *in vitro* PA-IC90 up to 4 weeks post IM injection. Cabotegravir has been detected in the CSF of HIV-1 infected patients receiving cabotegravir long-acting injectable suspensions.

Metabolism

Cabotegravir is primarily metabolized 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).

Elimination

Oral

Cabotegravir has a mean terminal half-life of 41 h and an apparent clearance (CL/F) of 0.21 L per hour based on population pharmacokinetic analyses.

Injectable Suspension

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 Populations and Conditions

No clinically significant differences in the pharmacokinetics of cabotegravir were observed based on age, sex, race/ethnicity, BMI, or UGT1A1 polymorphisms. There are no data available for the use of cabotegravir in participants with hepatitis B virus and hepatitis C virus co-infection in PrEP studies.

- **Pediatrics:** Population pharmacokinetic analyses revealed no clinically relevant differences in exposure between the HIV-1 infected adolescent (at least 12 years of age and weighing ≥ 35 kg) 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 15 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	30 mg once daily	193 (106, 346)	14.4 (8.02, 25.5)	5.79 (2.48, 12.6)
Initial injection[c]	600 mg IM Initial Dose	2123 (881, 4938)	11.2 (5.63, 21.5)	1.84 (0.64, 4.52)
Every 2-month injection	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-month dosing schedule for IM injections of extended-release injectable suspension.

[c] 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.

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

- **Geriatrics:** Population pharmacokinetic analysis of indicated age had no clinically relevant effect on the pharmacokinetics of cabotegravir. Pharmacokinetic data for cabotegravir in individuals aged 65 years and older are limited.
- **Gender:** Population pharmacokinetic analyses revealed that gender had no clinically relevant effect on the pharmacokinetics 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.
- **Genetic Polymorphism:** In a meta-analysis of healthy and HIV-infected participants, HIV-infected individuals 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 participants 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 individuals with either UGT1A1 or UGT1A9 polymorphisms.
- **Ethnic Origin:** Population pharmacokinetic analyses revealed no clinically relevant effect of race on the pharmacokinetics of cabotegravir.
- **Hepatic Insufficiency:** No clinically important pharmacokinetic differences between participants with moderate hepatic impairment and matching healthy participants 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.
- **Renal Insufficiency:** No clinically important pharmacokinetic differences between participants with severe renal impairment (CrCL <30 mL/min and not on dialysis) and matching healthy participants 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.
- **Obesity:** Population pharmacokinetic analyses revealed no clinically relevant effect of BMI on the pharmacokinetics of cabotegravir, therefore no dose adjustment is required on the basis of BMI.

11 STORAGE, STABILITY AND DISPOSAL

Store APRETUDE tablets up to 30°C.

Store APRETUDE injections at or below 30°C in the original carton. Do not freeze.

12 SPECIAL HANDLING INSTRUCTIONS

Injectable Suspension

If the pack has been stored in the refrigerator, the vial should be brought to room temperature prior to

administration (not to exceed 30°C).

Once the suspension has been drawn into the syringe, the injection should be administered as soon as possible, but may remain in the syringe for up to 2 hours at room temperature. The filled syringe should not be placed in the fridge. If 2 hours are exceeded, the medication, syringe, and needle must be discarded.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Cabotegravir – Oral Tablets

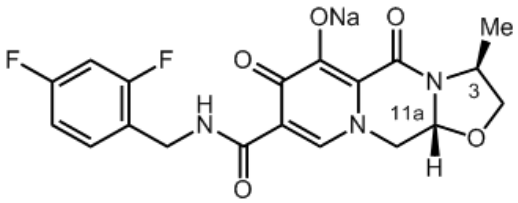
Proper name: cabotegravir sodium

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 and molecular mass: $C_{19}H_{16}F_2N_3NaO_5$

427.33 g/mol

Structural formula:



Physicochemical properties: Cabotegravir sodium is a white to almost white solid that is slightly soluble in water. Over most of the physiological pH range cabotegravir sodium is practically insoluble.

Cabotegravir – Extended Release Injectable Suspension

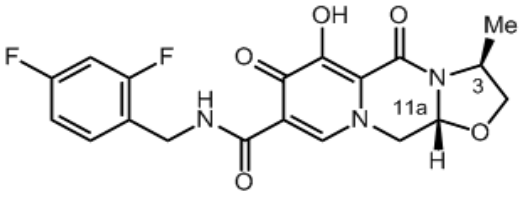
Proper name: cabotegravir

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 and molecular mass: $C_{19}H_{17}F_2N_3O_5$

405.35 g/mol

Structural formula:



Physicochemical properties: Cabotegravir is white to almost white solid that is practically insoluble in water. Over most of the physiological pH range cabotegravir is practically insoluble.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

HIV-1 Pre-Exposure Prophylaxis in Adults

The efficacy of APRETUDE has been evaluated in two randomized (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 behavior for HIV-1 infection and HPTN 084 in HIV-1–uninfected cisgender women at risk of acquiring HIV-1.

Participants randomized to receive APRETUDE initiated oral lead-in dosing with one 30 mg cabotegravir tablet and a placebo daily, for up to 5 weeks, followed by APRETUDE 3mL (600 mg) intramuscular (IM) injection at months 1, 2 and every 2 months thereafter and a daily placebo tablet. Participants randomized to receive TRUVADA initiated oral TRUVADA (TDF 300 mg/FTC 200 mg) and placebo for up to 5 weeks, followed by oral TRUVADA daily and placebo IM injection at months 1, 2 and every 2 months thereafter.

HPTN 083

In HPTN 083, a non-inferiority study, 4570 cisgender men and transgender women who have sex with men, were randomized 1:1 to receive either APRETUDE (n=2283) or TRUVADA (n=2287). Of these, 4566 participants were treated with APRETUDE (n=2281) or TRUVADA (n=2285) as blinded study medication up to Week 153. Four participants were randomized but did not receive study drug (2 participants each in the APRETUDE and TRUVADA groups).

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

A summary of the demographic characteristics for HPTN 083 is presented in Table 16.

Table 16 Summary of Demographics and Baseline Characteristics (Randomized Population) for HPTN 083

Demographic Characteristic	APRETUDE (N=2283)	TRUVADA (N=2287)
Age (years), n		
Median (minimum, maximum)	26.0 (18, 69)	26.0 (18, 69)
Cohort, n (%)		
MSM	2014 (88)	1982 (87)
TGW	266 (12)	304 (13)
Prefer not to answer	3 (<1)	1 (<1)
Race, n (%)		
White	618 (27)	649 (28)
American Indian or Alaska Native	616 (27)	600 (26)
Black or African American	565 (25)	569 (25)
Asian	417 (18)	406 (18)
Mixed race	49 (2)	54 (2)
Native Hawaiian or Other Pacific Islander	5 (<1)	2 (<1)
Unknown	13 (<1)	7 (<1)
Ethnicity, n (%)		
Hispanic or Latino	1043 (46)	1067 (47)
Not Hispanic or Latino	1240 (54)	1219 (53)

Demographic Characteristic	APRETUDE (N=2283)	TRUVADA (N=2287)
Not Reported	0	1 (<1)
SexPro Score, n (%)[a]		
≤16	1555 (68%)	1571 (69%)
BMI (kg/m^2)		
Median (minimum, maximum)	24.40 (14.7, 91.0)	24.50 (14.3, 67.4)

a. SexPro Score was only collected in North and South America.

HPTN 084

In HPTN 084, a superiority study, 3224 cisgender women were randomized 1:1 and received either APRETUDE (n=1614) or TRUVADA (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.

A summary of the demographic characteristics for HPTN 084 is presented in Table 17.

Table 17 Participant Demographics and Baseline Characteristics (Randomized Population) for HPTN 084

Demographic Characteristic	APRETUDE (N=1614)	TRUVADA (N=1610)
Age		
Median (minimum, maximum) age in years	25.0 (18, 44)	25.0 (18, 45)
<25 years age group, n (%)	800 (50)	794 (49)
Race/Ethnicity, n (%)		
Asian	2 (<1)	3 (<1)
Black or African American[a]	1612 (>99)	1606 (>99)
White	0	1 (<1)
Sex Assigned at Birth		
Male	0	0
Female	1614 (100)	1610 (100)
Self-Identified Gender		
Male	0	3 (<1)
Female	1612 (>99)	1607 (>99)
Transgender Male (female to male)	2 (<1)	0
VOICE Risk Score at Screening, n (%)		
<5	327 (20)	345 (21)
≥5	1287 (80)	1265 (79)
BMI (kg/m^2)		

Demographic Characteristic	APRETUDE (N=1614)	TRUVADA (N=1610)
Median (minimum, maximum)	25.7 (16.4, 54.3)	25.6 (15.0, 51.3)
BMI <30, n (%)	1149 (71)	1180 (73)
BMI ≥30, n (%)	465 (29)	430 7)

[a] Black or African American is an FDA race category. There were no African American participants in this study.

Study Results

HPTN 083

The primary endpoint was the rate of incident HIV infections among participants randomised to oral APRETUDE tablets and APRETUDE injections compared to oral TRUVADA (corrected for early stopping). The primary analysis demonstrated the superiority of APRETUDE compared to TRUVADA 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 APRETUDE to be prevalent then yielding a 69% reduction in the risk of incident infection relative to TRUVADA (see Table 18). At a pre-planned interim review of trial data, a multinational Data and Safety Monitoring Board (MDSMB) recommended that the blinded phase of HPTN 083 be stopped due to the demonstration of superior efficacy of APRETUDE when compared to daily, oral TRUVADA and that participants randomized to the active TRUVADA group be offered APRETUDE.

Table 18 Primary Efficacy Endpoint: Comparison of Rates of Incident HIV Infections during Randomised Phase in HPTN 083 (mITT[a], extended retrospective virologic testing)

	APRETUDE (N=2278)	TRUVADA (N=2281)	Superiority P-Value
Person years	3211	3193	
HIV-1 incident infections (incidence rate per 100 person years)	12[b] (0.37)	39 (1.22)	
Hazard ratio (95% CI)	0.31 (0.16, 0.58)		p=0.0003

[a] Modified intent-to-treat

[b] Following the primary analysis, extended retrospective virologic testing was performed to better characterize the timing of HIV infections. As a result, one of the 13 incident infections on 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).

Findings from all subgroup analyses were consistent with the overall protective effect, with a lower rate of incident HIV-1 infections observed for participants randomized to the APRETUDE group compared with participants randomized to the TRUVADA group (see Table 19).

Table 19 Rate of incident HIV-1 infection by subgroup in HPTN 083 (mITT, extended retrospective virologic testing)

Subgroup	APRETUDE incidence per 100 person years	APRETUDE person years	TRUVADA incidence per 100 person years	TRUVADA 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[a]	0.35	2836	1.14	2803	0.32 (0.16, 0.64)
TGW[b]	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)

[a]MSM= cisgender men who have sex with men
[b]TGW = Transgender women who have sex with men

HPTN 084

The primary endpoint was the rate of incident HIV infections among participants randomized to oral APRETUDE tablets and APRETUDE injections compared to oral TRUVADA (corrected for early stopping). The primary analysis demonstrated the superiority of APRETUDE compared to TRUVADA 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 TRUVADA (see Table 20). The MDSMB recommended early termination of the blinded, randomized portion of HPTN 084 after an interim analysis indicated that pre-specified stopping criteria had been met (superiority of APRETUDE compared with TRUVADA).

Table 20 Primary Efficacy Endpoint in HPTN 084: Comparison of Rates of Incident HIV Infections during Randomised Phase (mITT, extended retrospective virologic testing)

	APRETUDE (N=1613)	TRUVADA (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).

Findings from pre-planned subgroup analyses were consistent with the overall protective effect, with a lower rate of incident HIV-1 infections observed for participants randomized to the APRETUDE group compared with participants randomized to the TRUVADA group (see Table 21).

Table 21 Rate of incident HIV-1 infection by subgroup in HPTN 084 (mITT, extended retrospective virologic testing)

Subgroup	APRETUDE incidence per 100 person years	APRETUDE person years	TRUVADA incidence per 100 person years	TRUVADA person years)	HR (95% CI)
Age					
<25 years	0.23	868	2.34	853	0.12 (0.03, 0.46)
≥25 years	0.09	1093	1.46	1093	0.09 (0.02, 0.49)
BMI					
<30	0.22	1385	1.88	1435	0.12 (0.04, 0.38)
≥30	0.00	575	1.76	511	0.04 (0.00, 0.93)

HIV-1 Pre-Exposure Prophylaxis in Adolescents 12 Years Of Age and Older and Weighing At Least 35 kg

HPTN 083-01 and HPTN 084-01

The safety, tolerability and pharmacokinetics of injectable cabotegravir were assessed in two open-label multicentre Phase IIb clinical trials (HPTN 083-01 and HPTN 084-01). 64 HIV-uninfected, at-risk adolescents <18 years of age and weighing ≥ 35 kg were enrolled and received one 30 mg cabotegravir tablet daily, for up to 5 weeks, followed by cabotegravir injection (single 3 mL (600 mg) injection, at months 1, 2 and every 2 months thereafter, at months 4, 6, 8).

In study HPTN 083-01, at baseline, the median age of participants was 17.0 years, the median weight was 70.6 kg, 100% were male, and 44% were non-white.

In study HPTN084-01, the median age of participants was 16.0 years, the median weight was 55.7 kg, 100% were female, and 100% were non-white.

The primary objective of each study, which was to evaluate the safety, tolerability and acceptability of injectable cabotegravir in healthy, HIV uninfected adolescents <18 years of age, was met (see 8 ADVERSE REACTIONS).

MOCHA

The safety, tolerability and pharmacokinetics of oral and injectable cabotegravir are being assessed in an ongoing Phase I/II multicentre, open-label, non-comparative study, MOCHA (IMPAACT 2017, Study 208580). 8 HIV-1 infected and virologically supressed adolescents, aged 12 to <18 years, weighing at least 35 kg were enrolled and received one 30 mg cabotegravir tablet, daily, for 1 month followed by monthly cabotegravir injections (month 1: 600 mg injection, months 2 and 3: 400 mg injection) for a further 3 months, while continuing background cART.

At baseline, the median age of participants was 14.5 years, the median weight was 57.2 kg, 25% were female, 100% were non-white, no participants had a CD4+ cell count less than 350 cells per mm^3.

The primary endpoints at Week 16 for cabotegravir participants were to confirm the doses, safety and pharmacokinetics for oral and injectable cabotegravir, in HIV-infected, virologically suppressed adolescents.

In the Week 16 analysis, observed pharmacokinetics parameters in adolescents met the exposure targets, based on adult data for both oral and injectable cabotegravir (see 10.3 Pharmacokinetics).

15 MICROBIOLOGY

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 MT-4 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
No drugs with inherent anti-HIV activity were antagonistic to cabotegravir's antiretroviral activity (*in vitro* assessments were conducted in combination with rilpivirine, lamivudine, tenofovir and emtricitabine).

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:

Cabotegravir-resistant viruses were selected during passage of HIV-1 strain IIIB in MT-2 cells in the presence of cabotegravir. Amino acid substitutions in integrase that emerged and conferred decreased susceptibility to cabotegravir included Q146L (fold-change range 1.3-4.6), S153Y (fold-change range 2.8-8.4) and I162M (fold-change = 2.8). The integrase substitution T124A also emerged alone (fold change: 1.1 to 7.4 in cabotegravir susceptibility), in combination with S153Y (fold change: 3.6 to 6.6 in cabotegravir susceptibility) or I162M (2.8-fold change in cabotegravir susceptibility). Cell culture

passage of virus harboring integrase substitutions Q148H, Q148K, or Q148R selected for additional substitutions (C56S, V72I, L74M, V75A, T122N, E138K, G140S, G149A, and M154I), with substituted viruses having reduced susceptibility to cabotegravir of 2.0- to 410-fold change. The combinations of E138K+Q148K and V72I+E138K+Q148K conferred the greatest reductions of 53- to 260-fold change and 410-fold change, respectively.

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 analyze. 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 E138A 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.

HPTN 083-01 and HPTN 084-01

In studies HPTN 083-01 and HPTN 084-01, there were no incident infections observed among 64 at-risk adolescents (weighing ≥ 35 kg) receiving cabotegravir for HIV-1 PrEP.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

The effect of prolonged daily treatment with high doses of cabotegravir has been evaluated in repeat oral dose toxicity studies in rats (26 weeks) and in monkeys (39 weeks). There were no drug-related adverse effects in rats or monkeys given cabotegravir orally at doses up to 1000 mg/kg/day (>20 times the exposure at the oral MRHD) or 500 mg/kg/day (>4 times the exposure at the oral MRHD), respectively.

In the 14 day monkey toxicity study, a dose of 1000 mg/kg/day was not tolerated and resulted in morbidity associated with gastro-intestinal (GI) effects (body weight loss, emesis, loose/watery faeces, and moderate to severe dehydration).

In the 28 day monkey toxicity study, end of study exposure at 500 mg/kg/day was similar to that achieved in the 14-day study at 1000 mg/kg/day. This suggests that GI intolerance observed in the 14 day study was the result of local drug administration and not systemic toxicity.

In a 3 month study in rats, when cabotegravir was administered by monthly sub-cutaneous (SC) injection (up to 100 mg/kg/dose); monthly IM injection (up to 75 mg/kg/dose) or weekly SC injection (100 mg/kg/dose), there were no adverse effects noted and no new target organ toxicities (at exposures >30 times the exposure in humans at the MRHD of 400 mg IM dose). Local effects at the injection sites were observed and these included dose-proportional increases in redness and swelling at all dose-levels accompanied by inflammatory reactions (erythema and edema graded very slight to severe) in animals given monthly IM injections, at all doses in female animals given monthly SC

injections (≥5 mg/kg/month) and in males given ≥30 mg/kg/month. Treatment-related microscopic findings consisted of granulomatous inflammation and mixed inflammatory cell infiltration at the injection sites, with correlating macroscopic changes (pale areas, nodules, and masses).

Carcinogenicity/mutagenesis

Two-year carcinogenicity studies in mice and rats were conducted with cabotegravir. In mice, no drug-related increases in tumor incidence were observed at cabotegravir exposures (AUC) up to 8 times (males) and 7 times (females) MRHD. In rats, no drug-related increases in tumor incidence were observed at cabotegravir exposures up to 26 times MRHD. Cabotegravir was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the *vivo* rodent micronucleus assay.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]APRETUDE

Cabotegravir Tablets

Cabotegravir Extended Release Injectable Suspension

Read this carefully before you start taking **APRETUDE** and each time you get a refill or have a new injection visit. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APRETUDE**.

Serious Warnings and Precautions

- RISK OF DRUG RESISTANCE WITH USE OF APRETUDE IN UNDIAGNOSED HIV-1 INFECTION

  APRETUDE should only be used for pre-exposure prophylaxis (PrEP) if you are HIV-negative before and during treatment. Discuss with your healthcare professional if you have had a recent flu-like illness. Your healthcare professional will run tests to confirm that you are HIV-negative before and during APRETUDE treatment.

What is APRETUDE used for?

APRETUDE is used to reduce the risk of getting HIV-1 infection in people who are at least 12 years of age and weigh at least 35 kg. This is called pre-exposure prophylaxis (PrEP).

How does APRETUDE work?

APRETUDE contains the active ingredient cabotegravir, which belongs to a group of anti-retroviral medicines called *integrase inhibitors* (INIs).

APRETUDE reduces the risk of getting HIV-1 when the medicine is in your bloodstream before you are exposed to HIV-1.

What are the ingredients in APRETUDE?

Tablets

Medicinal ingredients: 30 mg cabotegravir (as cabotegravir sodium)

Non-medicinal ingredients: hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide

Cabotegravir Injections (3 mL)

Medicinal ingredients: 600 mg / 3 mL (200 mg / mL) cabotegravir

Non-medicinal ingredients: mannitol, polysorbate 20, polyethylene glycol (PEG) 3350, water for injection.

APRETUDE comes in the following dosage forms:

Tablets, 30 mg

Injectable suspension (extended-release), 600 mg / 3 mL (200 mg / mL)

Do not use APRETUDE if:

- You are allergic (hypersensitive) to cabotegravir or to any of the other ingredients of APRETUDE. See "What are the ingredients in APRETUDE?".
- You are taking any of these medicines as they may affect the way APRETUDE works:
    - rifampicin or rifapentine (to treat some bacterial infections such as tuberculosis).
    - phenytoin, phenobarbital, carbamazepine or oxcarbazepine (also known as anticonvulsants used to treat epilepsy and prevent fits).
- You do not know your HIV-1 infection status or you already have HIV-1 infection. APRETUDE can only help reduce your risk of getting HIV before you are infected so, you must get tested to make sure you don't already have HIV infection before taking APRETUDE.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APRETUDE. Talk about any health conditions or problems you may have, including if you

- have had an allergic (hypersensitivity) reaction to cabotegravir. See the **Serious Side effects and what to do about them** table, below, for more information on these and other serious side effects.
- have had liver problems. Let your healthcare professional know if you have liver problems. Your liver function may need to be closely monitored.

Other warnings you should know about:

Depression or Mood Changes

Depression and mood changes, including having thoughts of hurting yourself (suicidal ideation) or trying to hurt yourself (suicide attempt), have been reported in people taking APRETUDE. You may be more likely to experience suicidal ideation and/or a suicide attempt if you have a history of depression or a mental health illness. See the **Serious Side effects and what to do about them** table, below, for more information on these and other serious side effects.

Pregnancy

Talk to your healthcare professional if you are pregnant or plan to become pregnant. Your healthcare professional will consider the benefit to you and the risk to your baby when taking APRETUDE while you are pregnant.

It is not known if APRETUDE will harm your unborn baby. There is a registry for women who take antiretroviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare professional about how you can take part in this registry.

Breastfeeding

If you are thinking about breast-feeding, check with your healthcare professional who will consider the benefit and risk to you and your baby. It is not known whether the ingredients of APRETUDE can pass into breast milk and harm your baby.

Adolescents

Your doctor will discuss your mental health with you before and while receiving APRETUDE. Let your doctor know if you have mental health problems. You may need to be more closely monitored (also see section **What are possible side effects from using APRETUDE?**).

Just receiving APRETUDE may not stop you getting HIV.

You can still get HIV when taking this medicine, although APRETUDE lowers the risk. HIV infection is spread by sexual contact with someone who has the infection or by transfer of infected blood. To reduce your risk of getting HIV:

- **Use a condom** when you have oral or penetrative sex.
- **Don't risk blood transfer** — for example, don't share needles.

Discuss with your healthcare professional the additional precautions needed to further decrease the risk getting HIV.

While receiving APRETUDE to reduce the risk of getting HIV:

- **If prescribed APRETUDE tablets as an Oral Lead-in, take APRETUDE tablets every day** to reduce your risk, not just when you think you have been at risk of HIV infection. Do not miss any doses of APRETUDE tablets or stop taking it. Missing doses may increase your risk of getting HIV infection.
- **It is important that you attend your planned appointments to receive your APRETUDE injection**. Talk to your healthcare professional if you are thinking about stopping injections as this may increase your risk of getting HIV infection. If you do stop or are late receiving your APRETUDE injection, you will need to take other medicines or precautions to reduce your risk of getting HIV and possibly developing viral resistance.
- Get **tested for HIV frequently as recommended by your healthcare professional.**
- **If you think you were infected with HIV (you may get a flu-like illness), tell your healthcare professional straight away**. They may want to do more tests to make sure you are still HIV negative.

APRETUDE injection is a long acting medication, so if you stop APRETUDE injections, cabotegravir will remain in your system for up to a year or more after your last injection. It is important that you attend your planned appointments to receive APRETUDE injection and talk to your healthcare professional if you are thinking about stopping PrEP. You may need to take other medicines to reduce the risk of getting HIV infection or use other safe sex precautions if you stop APRETUDE Injections.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Some medicines can affect how APRETUDE works or make it more likely that you will have side effects. APRETUDE can also affect how some other medicines work.

Do not take APRETUDE tablets and APRETUDE injection with the following:

- carbamazepine, oxcarbazepine, phenobarbital, or phenytoin (also known as anticonvulsants used to treat epilepsy and prevent seizures).
- rifampicin or rifapentine (to treat some bacterial infections such as tuberculosis).

Tell your healthcare professional if you are taking the following:

- **rifabutin** (to treat some bacterial infections such as tuberculosis). You may need to receive APRETUDE injections more often.

The following may interact with APRETUDE tablets:

- medicines called antacids to treat indigestion and heartburn or laxatives, or other products that contain aluminum and/or calcium carbonate, magnesium or buffered medicines.
    - Taking antacids can stop or reduce APRETUDE Tablets from being absorbed into your body and not make it work as well.
    - Antacids should be taken at least 2 hours before or 4 hours after you take APRETUDE tablets.

How to take APRETUDE tablets:

Tablets

Your healthcare professional may advise you to take APRETUDE tablets before you are given a APRETUDE injection for the first time.

If you are being given APRETUDE injection but you are not able to receive your injection, your healthcare professional may also recommend that you take APRETUDE tablets instead, until you can receive the injection again.

If you are prescribed APRETUDE tablets as an Oral lead-in:

- Take APRETUDE tablets every day exactly as your healthcare professional has told you to, for as long as your healthcare professional has told you to.
- When starting to take APRETUDE tablets for the first time, it should be taken for at least 28 days. See dosing schedule below.
- APRETUDE tablets should be swallowed whole with some liquid. APRETUDE tablets can be taken with or without food.
- Check with your healthcare professional if you are not sure or if you have questions.

Usual dose of APRETUDE tablets:

The usual dose of APRETUDE tablets is one tablet (30 mg cabotegravir) taken once a day.

How to take APRETUDE injection:

If you and your healthcare professional decide to start with APRETUDE injection, see Dosing schedule when starting with APRETUDE injection directly.

APRETUDE injection will be administered by your healthcare professional.

Usual dose of APRETUDE injection:

APRETUDE injection is given by your healthcare professional as one injection into the muscle of your buttocks.

Dosing schedule when taking APRETUDE tablets as an oral lead-in:

ORAL LEAD-IN	INITIATION INJECTIONS	CONTINUATION INJECTIONS
Month Prior to Starting injections[a]	Month 1[b] and Month 2[c]	Month 4[c] onwards
APRETUDE tablet cabotegravir tablet once daily	APRETUDE injection	APRETUDE injection
	3 mL cabotegravir injection	3 mL cabotegravir injection

[a]It is important to take your oral lead-in tablets, for at least 28 days
[b]You should have your first injection on the same day as your last tablet or no later than 3 days after
[c]First and second injections one month apart, third injection onwards, every two months

Dosing schedule when starting with APRETUDE injection directly:

INITIATION INJECTIONS	CONTINUATION INJECTIONS
Month 1 and Month 2[a]	Month 4[a] onwards
APRETUDE injection	APRETUDE injection
3 mL cabotegravir injection	3 mL cabotegravir injection

[a]First and second injections one month apart, third injection onwards, every two months

Overdose:

If you think you, or a person you are caring for, have taken too much APRETUDE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a tablet, take it soon as you remember. If your next dose is due within 12 hours, skip the dose you missed and take the next one at the usual time. Then continue your treatment as before. Don't take a double dose to make up for a missed dose.

Missed Injections:

It is important to not miss any of your planned appointments. If you are going to miss, or have missed, an injection of APRETUDE, talk to your healthcare professional as soon as possible. Your healthcare professional may recommend you take APRETUDE tablets until you are able to take APRETUDE injections again.

What are possible side effects from using APRETUDE?

These are not all the possible side effects you may have when taking APRETUDE. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effects of APRETUDE injection are:

- Injection site reactions; such as pain and discomfort, a hardened mass or lump, swelling, redness, itching, bruising (which may include discolouration or a collection of blood under the skin), and warmth at the site of the injection. Tell your healthcare professional if the symptoms you experience at the injection site becomes severe or troublesome.

The most common side effects of APRETUDE tablets and APRETUDE injection are:

- Headache
- Diarrhea
- Feeling hot (pyrexia)

Additional side effects that may occur with APRETUDE tablets and APRETUDE injection include: abnormal dreams, difficulty in sleeping (insomnia), feeling anxious, dizziness, feeling sick (nausea), vomiting, stomach pain (abdominal pain), passing gas (flatulence), rash, muscle pain (myalgia), lack of energy (fatigue), generally feeling unwell (malaise), weight gain.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Allergic (hypersensitivity) reactions: • Skin rash, fever, lack of energy (fatigue), difficulty breathing, swelling of the mouth or face causing difficulty in breathing, blisters or peeling of the skin, sores in mouth, muscle or joint aches			✓
Depression or mood changes: • Feelings of deep sadness • Feelings of unworthiness • Have thoughts of hurting yourself (suicide)* • Have tried to hurt yourself (behavior)*		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
*Mainly in individuals who have had depression or mental health conditions before.			
Liver problems and blood test results: • Yellowing of the skin and the whites of the eyes • Loss of appetite • Itching • Tenderness of the stomach • Pale coloured stools/ or unusually dark urine		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store APRETUDE tablets at up to 30°C.

Store APRETUDE injections at or below 30°C in the original carton until ready to use. Do not freeze.

Keep out of reach and sight of children.

If you want more information about APRETUDE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.viivhealthcare.ca, or by calling 1-877-393-8448.

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