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Apretude
600 mg
prolonged-release suspension for injection
cabotegravir
For intramuscular use
Instructions for Use

3 mL

APRETUDE

Cabotegravir
Pre-exposure Prophylaxis (PrEP)

QUALITATIVE AND QUANTITATIVE COMPOSITION

Film-coated Tablet
White, film-coated, oval tablet.
Each film-coated tablet contains 30 mg of cabotegravir (as cabotegravir sodium).

Suspension for Injection
White to light pink, prolonged-release suspension for injection.
Each 3 mL vial contains 600 mg cabotegravir (as cabotegravir free acid).

CLINICAL INFORMATION

Indications

Film-coated Tablets:
APRETUDE tablets are indicated for short term pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in at-risk individuals weighing at least 35 kg (*see Dosage and Administration and Warnings and Precautions*). *APRETUDE* tablets may be used as:
- oral lead in to assess tolerability of cabotegravir prior to administration of *APRETUDE* injection.
- oral PrEP in individuals who will miss planned dosing with *APRETUDE* injection.

Suspension for Injection:
APRETUDE injections are indicated for PrEP to reduce the risk of sexually acquired HIV-1 infection in at-risk individuals weighing at least 35 kg (*see Dosage and Administration and Warnings and Precautions*).

Dosage and Administration
Pharmaceutical Form: Film-coated tablet and suspension for injection

Posology
Individuals must have had a documented negative HIV-1 test, in accordance with applicable guidelines, prior to initiating *APRETUDE*.
Prior to starting *APRETUDE*, individuals should be carefully selected to agree to the required dosing schedule and counselled about the importance of adherence to scheduled dosing visits to help reduce the risk of acquiring HIV-1 infection.

Method of Administration

Film-coated Tablet
APRETUDE may be taken with or without food.

Suspension for Injection
Refer to the Instructions for Use for detailed step by step injection procedure (*see Use & Handling*).
The BMI of the individual should be taken into consideration to ensure that the needle length is sufficient to reach the gluteus muscle.

Adults, adolescents weighing at least 35 kg
Following discussion with the individual, the physician may proceed directly to *APRETUDE* injection, (see Table 2 for dosing recommendations).
Alternatively, *APRETUDE* tablets may be used as an oral lead in prior to the initiation of *APRETUDE* injection to assess tolerability to cabotegravir (see Table 1).

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

Table 1 Oral Lead-in Dosing Schedule

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

Suspension for Injection
Initiation Injections
The recommended initial *APRETUDE* injection dose is a single 3 mL (600 mg) intramuscular injection. If oral lead-in has been used, the first injection should be planned for the last day of oral lead-in or within 3 days thereafter.
One month later, a second 3 mL (600 mg) intramuscular injection should be administered. Individuals may be given the second 3 mL (600 mg) initiation injection up to 7 days before or after the scheduled dosing date.
Continuation Injections
After the second initiation injection, the recommended *APRETUDE* continuation injection dose is a single 3 mL (600 mg) intramuscular injection administered every 2 months. Individuals may be given injections up to 7 days before or after the scheduled dosing date.

Table 2 Recommended Intramuscular Dosing Schedule

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

Missed dose

Film-coated Tablet
If the individual misses a dose of oral *APRETUDE*, they should take the missed dose as soon as possible.

Suspension for 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. See Table 3 for dosing recommendations after a missed injection.
If a delay of more than 7 days from a scheduled injection visit cannot be avoided, *APRETUDE* tablets (30 mg) may be used once daily to replace one scheduled injection visit. For oral PrEP durations greater than two months, an alternative regimen is recommended.
The first dose of oral PrEP should be taken two months (+/- 7 days) after the last injection dose of *APRETUDE*. Injection dosing should be planned to resume on the last day of oral PrEP or within 3 days, thereafter, as recommended in Table 3.

Table 3: Injection dosing recommendations after missed injections or following oral PrEP to replace an injection

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

Adolescents and Children
The safety and efficacy of *APRETUDE* in children and adolescents weighing less than 35 kg have not been established.

Elderly
No dose adjustment is required in elderly individuals. There are limited data available on the use of *APRETUDE* in individuals aged 65 years and over (*see Pharmacokinetics – Special Patient Populations*).

Renal impairment
No dosage adjustment is required in individuals with mild to severe renal impairment and not on dialysis (*see Pharmacokinetics - Special Patient Populations*).

Hepatic impairment
No dosage adjustment is required in individuals with mild or moderate hepatic impairment (Child-Pugh score A or B). *APRETUDE* has not been studied in individuals with severe hepatic impairment (Child-Pugh score C) (*see Pharmacokinetics – Special Patient Populations*).

Contraindications
APRETUDE PrEP is contraindicated in individuals:
- with known hypersensitivity to *APRETUDE* or to any of the excipients in the tablets or the injection formulation.
- receiving rifampicin, rifapentine, phenytoin, phenobarbital, carbamazepine and oxcarbazepine.
- with a positive HIV-1 status

Warnings and Precautions
Overall HIV-1 infection prevention strategy
APRETUDE is not always effective in preventing HIV-1 acquisition (*see Clinical studies*). The time to onset of protection after commencing *APRETUDE* is unknown.
APRETUDE should be used for pre-exposure prophylaxis as part of an overall HIV-1 infection prevention strategy including the use of other HIV-1 prevention measures (e.g. knowledge of HIV-1 status, regular testing for other sexually transmitted infections, condom use).
APRETUDE should only be used to reduce the risk of acquiring HIV-1 in individuals confirmed to be HIV negative (see Contraindications). Individuals should be re-confirmed to be HIV-negative at frequent intervals (e.g. in line with local guidelines, but at no more than 3 month intervals) while taking *APRETUDE* for pre-exposure prophylaxis.
If clinical symptoms consistent with acute viral infection are present and recent (< 1 month) exposures to HIV-1 are suspected, HIV-1 status should be reconfirmed.
Potential risk of resistance
There is a potential risk of developing resistance to *APRETUDE* if an individual acquires HIV-1 either before or during administration of *APRETUDE*, or following discontinuation of *APRETUDE* PrEP, (see *Long acting properties of APRETUDE injection*).
To minimise this, it is essential to clinically reassess individuals for risk of HIV acquisition and to frequently test to confirm HIV negative status. Individuals who are suspected or confirmed with HIV-1 should immediately begin ART.
Alternative forms of PrEP should be considered following discontinuation of *APRETUDE* for those individuals at continuing risk of HIV acquisition and initiated within 2 months of the final *APRETUDE* injection.
Long acting properties of APRETUDE injection
Residual concentrations of cabotegravir may remain in the systemic circulation of individuals for prolonged periods (up to 12 months or longer), therefore, physicians should take the prolonged release characteristics of *APRETUDE* into consideration when the medicinal product is discontinued (*see Interactions, Pregnancy and Lactation and Overdosage*).
Importance of adherence
Individuals should be counselled periodically to strictly adhere to the recommended *APRETUDE* dosing schedule in order to reduce the risk of HIV-1 acquisition and the potential development of resistance.
Hypersensitivity reactions
Hypersensitivity reactions have been reported in association with other integrase inhibitors. These reactions were characterised by rash, constitutional findings and sometimes organ dysfunction, including liver injury. Administration of *APRETUDE* oral lead-in was used in clinical studies to help identify participants who may be at risk of a hypersensitivity reaction. While no such reactions have been observed to date in association with *APRETUDE*, physicians should remain vigilant and should discontinue *APRETUDE* and other suspected agents immediately, should signs or symptoms of hypersensitivity develop (including, but not limited to, severe rash, or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia or angioedema). Clinical status, including liver aminotransferases should be monitored and appropriate therapy initiated. (*see Dosage and Administration, Contraindications and Long acting properties of APRETUDE injection, Clinical studies*).
Hepatotoxicity
Hepatotoxicity has been reported in a limited number of individuals receiving *APRETUDE* with or without known pre-existing hepatic disease *(see Adverse reactions)*.
Clinical and laboratory monitoring should be considered and *APRETUDE* should be discontinued if hepatotoxicity is confirmed and individuals managed as clinically indicated *(see Long acting properties of APRETUDE injection)*.
Interactions with medicinal products
Caution should be given when prescribing *APRETUDE* with medicinal products that may reduce its exposure *(see Interactions)*.

Interactions
Effect of cabotegravir on the pharmacokinetics of other agents
In vivo, cabotegravir did not have an effect on midazolam, a CYP3A4 probe. Cabotegravir is not a clinically relevant inhibitor of the following enzymes and transporters: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B4, UGT2B7, UGT2B15, and UGT2B17, P-gp, breast cancer resistance protein (BCRP), Bile salt export pump (BSEP), organic cation transporter (OCT)1, OCT2, OATP1B1, OATP1B3, multidrug and toxin extrusion transporter (MATE) 1, MATE 2-K, multidrug resistance protein (MRP) 2 or MRP4.
Cabotegravir inhibited the organic anion transporters (OAT) 1 (IC50=0.81 μM) and OAT3 (IC50=0.41 μM) *in vitro*, however, based on physiologically based pharmacokinetic (PBPK) modelling no interaction with OAT substrates is expected at clinically relevant concentrations.
In vitro, cabotegravir did not induce CYP1A2, CYP2B6, or CYP3A4.
Based on these data and the results of drug interaction studies, cabotegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.
Based on the *in vitro* and clinical drug interaction profile, cabotegravir is not expected to alter concentrations of other 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 primarily metabolised by UGT1A1 with some contribution from UGT1A9. Medicinal products which are strong inducers of UGT1A1 or UGT1A9 are expected to decrease cabotegravir plasma concentrations leading to lack of efficacy (*see Contraindications*).
Simulations using PBPK show that no clinically significant interaction is expected following co-administration of cabotegravir with drugs that inhibit UGT enzymes.
In vitro, cabotegravir was not a substrate of OATP1B1, OATP1B3, OATP2B1 or OCT1. Cabotegravir is a substrate of P-gp and BCRP, however, because of its high permeability, no alteration in absorption is expected when co-administered with either P-gp or BCRP inhibitors.
No drug interaction studies have been performed with *APRETUDE* injection. The drug interaction data provided in Table 4 is obtained from studies with oral cabotegravir.

Table 4 Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Cabotegravir or Concomitant Drug	Clinical Comment
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine	Cabotegravir ↔ AUC ↑ 1% C_{max} ↑ 4% C_τ ↔ 0%	Etravirine did not significantly change cabotegravir plasma concentration. No dosage adjustment is required.
Non-nucleoside Reverse Transcriptase Inhibitor: Rilpivirine	Cabotegravir ↔ AUC ↑ 12% C_{max} ↑ 5% C_τ ↑ 14% Rilpivirine ↔ AUC ↓1% C_{max} ↓ 4% C_τ ↓ 8%	Rilpivirine did not significantly change cabotegravir plasma concentration or vice versa. No dose adjustment of cabotegravir or rilpivirine is necessary when co-administered.
Rifampicin	Cabotegravir ↓ AUC ↓ 59% C_{max} ↓ 6%	Rifampicin significantly decreased cabotegravir plasma concentration, which is likely to result in loss of therapeutic effect. Co-administration of cabotegravir with rifampicin is contraindicated. Dosing recommendations for co-administration of *APRETUDE* (oral and injection) with rifampicin have not been established.
Rifapentine	Cabotegravir ↓	Rifapentine may significantly decrease cabotegravir plasma concentrations, concomitant use is contraindicated.
Rifabutin	Cabotegravir ↓ AUC ↓ 21% C_{max} ↓ 17% Cτ ↓ 8%	*APRETUDE* tablets: Rifabutin did not significantly change cabotegravir plasma concentration. No dose adjustment is required. *APRETUDE* injection: When rifabutin is started before or concomitantly with the first *APRETUDE* initiation injection the recommended *APRETUDE* dosing schedule is one 3 mL (600 mg) injection followed 2 weeks later by a second 3 mL (600 mg) initiation injection and monthly, thereafter, while on rifabutin. When rifabutin is started at the time of the second initiation injection or later, the recommended dosing schedule is 3 mL (600 mg), monthly, while on rifabutin. After stopping rifabutin, the recommended *APRETUDE* dosing schedule is 3 mL (600 mg) every 2 months.
Anticonvulsants: Carbamazepine Oxcarbazepine Phenytoin Phenobarbital	Cabotegravir ↓	Metabolic inducers may significantly decrease cabotegravir plasma concentrations. Concomitant use is contraindicated.
Antacids (e.g., magnesium, calcium or aluminium)	Cabotegravir ↓	*APRETUDE* tablets: Co-administration of antacid supplements has the potential to decrease oral cabotegravir absorption and has not been studied. Antacid products containing polyvalent cations are recommended to be administered at least 2 hours before or 4 hours after oral *APRETUDE*. *APRETUDE* injection: Interaction is not relevant following parenteral administration.
Oral contraceptives (Ethinyl estradiol (EE) and levonorgestrel	EE ↔ AUC ↑ 2% C_{max} ↓ 8% Cτ ↔ 0% LNG ↔	Cabotegravir did not significantly change ethinyl estradiol and levonorgestrel plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with *APRETUDE*.

Pregnancy and Lactation

Fertility
Animal studies indicate no effects of cabotegravir on male or female fertility (*see Non-clinical Information*).

Pregnancy
There are limited data for *APRETUDE* in pregnant women. The effect on human pregnancy is unknown.
Cabotegravir was not teratogenic when studied in pregnant rats and rabbits but caused a delay in delivery that was associated with reduced survival and viability of rat offspring at exposures higher than for therapeutic doses (*see Non-clinical Information*). The relevance to human pregnancy is unknown.
APRETUDE should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus.
Cabotegravir has been detected in systemic circulation for up to 12 months or longer after an injection, therefore, consideration should be given to the potential for foetal exposure during pregnancy (*see Warnings and Precautions*).

Lactation
It is expected that cabotegravir will be secreted into human milk based on animal data, although this has not been confirmed in humans. Cabotegravir may be present in human milk for up to 12 months or longer after the last *APRETUDE* injection.
It is recommended that women breast-feed only if the expected benefit justifies the potential risk to the infant.

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

Adverse Reactions

Clinical trial data
Adverse drug reactions (ADRs) for cabotegravir were identified from the Phase III clinical studies; HPTN 083 and HPTN 084. In HPTN 083, the median time on blinded study product was 65 weeks and 2 days (1 day to 156 weeks and 1 day), with a total exposure on cabotegravir of 3270 person years. In HPTN 084, the median time on blinded study product was 64 weeks and 1 days (1 day to 153 weeks and 1 day), with a total exposure on cabotegravir of 1920 person years.
ADRs listed include those attributable to the oral or injectable formulations of cabotegravir. When frequencies differed between HPTN 083 and 084, the highest frequency category is quoted.
The most frequently reported ADRs in HPTN 083 were: Injection site reactions (82%), headache (17%) and diarrhoea (14%).
The most frequently reported ADRs in HPTN 084 were: Injection site reactions (38%), headache (23%) and transaminase increased (19%).
The ADRs identified in these studies are listed below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000) and very rare (<1/10,000), including isolated reports.

Table 5 Adverse reactions[1]

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

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

Local Injection Site Reactions
In HPTN 083, 2% of participants discontinued cabotegravir because of ISRs.
Out of 20286 injections, 8900 ISRs were reported.
A total of 2117 participants received at least one injection. Of the 1740 (82%) participants who experienced at least one ISR, the maximum severity of ISRs reported was mild (Grade 1, 34% of participants), moderate (Grade 2, 46% of participants) or severe (Grade 3, 3% of participants). No participants experienced Grade 4 ISRs. The median duration of overall ISR events was 4 days. The proportion of participants reporting ISRs at each visit and the severity of the ISRs decreased over time.
In HPTN 084, no participants discontinued cabotegravir because of ISRs.
Out of 13068 injections, 1171 ISRs were reported.
A total of 1519 participants received at least one injection. Of the 578 (38%) participants who experienced at last one ISR, the maximum severity of ISRs reported was mild (Grade 1, 25% of participants), moderate (Grade 2, 13% of participants) or severe (Grade 3, <1% of participants). No participants experienced Grade 4 ISRs. The median duration of overall ISR events was 8 days. The proportion of participants reporting ISRs at each visit and the severity of the ISRs generally decreased over time.

Weight increased
At the Week 41 and 97 timepoints in HPTN 083, participants who received cabotegravir gained a median of 1.2 kg (IQR -1.0, 3.5; n=1623) and 2.1 kg (IQR; -0.9, 5.9 n=601) in weight from baseline, respectively; those in the tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) group gained a median of 0.0 kg (IQR -2.1, 2.4, n=1611) and 1.0 kg (IQR; -1.9, 4.0 n=598) in weight from baseline, respectively.
At the Week 41 and 97 timepoints in HPTN 084, participants who received cabotegravir gained a median of 2.0 kg (IQR 0.0, 5.0; n=1151) and 4.0 kg (IQR; 0.0, 8.0, n=216) in weight from baseline, respectively; those in the tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) group gained a median of 1.0 kg (IQR -1.0, 4.0, n=1131) and 3.0 kg (IQR; -1.0, 6.0 n=218) in weight from baseline, respectively.

Changes in laboratory chemistries
In both HPTN 083 and HPTN 084, a similar proportion of participants in the cabotegravir and TDF/FTC groups were observed to have elevated hepatic transaminases (ALT/AST) levels and maximum post baseline increases were mostly Grades 1 and 2. In HPTN 083, the number of participants in the cabotegravir vs TDF/FTC groups who experienced maximum post baseline Grade 3 or 4 ALT levels were 40 (2%) vs 44 (2%) and Grade 3 or 4 AST levels were; 68 (3%) vs 79 (3%), respectively. In HPTN 084, the number of participants in the cabotegravir vs TDF/FTC groups who experienced maximum post baseline Grade 3 or 4 ALT levels were 12 (<1%) vs 18 (1%) and Grade 3 and 4 AST levels were; 15 (<1%) vs 14 (<1%), respectively.
A few participants in both the cabotegravir and TDF/FTC groups had adverse events of AST or ALT increased which resulted in discontinuation of study product. In HPTN 083, the number of participants in the cabotegravir vs TDF/FTC groups who discontinued due to ALT increased were: 29 (1%) vs 31 (1%) and due to AST increased were 7 (<1%) vs 8 (<1%), respectively. In HPTN 084, the number of participants in the cabotegravir vs TDF/FTC groups who discontinued due to ALT increased were 12 (<1%) vs 15 (<1%) and there were no discontinuations due to AST increased.

Post-marketing data
No data

Overdosage

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

Treatment
There is no specific treatment for overdose with *APRETUDE*. If overdose occurs, the individual should be treated supportively with appropriate monitoring as necessary. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.
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 *APRETUDE* injection should take into consideration the prolonged exposure to drug following an injection (*see Warnings and Precautions*).

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC code
Pharmacotherapeutic group: Antiviral for systemic use, integrase inhibitor, ATC code: J05AJ04

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

Pharmacodynamic effects
Antiviral Activity in cell culture
Cabotegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean concentration of cabotegravir necessary to reduce viral replication by 50 percent (EC_{50}) values of 0.22 nM in peripheral blood mononuclear cells (PBMCs), 0.74 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: Viruses with >10-fold increase in cabotegravir EC_{50} were not observed during the 112-day passage of strain IIIB. The following integrase (IN) mutations emerged after passaging wild type HIV-1 (with T124A polymorphism) in the presence of cabotegravir: Q146L (fold-change range 1.3-4.6), S153Y (fold-change range 2.8-8.4) and I162M (fold-change = 2.8). As noted above, the detection of T124A is selection of a pre-existing minority variant that does not have differential susceptibility to cabotegravir. No amino acid substitutions in the integrase region were selected when passaging the wild-type HIV-1 NL-432 in the presence of 6.4 nM of cabotegravir through Day 56.
Among the multiple mutants, the highest fold-change was observed with mutants containing Q148K or Q148R. E138K/Q148H resulted in a 0.92-fold decrease in susceptibility to cabotegravir but E138K/Q148K resulted in an 81-fold decrease in susceptibility to cabotegravir. G140C/Q148R and G140S/Q148R resulted in a 22- and 12-fold decrease in susceptibility to cabotegravir, respectively. While N155H did not alter susceptibility to cabotegravir, N155H/Q148R resulted in a 61-fold decrease in susceptibility to cabotegravir.
Resistance in vivo
HPTN 083
In the primary analysis of the HPTN 083 study, there were 13 incident infections on the cabotegravir arm and 39 incident infections on the tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) arm. In the cabotegravir arm, 5 incident infections occurred when receiving cabotegravir PrEP injections, of which 4 participants received on-time injections and 1 participant had one injection off-schedule. Five incident infections occurred ≥6 months after the last dose of cabotegravir PrEP. Three incident infections occurred during the oral lead-in period.
HIV genotyping and phenotyping were attempted at the first visit where HIV viral load was >500 copies/mL. Of the 13 incident infections in the cabotegravir arm, 4 participants had INSTI resistance mutations. In the TDF/FTC arm, the 4 participants with NRTI resistance (including 3 who had multi-class resistance) included 3 with M184V/I and one with K65R. None of the 5 participants who were infected after prolonged interruption from cabotegravir administration had INSTI resistance mutations. Neither genotype nor phenotype could be generated for one of the 5 participants, with just 770 copies/mL HIV-1 RNA. Integrase phenotype could not be generated for one of the remaining 4 participants. The remaining 3 participants retained susceptibility to all INSTIs.
Three participants became infected during the oral lead-in phase, prior to receiving cabotegravir injections. One participant with undetectable plasma cabotegravir levels had no INSTI resistance mutations and was susceptible to all INSTIs. Two participants with detectable plasma cabotegravir concentrations had INSTI resistance mutations. The first participant had INSTI resistant mutations E138E/K, G140G/S, Q148R and E157Q. Integrase phenotype could not be generated. The second participant had INSTI resistance mutations E138A and Q148R. This virus was resistant to cabotegravir (fold-change =5.92) but susceptible to dolutegravir (fold-change=1.69).
Five participants acquired HIV-1, despite on time cabotegravir injections for 4 participants and one off-schedule injection for one participant. Two participants had viral loads too low to analyse. The third participant had no INSTI resistance mutations at the first viraemic visit (Week 17) but had R263K at 112 and 117 days later. While phenotype could not be determined 112 days later, day 117 phenotype showed this virus to be susceptible to both cabotegravir (fold-change= 2.32) and dolutegravir (fold-change=2.29). The fourth participant had INSTI resistance mutations G140A and Q148R. Phenotype showed resistance to cabotegravir (fold-change=13) but susceptibility to dolutegravir (fold-change=2.09). The fifth participant had no INSTI resistance mutations.
In addition to the 13 incident infections, one further participant was HIV-1 infected at enrolment and had no INSTI resistance mutations at that time, however, 60 days later, INSTI resistance mutation E138K and Q148K were detected. Phenotype could not be generated.
Following the primary analysis, extended retrospective virologic testing was performed to better characterise the timing of HIV infections. As a result, one of the 13 incident infections in a participant receiving on time cabotegravir injections was determined to be a prevalent infection.
HPTN 084
In the primary analysis of the HTPN 084 study, there were 4 incident infections on the cabotegravir arm and 36 incident infections on the TDF/FTC arm.
In the cabotegravir arm, 2 incident infections occurred while receiving injections; one participant had 3 delayed cabotegravir injections and both had been non-adherent to oral cabotegravir.
Two incident infections occurred after the last dose of oral cabotegravir; both participants were non-adherent to oral cabotegravir. The first HIV positive visit occurred approx. 11 weeks after enrolment for one participant and 57 weeks after enrolment for the other.
HIV genotyping was attempted at the first visit where HIV viral load was >500 c/mL (first viraemic visit). HIV genotyping results were available for 3 of the 4 cabotegravir arm participants. No major INSTI resistance mutations were detected.
HIV genotyping results were available for 33 of the 36 incident infections in the TDF/FTC group. One participant had a major NRTI mutation (M184V); this participant also had NNRTI resistance with the mutation K103N. Nine other participants had NNRTI resistance (7 had K103N, alone or with E138A or P225H; 1 had K101E alone; 1 had E138K alone).
Effects on Electrocardiogram
In a randomised, placebo-controlled, three-period cross-over trial, 42 healthy subjects were randomized into 6 random sequences and received three doses of oral administration of placebo, cabotegravir 150 mg every 12 hours (mean steady-state C_{max} was approximately 2.8-fold and 5.6-fold above the 30 mg oral once-daily dose and the 600 mg cabotegravir injection every 2 month dose, respectively), or single dose of moxifloxacin 400 mg (active control). After baseline and placebo adjustment, the maximum time-matched mean QTc change based on Fridericia's correction method (QTcF) for cabotegravir was 2.62 msec (1-side 90% upper CI:5.26 msec). Cabotegravir did not prolong the QTc interval over 24 hours post-dose.

Pharmacokinetics

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

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

Table 6. Pharmacokinetic parameters following cabotegravir orally once daily, and initiation and every 2 month continuation intramuscular injections

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

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

Absorption

Oral
Cabotegravir is rapidly absorbed following oral administration, with median T_{max} at 3 hours post dose for tablet formulation. The linearity of cabotegravir pharmacokinetics is dependent on dose and formulation. Following oral administration of tablet formulations, cabotegravir pharmacokinetics was dose-proportional to slightly less than proportional to dose from 5 mg to 60 mg. With once daily dosing, pharmacokinetic steady-state is achieved by 7 days.
APRETUDE may be administered with or without food. Food increased the extent of absorption of cabotegravir. Bioavailability of cabotegravir is independent of meal content: high fat meals increased cabotegravir $AUC_{(0-\infty)}$ by 14% and increased C_{max} by 14% relative to fasted conditions. These increases are not clinically significant.
The absolute bioavailability of cabotegravir has not been established.

Suspension for Injection
Cabotegravir injection exhibits absorption-limited pharmacokinetics because cabotegravir is slowly absorbed into the systemic circulation from the gluteal muscle resulting in sustained plasma concentrations. Following a single 600 mg intramuscular dose, plasma cabotegravir concentrations are detectable on the first day with median cabotegravir concentrations at 4 hours post dose of 0.290 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 6). 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.

Metabolism
Cabotegravir is primarily metabolised by UGT1A1 with a minor UGT1A9 component. Cabotegravir is the predominant circulating compound in plasma, representing > 90% of plasma total radiocarbon. Following oral administration in humans, cabotegravir is primarily eliminated through metabolism; renal elimination of unchanged cabotegravir is low (<1% of the dose). Forty-seven percent of the total oral dose is excreted as unchanged cabotegravir in the faeces. It is unknown if all or part of this is due to unabsorbed drug or biliary excretion of the glucuronide 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.

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

Special patient populations

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

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

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

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

Table 7. Predicted pharmacokinetic parameters following cabotegravir orally once daily, and initiation and every 2 month continuation intramuscular injections in Adolescent Participants aged 12 to less than 18 years (≥35 kg)

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

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

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

Elderly
Population pharmacokinetic analysis of cabotegravir revealed no clinically relevant effect of age on cabotegravir exposure.
Pharmacokinetic data for cabotegravir in subjects of >65 years old are limited.

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

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

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

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

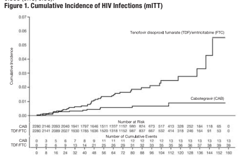
Clinical studies
Clinical efficacy and safety
The efficacy of cabotegravir for PrEP has been evaluated in two randomised (1:1), double blind, multi-site, two-arm, controlled studies. The efficacy of cabotegravir was compared with daily oral tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC).
Participants randomised to receive cabotegravir initiated oral lead-in dosing with one 30 mg cabotegravir tablet and a placebo daily, for up to 5 weeks, followed by cabotegravir intramuscular (IM) injection (single 600 mg [3 mL] injection, at months 1, 2 and every 2 months thereafter and a daily placebo tablet. Participants randomised to receive TDF/FTC initiated oral TDF 300 mg/FTC 200 mg and placebo for up to 5 weeks, followed by oral TDF 300 mg/FTC 200 mg daily and placebo (IM) injection (3 mL, 20% lipid injectable emulsion at months 1, 2 and every 2 months thereafter).
HPTN 083
In HPTN 083, a non-inferiority study, 4566 cisgender men and transgender women who have sex with men, were randomised 1:1 and received either cabotegravir (n=2281) or TDF/FTC (n=2285) as blinded study medication up to Week 153.
At baseline, the median age of participants was 26 years, 12% were transgender women, 72% were non-white and 67% were < 30 years.
The primary endpoint was the rate of incident HIV infections among participants randomised to oral cabotegravir and cabotegravir injections compared to oral TDF/FTC. The primary analysis demonstrated the superiority of cabotegravir compared to TDF/FTC with a 66% reduction in the risk of acquiring incident HIV infection; further testing revealed one of the infections on cabotegravir to be prevalent then yielding a 70% reduction in the risk of incident infection relative to TDF/FTC (see Table 8).

Table 8. Primary Efficacy Endpoint: Comparison of Rates of Incident HIV Infections during Randomised Phase (mITT)

	Cabotegravir (N=2280)	TDF/FDC (N=2281)	Superiority P-Value
Person years	3211	3193	
HIV-1 incident infections (incidence rate per 100 person years)	13[1] (0.40)	39 (1.22)	
Hazard ratio (95% CI)	0.34 (0.18, 0.62)		p=0.0005

[1]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 CAB was determined to be a prevalent infection. The revised HR (95% CI) is 0.303 (0.16, 0.58).

Figure 1. Cumulative Incidence of HIV Infections (mITT)



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

Table 9. Rate of incident HIV-1infection by subgroup

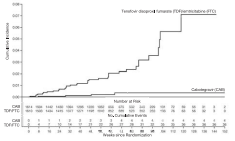
Subgroup	Cabotegravir incidence per 100 person years	Cabotegravir person years	TDF/FTC incidence per 100 person years	TDF/FTC person years)	HR (95% CI)
Age					
<30 years	0.52	2110	1.66	1987	0.32 (0.16, 0.63)
≥30 years	0.18	1101	0.50	1206	0.39 (0.08, 1.84)
Gender					
MSM	0.39	2837	1.14	2803	0.35 (0.18, 0.68)
TGW	0.54	371	1.80	389	0.34 (0.08, 1.56)
Race (US)					
Black	0.58	691	2.28	703	0.26 (0.09, 0.76)
Non-Black	0.00	836	0.50	801	0.11 (0.00, 2.80)
Region					
US	0.26	1528	1.33	1504	0.21 (0.07, 0.60)
Latin America	0.59	1021	1.09	1011	0.56 (0.21, 1.51)
Asia	0.35	570	1.03	581	0.39 (0.08, 1.82)
Africa	1.08	93	2.07	97	0.63 (0.06, 6.50)

MSM= cisgender men who have sex with men
TGW = Transgender women who have sex with men
HPTN 084
In HPTN 084, a superiority study, 3224 cisgender women were randomised 1:1 and received either cabotegravir (n=1614) or TDF/FTC (n=1610) as blinded study medication up to Week 153.
At baseline, the median age of participants was 26 years, >99% were non-white, >99% were cisgender women and 49% were <25 years of age.
The primary endpoint was the rate of incident HIV infections among participants randomised to oral cabotegravir and cabotegravir injections compared to oral TDF/FTC. The primary analysis demonstrated the superiority (p<0.0001) of cabotegravir compared to TDF/FTC with an 89% reduction in the risk of acquiring incident HIV-1 infection (see Table 10).

Table 10. Primary Efficacy Endpoint: Comparison of Rates of Incident HIV Infections during Randomized Phase (mITT)

	Cabotegravir (N=1614)	TDF/FDC (N=1610)	Superiority P-Value
Person years	1361	1346	
HIV-1 incident infections (incidence rate per 100 person years)	4 (0.20)	36 (1.85)	
Hazard ratio (95% CI)	0.11 (0.04, 0.31)		p<0.0001

Figure 2. Cumulative Incidence of HIV Infections (mITT)



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 randomised to the cabotegravir group compared with participants randomised to the TDF/FTC group (see Table 11).

Table 11. Rate of incident HIV-1infection by subgroup

Subgroup	Cabotegravir incidence per 100 person years	Cabotegravir person years	TDF/FTC incidence per 100 person years	TDF/FTC person years)	HR (95% CI)
Age					
<25 years	0.35	868	2.34	853	0.17 (0.05, 0.54)
≥25 years	0.09	1093	1.46	1093	0.09 (0.02, 0.49)
BMI					
<30	0.29	1385	1.88	1435	0.16 (0.06, 0.44)
≥30	0.00	575	1.76	511	0.04 (0.00, 0.93)

MOCHA (HIV-infected adolescents)
The safety, tolerability and pharmacokinetics of oral and injectable cabotegravir is being assessed in an ongoing Phase I/II multicentre, open-label, non-comparative study, MOCHA (IMPAACT 2017, Study 2085BD). 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 mm³.
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, no new safety concerns or safety signals were identified in adolescents receiving either oral or injectable cabotegravir. The observed pharmacokinetics parameters in adolescents met the exposure targets, based on adult data for both oral and injectable cabotegravir (see Pharmacokinetics, Special Populations).
Non-Clinical Information
Carcinogenesis/mutagenesis
Cabotegravir was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay. Cabotegravir was not carcinogenic in long term studies in the mouse and rat.
Reproductive Toxicology
Fertility
Cabotegravir when administered orally to male and female rats at 1000 mg/kg/day (>30 times the exposure in humans at the Maximum Recommended Human Dose [MRHD] of 30 mg oral or 400 mg IM dose) for up to 26 weeks did not cause adverse effects on male or female reproductive organs or spermatogenesis. No functional effects on male or female mating or fertility were observed in rats given cabotegravir at doses up to 1000 mg/kg/day.
Pregnancy
In an embryo-foetal development study there were no adverse developmental outcomes following oral administration of cabotegravir to pregnant rabbits at doses up to 2000mg/kg/day (0.66 times the exposure in humans at the MRHD of 30 mg oral or approximately 1 times 400 mg IM dose) or to pregnant rats at doses up to 1000 mg/kg/day (>30 times the exposure in humans at the MRHD of 30 mg oral or 400 mg IM dose). In rats, alterations in foetal growth (decreased body weights) in the absence of maternal toxicity were observed at 1,000 mg/kg/day. Studies in pregnant rats showed that cabotegravir crosses the placenta and can be detected in foetal tissue.
Non-clinical data from rat pre- and post-natal (PPN) studies at 1,000 mg/kg/day (>30 times the exposure in humans at the MRHD of 30 mg oral or 400 mg IM dose) cabotegravir delayed the onset of parturition, and in some rats, this delay was associated with an increased number of stillbirths and neonatal mortalities immediately after birth. A lower dose of 5 mg/kg/day cabotegravir (>10 times the exposure in humans 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 foetuses were delivered by caesarean section. When rat pups born to cabotegravir-treated dams were cross-fostered at birth and nursed by control mothers, similar incidences of neonatal mortalities were observed.
Animal toxicology and/or pharmacology
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 or 500 mg/kg/day, 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).
PHARMACEUTICAL INFORMATION
List of Excipients
Film-coated tablets
Tablet core
Lactose Monohydrate
Microcrystalline Cellulose
Hypromellose (E464)
Sodium Starch Glycolate (Type A)
Magnesium Stearate
Tablet coating
Hypromellose (E464)
Titanium Dioxide (E171)
Macrogol 400 (E1521)
Suspension for injection
Mannitol (E421)
Polysorbate 20 (E432)
Macrogol (E1521)
Water for injections
Shelf Life
The expiry date is indicated on the packaging.
Storage
Unopened packs (Suspension for Injection and Film-coated tablets)
The storage conditions are detailed on the packaging.
Open packs
Suspension for Injection
Once the suspension has been drawn into the syringe, the injection should be administered as soon as possible, but may be stored for up to 2 hours at room temperature. If 2 hours are exceeded, the medication, syringe and needle must be discarded.
Nature and Contents of Container
Film-coated tablets
APRETUDE tablets are supplied in HDPE (high density polyethylene) bottles with child-resistant closures.
Suspension for Injection
Individual vial only pack (single entity vial SEV):
APRETUDE. 200 mg/mL prolonged-release suspension for injection. APRETUDE is presented in a glass vial.
Incompatibilities
Film-coated tablets
None
Suspension for Injection
In the absence of compatibility studies injection must not be mixed with other medicinal products.
Use and Handling
See the Instructions for Use leaflet for complete administration instructions with illustrations.
Not all presentations are available in every country.
Manufactured and packed by:
Glaxo Operations UK Ltd (trading as Glaxo Wellcome Operations)*
Harmire Road
Barnard Castle
County Durham, DL12 8DT
United Kingdom
*Member of the GSK group of companies
Version number: GZGH19PI01
Date of issue: 4 August 2021
Trade marks are owned by or licensed to the ViiV Healthcare group of companies

ViiV Healthcare

Apretude

600 mg

prolonged-release suspension for injection

cabotegravir

For intramuscular use

Instructions for Use

3 mL

INSTRUCTIONS FOR USE

The following information is intended for healthcare professionals only:
For Single Entity Vial (SEV) packs:

Overview

At each visit, one injection is required; *APRETUDE* 3 mL (600mg).

APRETUDE is a suspension that does not need further dilution or reconstitution.

APRETUDE is for intramuscular use only. It must be administered to the gluteal sites.

Note: The ventrogluteal site is recommended.

Storage information

- The storage conditions are detailed on packaging.

Do not freeze.

Your pack contains

- 1 vial of *APRETUDE*

To prepare the injection

- 1 Luer-Lock syringe (5 mL)
- 1 Luer-Lock aspiration needle or aspiration device (to draw up the suspension)

To administer the injection

- 1 additional Luer-Lock needle (use safety needle if available) of 23 gauge, 1.5 inches

Consider the patient's build and use medical judgment to select an appropriate injection needle length.

You will also need

- Non-sterile gloves
- 2 alcohol swabs
- 1 gauze pad
- A suitable sharps container

Preparation

1. Inspect vial

- Check that the expiry date has not passed.
- Inspect the vial immediately. If you can see foreign matter, do not use the product.

Note:
The *APRETUDE* vial has a brown tint to the glass.
Do not use if the expiry date has passed.

2. Shake vigorously

- Hold the vial firmly and vigorously shake for a full 10 seconds as shown.
- Invert the vial and check the resuspension. It should look uniform. If the suspension is not uniform, shake the vial again.
- It is also normal to see small air bubbles.
- Remove the cap from the vial.
- Wipe the rubber stopper with an alcohol swab.

Do not allow anything to touch the rubber stopper after wiping it.

3. Prepare syringe and needle

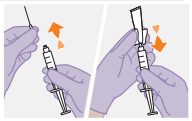
- Continue to prepare the injection in line with local guidelines.
- Example: attach the aspiration needle to the syringe.
- It is recommended that you inject 1 mL of air into the vial to allow the required volume to be drawn up.

4. Slowly draw up dose

- Invert the syringe and vial, and slowly withdraw as much of the liquid as possible into the syringe. There might be more liquid than dose amount.

Note: Check that the suspension looks uniform and white to light pink.

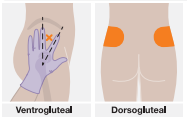
5. Attach injection needle



- Peel open the needle packaging part way to expose the needle base.
- Keeping the syringe upright, firmly twist the syringe onto the injection needle.
- Attach injection needle.
- Remove the needle packaging from the needle.

Injection

6. Prepare injection site



Injections must be administered to the gluteal sites. Select from the following areas for the injection:

- Ventrogluteal (recommended)
- Dorsogluteal (upper outer quadrant)

Note: For gluteal intramuscular use only.
Do not inject intravenously.

7. Remove extra liquid

- Pull off the injection needle cap.
- Hold the syringe with the needle pointing up. Press the plunger to the 3 mL dose to remove extra liquid and any air bubbles.

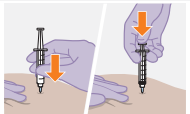
Note: Clean the injection site with an alcohol swab. Allow the skin to air dry before continuing.

8. Stretch skin

Use the z-track injection technique to minimise medicine leakage from the injection site.

- Firmly drag the skin covering the injection site, displacing it by about an inch (2.5 cm).
- Keep it held in this position for the injection.

9. Inject dose



- Insert the needle to its full depth, or deep enough to reach the muscle.
- Still holding the skin stretched – slowly press the plunger all the way down.
- Ensure the syringe is empty.
- Withdraw the needle and release the stretched skin immediately.

10. Assess the injection site

- Apply pressure to the injection site using a gauze pad.
- A small bandage may be used if a bleed occurs.
- Dispose of used needles, syringe and vial according to local health and safety laws.

Do not massage the area.

Questions and Answers

1. If the pack has been stored in the refrigerator, is it safe to warm the vial up to room temperature more quickly?
You should wait at least 15 minutes before you are ready to give the injection to allow the medication to come to room temperature.
It is best to let the vial come to room temperature naturally. However, you can use the warmth of your hands to speed up the warm-up time, but make sure the vial does not get above 30°C (86°F).
Do not use any other heating methods.

2. How long can the medicine be left in the syringe?
It is best to inject the (room temperature) medicine as soon as possible after drawing it up. However, the medicine can remain in the syringe for up to 2 hours before injecting.
If the medicine remains in the syringe for more than 2 hours, the filled syringe and needle must be discarded.

3. Why do I need to inject air into the vial?
Injecting 1 mL of air into the vial makes it easier to draw up the dose into the syringe.
Without the air, some liquid may flow back into the vial unintentionally, leaving less medicine than intended in the syringe.

4. Why is the ventrogluteal administration approach recommended?
The ventrogluteal approach, into the gluteus medius muscle, is recommended because it is located away from major nerves and blood vessels. A dorso-gluteal approach into the gluteus maximus muscle is acceptable, if preferred by the health care professional. The injection should not be administered in any other site.

620000000069095_A

62000000069097_A

Apretude

600 mg

prolonged-release suspension for injection

cabotegravir

For intramuscular use

Instructions for Use

3 mL

Pharma code Ref. No. 7695

APRETUDE

Cabotegravir

Pre-exposure Prophylaxis (PrEP)

QUALITATIVE AND QUANTITATIVE COMPOSITION

Film-coated Tablet

White, film-coated, oval tablet.

Each film-coated tablet contains 30 mg of cabotegravir (as cabotegravir sodium).

Suspension for Injection

White to light pink, prolonged-release suspension for injection.

Each 3 mL vial contains 600 mg cabotegravir (as cabotegravir free acid).

CLINICAL INFORMATION

Indications

Film-coated Tablets:

APRETUDE tablets are indicated for short term pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in at-risk individuals weighing at least 35 kg (*see Dosage and Administration and Warnings and Precautions*). *APRETUDE* tablets may be used as:

- oral lead in to assess tolerability of cabotegravir prior to administration of *APRETUDE* injection.
- oral PrEP in individuals who will miss planned dosing with *APRETUDE* injection.

Suspension for Injection:

APRETUDE injections are indicated for PrEP to reduce the risk of sexually acquired HIV-1 infection in at-risk individuals weighing at least 35 kg (*see Dosage and Administration and Warnings and Precautions*).

Dosage and Administration

Pharmaceutical Form: Film-coated tablet and suspension for injection

Posology

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

Prior to starting *APRETUDE*, individuals should be carefully selected to agree to the required dosing schedule and counselled about the importance of adherence to scheduled dosing visits to help reduce the risk of acquiring HIV-1 infection.

Method of Administration

Film-coated Tablet

APRETUDE may be taken with or without food.

Suspension for Injection

Refer to the Instructions for Use for detailed step by step injection procedure (*see Use & Handling*).

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

Adults, adolescents weighing at least 35 kg

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

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

***Oral lead-in* (Film-coated Tablets)**

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

Table 1 Oral Lead-in Dosing Schedule

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

Suspension for Injection

Initiation Injections

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

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

Continuation Injections

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

Table 2 Recommended Intramuscular Dosing Schedule

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

Missed dose

Film-coated Tablet

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

Suspension for 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. See Table 3 for dosing recommendations after a missed injection.

If a delay of more than 7 days from a scheduled injection visit cannot be avoided, *APRETUDE* tablets (30 mg) may be used once daily to replace one scheduled injection visit. For oral PrEP durations greater than two months, an alternative regimen is recommended.

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

Table 3: Injection dosing recommendations after missed injections or following oral PrEP to replace an injection

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

Adolescents and Children

The safety and efficacy of *APRETUDE* in children and adolescents weighing less than 35 kg have not been established.

Elderly

No dose adjustment is required in elderly individuals. There are limited data available on the use of *APRETUDE* in individuals aged 65 years and over (*see Pharmacokinetics – Special Patient Populations*).

Renal impairment

No dosage adjustment is required in individuals with mild to severe renal impairment and not on dialysis (*see Pharmacokinetics - Special Patient Populations*).

Hepatic impairment

No dosage adjustment is required in individuals with mild or moderate hepatic impairment (Child-Pugh score A or B). *APRETUDE* has not been studied in individuals with severe hepatic impairment (Child-Pugh score C) (*see Pharmacokinetics – Special Patient Populations*).

Contraindications

APRETUDE PrEP is contraindicated in individuals:

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

Warnings and Precautions

Overall HIV-1 infection prevention strategy

APRETUDE is not always effective in preventing HIV-1 acquisition (*see Clinical studies*). The time to onset of protection after commencing *APRETUDE* is unknown.

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

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

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

Potential risk of resistance

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

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

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

Long acting properties of APRETUDE injection

Residual concentrations of cabotegravir may remain in the systemic circulation of individuals for prolonged periods (up to 12 months or longer), therefore, physicians should take the prolonged release characteristics of *APRETUDE* into consideration when the medicinal product is discontinued (*see Interactions, Pregnancy and Lactation and Overdosage*).

Importance of adherence

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

Hypersensitivity reactions

Hypersensitivity reactions have been reported in association with other integrase inhibitors. These reactions were characterised by rash, constitutional findings and sometimes organ dysfunction, including liver injury. Administration of *APRETUDE* oral lead-in was used in clinical studies to help identify participants who may be at risk of a hypersensitivity reaction. While no such reactions have been observed to date in association with *APRETUDE*, physicians should remain vigilant and should discontinue *APRETUDE* and other suspected agents immediately, should signs or symptoms of hypersensitivity develop (including, but not limited to, severe rash, or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia or angioedema). Clinical status, including liver aminotransferases should be monitored and appropriate therapy initiated. (*see Dosage and Administration, Contraindications and Long acting properties of APRETUDE injection, Clinical studies).*

Hepatotoxicity

Hepatotoxicity has been reported in a limited number of individuals receiving *APRETUDE* with or without known pre-existing hepatic disease *(see Adverse reactions).*

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

Interactions with medicinal products

Caution should be given when prescribing *APRETUDE* with medicinal products that may reduce its exposure *(see Interactions).*

Interactions

Effect of cabotegravir on the pharmacokinetics of other agents

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

Cabotegravir inhibited the organic anion transporters (OAT) 1 (IC50=0.81 µM) and OAT3 (IC50=0.41 µM) *in vitro*, however, based on physiologically based pharmacokinetic (PBPK) modelling no interaction with OAT substrates is expected at clinically relevant concentrations.

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

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

Based on the *in vitro* and clinical drug interaction profile, cabotegravir is not expected to alter concentrations of other 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 primarily metabolised by UGT1A1 with some contribution from UGT1A9.

Medicinal products which are strong inducers of UGT1A1 or UGT1A9 are expected to decrease cabotegravir plasma concentrations leading to lack of efficacy (*see Contraindications*).

Simulations using PBPK show that no clinically significant interaction is expected following co-administration of cabotegravir with drugs that inhibit UGT enzymes.

In vitro, cabotegravir was not a substrate of OATP1B1, OATP1B3, OATP2B1 or OCT1.

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

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

Table 4 Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Cabotegravir or Concomitant Drug	Clinical Comment
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine	Cabotegravir ↔ AUC ↑ 1% C_{max} ↑ 4% C_{τ} ↔ 0%	Etravirine did not significantly change cabotegravir plasma concentration. No dosage adjustment is required.
Non-nucleoside Reverse Transcriptase Inhibitor: Rilpivirine	Cabotegravir ↔ AUC ↑ 12% C_{max} ↑ 5% C_{τ} ↑ 14% Rilpivirine ↔ AUC ↓1% C_{max} ↓ 4% C_{τ} ↓ 8%	Rilpivirine did not significantly change cabotegravir plasma concentration or vice versa. No dose adjustment of cabotegravir or rilpivirine is necessary when co-administered.
Rifampicin	Cabotegravir ↓ AUC ↓ 59% C_{max} ↓ 6%	Rifampicin significantly decreased cabotegravir plasma concentration, which is likely to result in loss of therapeutic effect. Co-administration of cabotegravir with rifampicin is contraindicated. Dosing recommendations for co-administration of *APRETUDE* (oral and injection) with rifampicin have not been established.
Rifapentine	Cabotegravir ↓	Rifapentine may significantly decrease cabotegravir plasma concentrations, concomitant use is contraindicated.
Rifabutin	Cabotegravir ↓ AUC ↓ 21% C_{max} ↓ 17% Cτ ↓ 8%	*APRETUDE* tablets: Rifabutin did not significantly change cabotegravir plasma concentration. No dose adjustment is required. *APRETUDE* injection: When rifabutin is started before or concomitantly with the first *APRETUDE* initiation injection the recommended *APRETUDE* dosing schedule is one 3 mL (600 mg) injection followed 2 weeks later by a second 3 mL (600 mg) initiation injection and monthly, thereafter, while on rifabutin. When rifabutin is started at the time of the second initiation injection or later, the recommended dosing schedule is 3 mL (600 mg), monthly, while on rifabutin. After stopping rifabutin, the recommended *APRETUDE* dosing schedule is 3 mL (600 mg) every 2 months.
Anticonvulsants: Carbamazepine Oxcarbazepine Phenytoin Phenobarbital	Cabotegravir ↓	Metabolic inducers may significantly decrease cabotegravir plasma concentrations. Concomitant use is contraindicated.
Antacids (e.g., magnesium, calcium or aluminium)	Cabotegravir ↓	*APRETUDE* tablets: Co-administration of antacid supplements has the potential to decrease oral cabotegravir absorption and has not been studied. Antacid products containing polyvalent cations are recommended to be administered at least 2 hours before or 4 hours after oral *APRETUDE*. *APRETUDE* injection: Interaction is not relevant following parenteral administration.
Oral contraceptives (Ethinyl estradiol (EE) and levonorgestrel	EE ↔ AUC ↑ 2% C_{max} ↓ 8% Cτ ↔ 0% LNG ↔	Cabotegravir did not significantly change ethinyl estradiol and levonorgestrel plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with *APRETUDE*.

Pregnancy and Lactation

Fertility

Animal studies indicate no effects of cabotegravir on male or female fertility (*see Non-clinical Information*).

Pregnancy

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

Cabotegravir was not teratogenic when studied in pregnant rats and rabbits but caused a delay in delivery that was associated with reduced survival and viability of rat offspring at exposures higher than for therapeutic doses (*see Non-clinical Information*). The relevance to human pregnancy is unknown.

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

Cabotegravir has been detected in systemic circulation for up to 12 months or longer after an injection, therefore, consideration should be given to the potential for foetal exposure during pregnancy (*see Warnings and Precautions*).

Lactation

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

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

Effects on Ability to Drive and Use Machines

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

Adverse Reactions

Clinical trial data

Adverse drug reactions (ADRs) for cabotegravir were identified from the Phase III clinical studies; HPTN 083 and HPTN 084. In HPTN 083, the median time on blinded study product was 65 weeks and 2 days (1 day to 156 weeks and 1 day), with a total exposure on cabotegravir of 3270 person years. In HPTN 084, the median time on blinded study product was 64 weeks and 1 days (1 day to 153 weeks and 1 day), with a total exposure on cabotegravir of 1920 person years. ADRs listed include those attributable to the oral or injectable formulations of cabotegravir.

When frequencies differed between HPTN 083 and 084, the highest frequency category is quoted.

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

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

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

Table 5 Adverse reactions[1]

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

[1] The frequency of the identified ARs are based on all reported occurrences of the events and are not limited to those considered at least possibly related by the investigator.

[2] Abdominal pain includes the following grouped MedDRA preferred terms: upper abdominal pain and abdominal pain.

[3] Rash includes the following grouped MedDRA preferred terms: rash, rash erythematous, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic.

[4] Pyrexia includes the following grouped MedDRA preferred terms: pyrexia and feeling hot. The majority of pyrexia events were reported within one week of injections.

[5] ISRs listed in the table have been seen in 2 participants or more.

Local Injection Site Reactions

In HPTN 083, 2% of participants discontinued cabotegravir because of ISRs.

Out of 20286 injections, 8900 ISRs were reported.

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

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

Out of 13068 injections, 1171 ISRs were reported.

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

Weight increased

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

At the Week 41 and 97 timepoints in HPTN 084, participants who received cabotegravir gained a median of 2.0 kg (IQR 0.0, 5.0; n=1151) and 4.0 kg (IQR; 0.0, 8.0, n=216) in weight from baseline, respectively; those in the tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) group gained a median of 1.0 kg (IQR -1.0, 4.0, n=1131) and 3.0 kg (IQR; -1.0, 6.0 n=218) in weight from baseline, respectively.

Changes in laboratory chemistries

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

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

Post-marketing data

No data

Overdosage

Symptoms and signs

There is currently no experience of overdose with *APRETUDE*.

Treatment

There is no specific treatment for overdose with *APRETUDE*. If overdose occurs, the individual should be treated supportively with appropriate monitoring as necessary. Further management should be as clinically indicated or as recommended by the national poisons centre, where available. 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 *APRETUDE* injection should take into consideration the prolonged exposure to drug following an injection (*see Warnings and Precautions*).

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC code

Pharmacotherapeutic group: Antiviral for systemic use, integrase inhibitor, ATC code: J05AJ04

Mechanism of action

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

Pharmacodynamic effects

Antiviral Activity in cell culture

Cabotegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean concentration of cabotegravir necessary to reduce viral replication by 50 percent (EC_{50}) values of 0.22 nM in peripheral blood mononuclear cells (PBMCs), 0.74 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: Viruses with >10-fold increase in cabotegravir EC_{50} were not observed during the 112-day passage of strain IIIB. The following integrase (IN) mutations emerged after passaging wild type HIV-1 (with T124A polymorphism) in the presence of cabotegravir: Q146L (fold-change range 1.3-4.6), S153Y (fold-change range 2.8-8.4) and I162M (fold-change = 2.8). As noted above, the detection of T124A is selection of a pre-existing minority variant that does not have differential susceptibility to cabotegravir. No amino acid substitutions in the integrase region were selected when passaging the wild-type HIV-1 NL-432 in the presence of 6.4 nM of cabotegravir through Day 56. Among the multiple mutants, the highest fold-change was observed with mutants containing Q148K or Q148R. E138K/Q148H resulted in a 0.92-fold decrease in susceptibility to cabotegravir but E138K/Q148K resulted in an 81-fold decrease in susceptibility to cabotegravir. G140C/Q148R and G140S/Q148R resulted in a 22- and 12-fold decrease in susceptibility to cabotegravir, respectively. While N155H did not alter susceptibility to cabotegravir, N155H/Q148R resulted in a 61-fold decrease in susceptibility to cabotegravir.

Resistance in vivo

HPTN 083

In the primary analysis of the HPTN 083 study, there were 13 incident infections on the cabotegravir arm and 39 incident infections on the tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) arm. In the cabotegravir arm, 5 incident infections occurred when receiving cabotegravir PrEP injections, of which 4 participants received on-time injections and 1 participant had one injection off-schedule. Five incident infections occurred ≥6 months after the last dose of cabotegravir PrEP. Three incident infections occurred during the oral lead-in period. HIV genotyping and phenotyping were attempted at the first visit where HIV viral load was >500 copies/mL. Of the 13 incident infections in the cabotegravir arm, 4 participants had INSTI resistance mutations. In the TDF/FTC arm, the 4 participants with NRTI resistance (including 3 who had multi-class resistance) included 3 with M184V/I and one with K65R.

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

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

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

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

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

HPTN 084

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

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

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

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

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

Effects on Electrocardiogram

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

Pharmacokinetics

Oral

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

Suspension for Injection

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

Table 6. Pharmacokinetic parameters following cabotegravir orally once daily, and initiation and every 2 month continuation intramuscular injections

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

[a] Pharmacokinetic (PK) parameter values were based on individual post-hoc estimates from population PK models for patients in Phase III treatment studies of HIV treatment studies.

[b] tau is dosing interval: 24 hours for oral administration; 1 month for the initial injection and 2 months for every 2 months for IM injections of extended-release injectable suspension.

[c] Oral lead-in pharmacokinetic parameter values represent steady-state.

[d] Initial injection C_{max} values primarily reflect oral dosing because the initial injection was administered on the same day as the last oral dose; however, the $AUC_{(0-tau)}$ 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 mcg/mL (0.438, 5.69) and C_{tau} was 1.43 mcg/mL (0.403, 3.90).

[e] Pharmacokinetic parameter values represent steady state.

Absorption

Oral

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

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

The absolute bioavailability of cabotegravir has not been established.

Suspension for Injection

Cabotegravir injection exhibits absorption-limited pharmacokinetics because cabotegravir is slowly absorbed into the systemic circulation from the gluteal muscle resulting in sustained plasma concentrations. Following a single 600 mg intramuscular dose, plasma cabotegravir concentrations are detectable on the first day with median cabotegravir concentrations at 4 hours post dose of 0.290 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 6). 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.

Metabolism

Cabotegravir is primarily metabolised by UGT1A1 with a minor UGT1A9 component.

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

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.

Suspension for Injection

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

Special patient populations

Gender

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

Race

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

BMI

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

Adolescents

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

Table 7. 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)

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

[a] Pharmacokinetic (PK) parameter values were based on population PK model simulations in a virtual HIV-1 infected adolescent population weighing 35-156 kg.

[b] tau is dosing interval: 24 hours for oral administration; 1 month for the initial injection, 2 months for every 2 months for IM injections of extended-release injectable suspension.

[c] Oral lead-in pharmacokinetic parameter values represent steady-state.

[d] Initial injection C_{max} values primarily reflect oral dosing because the initial injection was administered on the same day as the last oral dose; however, the $AUC_{(0-tau)}$ and C_{tau} values reflect the initial injection.

[e] Pharmacokinetic parameter values represent steady state.

Children

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

Elderly

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

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

Renal impairment

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

Hepatic impairment

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

HBV and HCV Infected Individuals

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

Polymorphisms in Drug Metabolising Enzymes

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

Clinical studies

Clinical efficacy and safety

The efficacy of cabotegravir for PrEP has been evaluated in two randomised (1:1), double blind, multi-site, two-arm, controlled studies. The efficacy of cabotegravir was compared with daily oral tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC).

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

HPTN 083

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

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

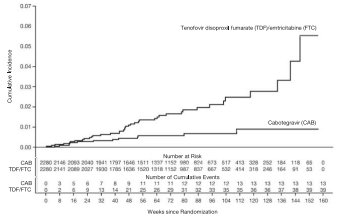
The primary endpoint was the rate of incident HIV infections among participants randomised to oral cabotegravir and cabotegravir injections compared to oral TDF/FTC. The primary analysis demonstrated the superiority of cabotegravir compared to TDF/FTC with a 66% reduction in the risk of acquiring incident HIV infection; further testing revealed one of the infections on cabotegravir to be prevalent then yielding a 70% reduction in the risk of incident infection relative to TDF/FTC (see Table 8).

Table 8. Primary Efficacy Endpoint: Comparison of Rates of Incident HIV Infections during Randomised Phase (mITT)

	Cabotegravir (N=2280)	TDF/FDC (N=2281)	Superiority P-Value
Person years	3211	3193	
HIV-1 incident infections (incidence rate per 100 person years)	13[1] (0.40)	39 (1.22)	
Hazard ratio (95% CI)	0.34 (0.18, 0.62)		p=0.0005

[1]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 CAB was determined to be a prevalent infection. The revised HR (95% CI) is 0.303 (0.16, 0.58).

Figure 1. Cumulative Incidence of HIV Infections (mITT)



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

Table 9. Rate of incident HIV-1infection by subgroup

Subgroup	Cabotegravir incidence per 100 person years	Cabotegravir person years	TDF/FTC incidence per 100 person years	TDF/FTC person years)	HR (95% CI)
Age					
<30 years	0.52	2110	1.66	1987	0.32 (0.16, 0.63)
≥30 years	0.18	1101	0.50	1206	0.39 (0.08, 1.84)
Gender					
MSM	0.39	2837	1.14	2803	0.35 (0.18, 0.68)
TGW	0.54	371	1.80	389	0.34 (0.08, 1.56)
Race (US)					
Black	0.58	691	2.28	703	0.26 (0.09, 0.76)
Non-Black	0.00	836	0.50	801	0.11 (0.00, 2.80)
Region					
US	0.26	1528	1.33	1504	0.21 (0.07, 0.60)
Latin America	0.59	1021	1.09	1011	0.56 (0.21, 1.51)
Asia	0.35	570	1.03	581	0.39 (0.08, 1.82)
Africa	1.08	93	2.07	97	0.63 (0.06, 6.50)

MSM= cisgender men who have sex with men
TGW = Transgender women who have sex with men

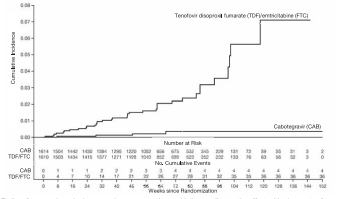
HPTN 084

In HPTN 084, a superiority study, 3224 cisgender women were randomised 1:1 and received either cabotegravir (n=1614) or TDF/FTC (n=1610) as blinded study medication up to Week 153.
At baseline, the median age of participants was 25 years, >99% were non-white, >99% were cisgender women and 49% were <25 years of age.
The primary endpoint was the rate of incident HIV infections among participants randomised to oral cabotegravir and cabotegravir injections compared to oral TDF/FTC. The primary analysis demonstrated the superiority (p<0.0001) of cabotegravir compared to TDF/FTC with an 89% reduction in the risk of acquiring incident HIV-1 infection (see Table 10).

Table 10. Primary Efficacy Endpoint: Comparison of Rates of Incident HIV Infections during Randomised Phase (mITT)

	Cabotegravir (N=1614)	TDF/FDC (N=1610)	Superiority P-Value
Person years	1961	1946	
HIV-1 incident infections (incidence rate per 100 person years)	4 (0.20)	36 (1.85)	
Hazard ratio (95% CI)	0.11 (0.04, 0.31)		p<0.0001

Figure 2. Cumulative Incidence of HIV Infections (mITT)



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 randomised to the cabotegravir group compared with participants randomised to the TDF/FTC group (see Table 11).

Table 11. Rate of incident HIV-1infection by subgroup

Subgroup	Cabotegravir incidence per 100 person years	Cabotegravir person years	TDF/FTC incidence per 100 person years	TDF/FTC person years)	HR (95% CI)
Age					
<25 years	0.35	868	2.34	853	0.17 (0.05, 0.54)
≥25 years	0.09	1093	1.46	1093	0.09 (0.02, 0.49)
BMI					
<30	0.29	1385	1.88	1435	0.16 (0.06, 0.44)
≥30	0.00	575	1.76	511	0.04 (0.00, 0.93)

MOCHA (HIV-infected adolescents)

The safety, tolerability and pharmacokinetics of oral and injectable cabotegravir is 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 mm³.
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, no new safety concerns or safety signals were identified in adolescents receiving either oral or injectable cabotegravir. The observed pharmacokinetics parameters in adolescents met the exposure targets, based on adult data for both oral and injectable cabotegravir (see Pharmacokinetics, Special Populations).

Non-Clinical Information

Carcinogenesis/mutagenesis

Cabotegravir was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay. Cabotegravir was not carcinogenic in long term studies in the mouse and rat.

Reproductive Toxicology

Fertility

Cabotegravir when administered orally to male and female rats at 1000 mg/kg/day (>30 times the exposure in humans at the Maximum Recommended Human Dose [MRHD] of 30 mg oral or 400 mg IM dose) for up to 26 weeks did not cause adverse effects on male or female reproductive organs or spermatogenesis. No functional effects on male or female mating or fertility were observed in rats given cabotegravir at doses up to 1000 mg/kg/day.

Pregnancy

In an embryo-foetal development study there were no adverse developmental outcomes following oral administration of cabotegravir to pregnant rabbits at doses up to 2000mg/kg/day (0.66 times the exposure in humans at the MRHD of 30 mg oral or approximately 1 times 400 mg IM dose) or to pregnant rats at doses up to 1000 mg/kg/day (>30 times the exposure in humans at the MRHD of 30 mg oral or 400 mg IM dose). In rats, alterations in foetal growth (decreased body weights) in the absence of maternal toxicity were observed at 1,000 mg/kg/day. Studies in pregnant rats showed that cabotegravir crosses the placenta and can be detected in foetal tissue.
Non-clinical data from rat pre- and post-natal (PPN) studies at 1,000 mg/kg/day (>30 times the exposure in humans at the MRHD of 30 mg oral or 400 mg IM dose) cabotegravir delayed the onset of parturition, and in some rats, this delay was associated with an increased number of stillbirths and neonatal mortalities immediately after birth. A lower dose of 5 mg/kg/day cabotegravir (>10 times the exposure in humans 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 foetuses were delivered by caesarean section. When rat pups born to cabotegravir-treated dams were cross-fostered at birth and nursed by control mothers, similar incidences of neonatal mortalities were observed.

Animal toxicology and/or pharmacology

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 or 500 mg/kg/day, 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).

PHARMACEUTICAL INFORMATION

List of Excipients

Film-coated tablets

Tablet core
Lactose Monohydrate
Microcrystalline Cellulose
Hypromellose (E464)
Sodium Starch Glycolate (Type A)
Magnesium Stearate
Tablet coating
Hypromellose (E464)
Titanium Dioxide (E171)
Macrogol 400 (E1521)

Suspension for Injection

Mannitol (E421)
Polysorbate 20 (E432)
Macrogol (E1521)
Water for injections

Shelf Life

The expiry date is indicated on the packaging.

Storage

Unopened packs (Suspension for Injection and Film-coated tablets)

The storage conditions are detailed on the packaging.

Open packs

Suspension for Injection

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

Nature and Contents of Container

Film-coated tablets

APRETUDE tablets are supplied in HDPE (high density polyethylene) bottles with child-resistant closures.

Suspension for Injection

Individual vial only pack (single entity vial SEV):

APRETUDE, 200 mg/mL prolonged-release suspension for injection. APRETUDE is presented in a glass vial.

Incompatibilities

Film-coated tablets

None

Suspension for Injection

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

Use and Handling

See the Instructions for Use leaflet for complete administration instructions with illustrations.
Not all presentations are available in every country.

Manufactured and packed by:

Glaxo Operations UK Ltd (trading as Glaxo Wellcome Operations)*
Harmire Road
Barnard Castle
County Durham, DL12 8DT
United Kingdom
*Member of the GSK group of companies

Version number: GDS01/IPI01

Date of issue: 4 August 2021

ViiV Healthcare

Apretude

600 mg

prolonged-release suspension for injection

cabotegravir

For intramuscular use

Instructions for Use

3 mL

INSTRUCTIONS FOR USE

The following information is intended for healthcare professionals only:
For Single Entity Vial (SEV) packs:

Overview

At each visit, one injection is required; *APRETUDE* 3 mL (600mg).

APRETUDE is a suspension that does not need further dilution or reconstitution.

APRETUDE is for intramuscular use only. It must be administered to the gluteal sites.

Note: The ventrogluteal site is recommended.

Storage information

- The storage conditions are detailed on packaging.

Do not freeze.

Your pack contains

- 1 vial of *APRETUDE*

To prepare the injection

- 1 Luer-Lock syringe (5 mL)
- 1 Luer-Lock aspiration needle or aspiration device (to draw up the suspension)

To administer the injection

- 1 additional Luer-Lock needle (use safety needle if available) of 23 gauge, 1.5 inches

Consider the patient's build and use medical judgment to select an appropriate injection needle length.

You will also need

- Non-sterile gloves
- 2 alcohol swabs
- 1 gauze pad
- A suitable sharps container

Preparation

1. Inspect vial

- Check that the expiry date has not passed.
- Inspect the vial immediately. If you can see foreign matter, do not use the product.

Note:
The *APRETUDE* vial has a brown tint to the glass.
Do not use if the expiry date has passed.

2. Shake vigorously

- Hold the vial firmly and vigorously shake for a full 10 seconds as shown.
- Invert the vial and check the resuspension. It should look uniform. If the suspension is not uniform, shake the vial again.
- It is also normal to see small air bubbles.
- Remove the cap from the vial.
- Wipe the rubber stopper with an alcohol swab.

Do not allow anything to touch the rubber stopper after wiping it.

3. Prepare syringe and needle

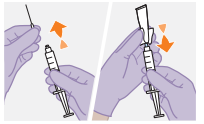
- Continue to prepare the injection in line with local guidelines.
- Example: attach the aspiration needle to the syringe.
- It is recommended that you inject 1 mL of air into the vial to allow the required volume to be drawn up.

4. Slowly draw up dose

- Invert the syringe and vial, and slowly withdraw as much of the liquid as possible into the syringe. There might be more liquid than dose amount.

Note: Check that the suspension looks uniform and white to light pink.

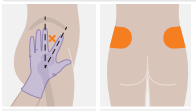
5. Attach injection needle



- Peel open the needle packaging part way to expose the needle base.
- Keeping the syringe upright, firmly twist the syringe onto the injection needle.
- Attach injection needle.
- Remove the needle packaging from the needle.

Injection

6. Prepare injection site



Injections must be administered to the gluteal sites. Select from the following areas for the injection:

- Ventrogluteal (recommended)
- Dorsogluteal (upper outer quadrant)

Note: For gluteal intramuscular use only.
Do not inject intravenously.

7. Remove extra liquid

- Pull off the injection needle cap.
- Hold the syringe with the needle pointing up. Press the plunger to the 3 mL dose to remove extra liquid and any air bubbles.

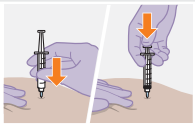
Note: Clean the injection site with an alcohol swab. Allow the skin to air dry before continuing.

8. Stretch skin

Use the z-track injection technique to minimise medicine leakage from the injection site.

- Firmly drag the skin covering the injection site, displacing it by about an inch (2.5 cm).
- Keep it held in this position for the injection.

9. Inject dose



- Insert the needle to its full depth, or deep enough to reach the muscle.
- Still holding the skin stretched – slowly press the plunger all the way down.
- Ensure the syringe is empty.
- Withdraw the needle and release the stretched skin immediately.

10. Assess the injection site

- Apply pressure to the injection site using a gauze pad.
- A small bandage may be used if a bleed occurs.
- Dispose of used needles, syringe and vial according to local health and safety laws.

Do not massage the area.

Questions and Answers

1. If the pack has been stored in the refrigerator, is it safe to warm the vial up to room temperature more quickly?

You should wait at least 15 minutes before you are ready to give the injection to allow the medication to come to room temperature.

It is best to let the vial come to room temperature naturally. However, you can use the warmth of your hands to speed up the warm-up time, but make sure the vial does not get above 30°C (86°F).

Do not use any other heating methods.

2. How long can the medicine be left in the syringe?

It is best to inject the (room temperature) medicine as soon as possible after drawing it up. However, the medicine can remain in the syringe for up to 2 hours before injecting.

If the medicine remains in the syringe for more than 2 hours, the filled syringe and needle must be discarded.

3. Why do I need to inject air into the vial?

Injecting 1 mL of air into the vial makes it easier to draw up the dose into the syringe.

Without the air, some liquid may flow back into the vial unintentionally, leaving less medicine than intended in the syringe.

4. Why is the ventrogluteal administration approach recommended?

The ventrogluteal approach, into the gluteus medius muscle, is recommended because it is located away from major nerves and blood vessels. A dorso-gluteal approach into the gluteus maximus muscle is acceptable, if preferred by the health care professional. The injection should not be administered in any other site.

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