ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

Apretude 600 mg prolonged-release suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 600 mg cabotegravir in 3 mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release suspension for injection.
White to light pink suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Apretude is indicated in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in high-risk adults and adolescents, weighing at least 35 kg (see sections 4.2, 4.4 and 5.1).

4.2 Posology and method of administration

Apretude should be prescribed by a healthcare professional experienced in the management of HIV PrEP.

Each injection should be administered by a healthcare professional.

Individuals must be tested for HIV-1 prior to initiating cabotegravir and at each subsequent injection of cabotegravir (see section 4.3). A combined antigen/antibody test as well as an HIV-RNA-based test should both be negative. Prescribers are advised to perform both tests, even if the result of the HIV-RNA-based test will become available after cabotegravir injection. If a combined testing strategy including both tests is not available, testing should follow local guidelines.

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.

The healthcare provider and individual may decide to use cabotegravir tablets as an oral lead-in prior to the initiation of Apretude injection to assess tolerability or may proceed directly to Apretude injections (see Table 1 and Table 2 for dosing recommendations).

Posology

Oral lead-in
Refer to the oral Apretude tablet SmPC for oral lead-in information.

Injection

Initiation injections
The recommended initial dose is a single 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 600 mg intramuscular injection should be administered. Individuals may be given the second 600 mg initiation injection up to 7 days before or after the scheduled dosing date.

Continuation injections – 2 months apart
After the second initiation injection, the recommended continuation injection dose in adults is a single 600 mg intramuscular injection administered every 2 months. Individuals may be given injections up to 7 days before or after the date of the scheduled injection date.

Table 1 Recommended intramuscular dosing schedule

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

Missed doses
Individuals who miss a scheduled injection visit should be reassessed to ensure resumption of PrEP remains appropriate.

If a delay of more than 7 days from a scheduled injection date cannot be avoided it will be a missed dose, therefore, cabotegravir 30 mg tablets may be used once daily, for a duration of up to two months, to replace one scheduled injection visit. The first dose of oral therapy should be taken approximately two months (+/- 7 days) after the last injection of cabotegravir. For oral PrEP durations greater than two months, an alternative PrEP regimen is recommended.

Injection dosing should be resumed on the day oral dosing completes or within 3 days, thereafter, as recommended in Table 2.

Table 2 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 600 mg injection as soon as possible and continue with the every 2 month injection dosing schedule.
> 2 months	Restart the individual on one 600 mg initiation injection, followed by a second 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 600 mg injection as soon as possible and continue with the every 2 month injection dosing schedule.
> 3 months	Restart the individual on one 600 mg initiation injection, followed by a second 600 mg initiation injection one month later. Then follow the every two month injection dosing schedule.

Special populations

Elderly
No dose adjustment is required in elderly individuals. There are limited data available on the use of cabotegravir in individuals aged 65 years and over (see section 5.2).

Hepatic impairment
No dose adjustment is required in individuals with mild or moderate hepatic impairment (Child-Pugh score A or B). Cabotegravir has not been studied in individuals with severe hepatic impairment (Child-Pugh score C, [see section 5.2]). If administered in an individual with severe hepatic impairment, cabotegravir should be used with caution.

Renal impairment
No dose adjustment is required in individuals with mild to severe renal impairment (CrCl < 30 mL/min and not on dialysis [see section 5.2]). Cabotegravir has not been studied in individuals with end-stage renal disease on renal replacement therapy. As cabotegravir is greater than 99% protein bound, dialysis is not expected to alter exposures of cabotegravir. If administered in an individual on renal replacement therapy, cabotegravir should be used with caution.

Paediatric population
The safety and efficacy of cabotegravir in children and adolescents weighing less than 35 kg have not been established. No data are available.

Method of administration

For intramuscular use. Injections must be administered to the ventrogluteal (recommended as it is located away from major nerves and blood vessels) or the dorsogluteal sites.

Care should be taken to avoid inadvertent injection into a blood vessel.

Once the suspension has been drawn into the syringe, the injection should be administered as soon as possible, but may remain in the syringe for up to 2 hours. If the medicinal product remains in the syringe for more than 2 hours, the filled syringe and needle must be discarded.

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

4.3 Contraindications

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

Individuals with an unknown or positive HIV-1 status (see sections 4.2 and 4.4).

Concomitant use with rifampicin, rifapentine, carbamazepine, oxcarbazepine, phenytoin or phenobarbital (see section 4.5).

4.4 Special warnings and precautions for use

Overall HIV-1 infection prevention strategy

Apretude may not always be effective in preventing HIV-1 infection (see section 5.1). Cabotegravir concentrations associated with significant antiviral activity (> 4x Protein Adjusted-Inhibitory Concentration, PA-IC90, see section 5.2) are achieved and maintained within hours after initiation of oral lead-in and within 7 days from the first injection (without oral lead-in). The exact time from initiation of Apretude for HIV-1 PrEP to maximal protection against HIV-1 infection is unknown.

Apretude should be used for PrEP 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 section 4.3). Individuals should be re-confirmed to be HIV negative at each subsequent injection of Apretude. A combined antigen/antibody test as well as an HIV-RNA-based test should both be negative. Prescribers are advised to perform both tests, even if the result of the HIV-RNA-based test will become available after cabotegravir injection. If a combined testing strategy including both tests is not available, testing should follow local guidelines while taking Apretude.

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 cabotegravir if an individual acquires HIV-1 either before or while taking Apretude, or following discontinuation of Apretude (see Long- acting properties of Apretude injection). To minimise this risk, it is essential to confirm HIV-1 negative status at each subsequent injection of Apretude. A combined antigen/antibody test as well as an HIV-RNA-based test should both be negative. Prescribers are advised to perform both tests, even if the result of the HIV-RNA-based test will become available after cabotegravir injection. If a combined testing strategy including both tests is not available, testing should follow local guidelines. Individuals who are diagnosed with HIV-1 should immediately begin anti-retroviral therapy (ART).

Apretude alone does not constitute a complete regimen for the treatment of HIV-1 and HIV-1 resistance mutations have emerged in some individuals with undetected HIV-1 infection who were only taking Apretude.

Importance of adherence

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

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, the prolonged release characteristics of Apretude injection should be taken into consideration when the medicinal product is discontinued and alternative not long-acting forms of PrEP are taken, as long as or at any time the risk of acquiring HIV is present in the months after discontinuation of Apretude (see section 5.2).

Healthcare professionals should discuss the benefit-risk of using Apretude with individuals of childbearing potential or during pregnancy (see section 4.6).

Hypersensitivity reactions

Hypersensitivity reactions have been reported in association with integrase inhibitors including cabotegravir. These reactions were characterised by rash, constitutional findings and sometimes organ dysfunction, including liver injury. Apretude and other suspected medicinal products should be discontinued 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 sections 4.2, Long-acting properties of Apretude injection and 4.8).

Hepatoxicity

Hepatotoxicity has been reported in a limited number of individuals receiving cabotegravir with or without known pre-existing hepatic disease (see section 4.8). Administration of cabotegravir oral lead-in was used in clinical studies to help identify individuals who may be at risk of hepatotoxicity.

Clinical and laboratory monitoring are recommended and Apretude should be discontinued if hepatotoxicity is confirmed, and individuals managed as clinically indicated (see Long-acting properties of Apretude injection).

Adolescents

Suicidal ideation and suicide attempt have been reported with cabotegravir, particularly in those with pre-existing psychiatric illness (see section 4.8). Although clinical studies did not show an increased incidence of psychiatric illness in adolescents compared to adult subjects, given the vulnerability of the adolescent population, adolescents should be counselled before prescribing, and periodically while receiving Apretude, and managed as clinically indicated.

Interactions with medicinal products

Caution should be given to prescribing Apretude injection with medicinal products that may reduce its exposure (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on the pharmacokinetics of cabotegravir

Cabotegravir is primarily metabolised by uridine diphosphate glucuronosyl transferase (UGT) 1A1 and to a lesser extent by UGT1A9. Medicinal products which are strong inducers of UGT1A1 or UGT1A9 are expected to decrease cabotegravir plasma concentrations leading to lack of efficacy (see section 4.3 and Table 3 below). In poor metabolisers of UGT1A1, representing a maximum clinical UGT1A1 inhibition, the mean AUC, C_{max} and C_{tau} of oral cabotegravir increased by up to 1.5-fold. No dosing adjustments for Apretude are recommended in the presence of UGT1A1 inhibitors.

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

Effect of cabotegravir on the pharmacokinetics of other medicinal products

In vivo, cabotegravir did not have an effect on midazolam, a cytochrome P450 (CYP) 3A4 probe. *In vitro*, cabotegravir did not induce CYP1A2, CYP2B6, or CYP3A4.

In vitro cabotegravir inhibited organic anion transporters (OAT) 1 (IC_{50}=0.81 μM) and OAT3 (IC_{50}=0.41 μM). Therefore, caution is advised when co-dosing with narrow therapeutic index OAT1/3 substrate medicinal products (e.g. methotrexate).

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

No drug interaction studies have been performed with cabotegravir injection. The drug interaction data provided in Table 3 is obtained from studies with oral cabotegravir (increase is indicated as "↑", decrease as "↓", no change as "↔", area under the concentration versus time curve as "AUC", maximum observed concentration as "C_{max}", concentration at end of dosing interval as "Cτ").

Table 3Drug interactions

Medicinal products by therapeutic areas	**Interaction** Geometric mean change (%)	**Recommendations concerning co-administration**
HIV-1 Antiviral medicinal products		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine	Cabotegravir ↔ AUC ↑ 1% C_{max} ↑ 4% Cτ ↔ 0%	Etravirine did not significantly change cabotegravir plasma concentration. No dose adjustment of Apretude is necessary when initiating injections following etravirine use.
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 Apretude or rilpivirine is necessary when co-administered.
Anticonvulsants		
Carbamazepine Oxcarbazepine Phenytoin Phenobarbital	Cabotegravir ↓	Metabolic inducers may significantly decrease cabotegravir plasma concentration. Concomitant use is contraindicated (see section 4.3).
Antimycobacterials		
Rifampicin	Cabotegravir ↓ AUC ↓ 59% C_{max} ↓ 6%	Rifampicin significantly decreased cabotegravir plasma concentration which is likely to result in loss of therapeutic effect. Dosing recommendations for co-administration of Apretude with rifampicin have not been established and co-administration of Apretude with rifampicin is contraindicated (see section 4.3).
Rifapentine	Cabotegravir ↓	Rifapentine may significantly decrease cabotegravir plasma concentrations. Concomitant use is contraindicated (see section 4.3).
Rifabutin	Cabotegravir ↓ AUC ↓ 21% C_{max} ↓ 17% Cτ ↓ 26%	When rifabutin is started before or concomitantly with the first cabotegravir initiation injection the recommended cabotegravir dosing schedule is one 600 mg injection followed 2 weeks later by a

		second 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 600 mg, monthly, while on rifabutin. After stopping rifabutin, the recommended cabotegravir dosing schedule is 600 mg every 2 months.
Oral contraceptives		
Ethinyl estradiol (EE) and Levonorgestrel (LNG)	EE ↔ AUC ↑ 2% C_{max} ↓ 8% Cτ ↔ 0% LNG ↔ AUC ↑ 12% C_{max} ↑ 5% Cτ ↑ 7%	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.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be counselled about prolonged release characteristics of cabotegravir injection. If a woman plans a pregnancy, the benefits and the risks of starting/continuing PrEP with Apretude should be discussed (see section 4.4).

Pregnancy

There are limited data from the use of cabotegravir in pregnant women. The effect of cabotegravir on pregnancy is unknown.

Cabotegravir was not teratogenic when studied in pregnant rats and rabbits but exposures higher than the therapeutic dose showed reproductive toxicity in animals (see section 5.3). The relevance to human pregnancy is unknown.

Apretude injection is not recommended during pregnancy unless the expected benefit justifies the potential risk to the foetus.

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

Breast-feeding

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

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

Fertility

There are no data on the effects of cabotegravir on human male or female fertility. Animal studies indicate no effects of cabotegravir on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Individuals should be informed that dizziness, somnolence and fatigue have been reported during treatment with Apretude injection. The clinical status of the individual and the adverse reaction profile of Apretude injection should be borne in mind when considering the individual's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

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

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

Tabulated list of adverse reactions

Adverse reactions for cabotegravir were identified from the Phase III clinical studies; HPTN 083 and HPTN 084; and post-marketing data. 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 day (1 day to 153 weeks and 1 day), with a total exposure on cabotegravir of 1920 person years.

The adverse reactions considered at least possibly related to cabotegravir in adults and adolescents are listed in Table 4 by system organ class and frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000).

Table 4 Tabulated list of adverse reactions[1]

MedDRA System organ class (SOC)	Frequency category	Adverse reactions
Immune system disorders	Uncommon	Hypersensitivity*[6]
Psychiatric disorders	Common	Abnormal dreams Insomnia Depression Anxiety
	Uncommon	Suicide attempt[6]; Suicidal ideation[6] (particularly in individuals with a pre-existing psychiatric illness)
Nervous system disorders	Very common	Headache
	Common	Dizziness

	Uncommon	Somnolence Vasovagal reactions (in response to injections)
Gastrointestinal disorders	Very common	Diarrhoea
	Common	Nausea Abdominal pain[2] Flatulence Vomiting
Hepatobiliary Disorders	Uncommon	Hepatotoxicity
Skin and subcutaneous tissue disorders	Common	Rash[3]
	Uncommon	Urticaria*[6] Angioedema*[6]
Musculoskeletal and connective tissue disorders	Common	Myalgia
General disorders and administrative site conditions	Very common	Pyrexia[5] Injection site reactions[4] (pain and tenderness, nodule, induration)
	Common	Injection site reaction[4] (swelling, bruising, erythema, warmth, pruritus, anaesthesia) Fatigue Malaise
	Uncommon	Injection site reactions[4] (haematoma, discolouration, abscess)
Investigations	Very common	Transaminase increased
	Uncommon	Weight increased Blood bilirubin increased

[1] The frequency of the identified adverse reactions are based on all reported occurrences of the adverse reactions 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]ISRs listed in the table have been seen in 2 participants or more.
[5]Pyrexia includes the following grouped MedDRA preferred terms: pyrexia and feeling hot. The majority of pyrexia adverse reactions were reported within one week of injections.
[6]This adverse reaction was identified through post-marketing reporting. The frequency category is based on individuals exposed to cabotegravir in randomised clinical studies.
*Please refer to section 4.4

Description of selected adverse reactions

Local injection site reactions (ISRs)
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). The median duration of overall ISR adverse reactions 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). The median duration of overall ISR adverse reactions 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 week 97 timepoints in HPTN 083, participants who received cabotegravir gained a median of 1.2 kg (Interquartile Range [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 Week 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 reactions 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.

Adolescents

Based on data from two open-label multicenter clinical trials in 64 HIV-uninfected, at-risk adolescents (below 18 years of age and weighing ≥ 35 kg at enrolment) receiving cabotegravir, no new safety issues were identified in adolescents compared with the safety profile established in adults receiving cabotegravir for HIV-1 PrEP in studies HPTN 083 and HPTN 084.

Based on data from the Week 16 analysis of the MOCHA study in 23 HIV-infected adolescents (aged at least 12 years and weighing ≥35 kg) receiving background combination anti retroviral therapy, no new safety concerns were identified in adolescents with the addition of oral cabotegravir followed by injectable cabotegravir (n=8) when compared with the safety profile established with cabotegravir in adults (see section 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific treatment for Apretude overdose. If overdose occurs, the individual should be treated supportively with appropriate monitoring as necessary.

Cabotegravir is known to be highly protein bound in plasma; therefore, dialysis is unlikely to be helpful in removal of medicinal product from the body. Management of overdose with Apretude injection should take into consideration the prolonged exposure to the medicinal product following an injection (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 nM in 293T cells and 0.57 nM in MT-4 cells. Cabotegravir demonstrated antiviral activity in cell culture against a panel of 24 HIV-1 clinical isolates (three in each group of M clades A, B, C, D, E, F, and G, and 3 in group O) with EC_{50} values ranging from 0.02 nM to 1.06 nM for HIV-1. Cabotegravir EC_{50} values against three HIV-2 clinical isolates ranged from 0.10 nM to 0.14 nM.

Antiviral Activity in combination with other medicinal products
No medicinal products 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).

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/Q148R resulted in a 12-fold decrease in susceptibility and 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. Other multiple mutants, which resulted in a FC between 5 and 10, are: T66K/L74M (FC=6.3), G140S/Q148K (FC=5.6), G140S/Q148H (FC=6.1) and E92Q/N155H (FC=5.3).

Resistance in vivo

HPTN 083
In the primary analysis of the HPTN 083 study, there were 13 incident infections on the cabotegravir arm and 39 incident infections on the tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) arm. In the cabotegravir arm, 5 incident infections occurred when receiving cabotegravir PrEP injections, of which 4 participants received on-time injections and 1 participant had one injection off-schedule. Five incident infections occurred ≥ 6 months after the last dose of cabotegravir PrEP. Three incident infections occurred during the oral lead-in period.

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

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

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

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

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

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

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

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

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

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

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

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

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 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 medicinal products up to Week 153.

At baseline, the median age of participants was 26 years, 12% were transgender women, 72% were non-white, 67% were < 30 years and < 1% were over 60 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 (corrected for early stopping). The primary analysis demonstrated the superiority of cabotegravir compared to TDF/FTC with a 66% reduction in the risk of acquiring incident HIV infection, hazard ratio (95% CI) 0.34 (0.18, 0.62); further testing revealed one of the infections on cabotegravir to be prevalent then yielding a 69% reduction in the risk of incident infection relative to TDF/FTC (see Table 5).

Table 5 Primary Efficacy Endpoint: Comparison of Rates of Incident HIV Infections during Randomised Phase in HPTN 083 (mITT, extended retrospective virologic testing)

	Cabotegravir (N=2278)	**TDF/FTC (N=2281)**	**Superiority P-Value**

Person years	3211	3193	
HIV-1 incident infections (incidence rate per 100 person years)	12[1] (0.37)	39 (1.22)	
Hazard ratio (95% CI)	0.31 (0.16, 0.58)		p=0.0003

[1]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 on cabotegravir was determined to be a prevalent infection. The original hazard ratio (95% CI) from the primary analysis is 0.34 (0.18, 0.62).

Findings from all subgroup analyses were consistent with the overall protective effect, with a lower rate of incident HIV-1 infections observed for participants randomised to the cabotegravir group compared with participants randomised to the TDF/FTC group (see Table 6).

Table 6 Rate of incident HIV-1 infection by subgroup in HPTN 083 (mITT, extended retrospective virologic testing)

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

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

HPTN 084
In HPTN 084, a superiority study, 3224 cisgender women were randomised 1:1 and received either cabotegravir (n=1614) or TDF/FTC (n=1610) as blinded study medicinal product 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, with a maximum age of 45 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 (corrected for early stopping). The primary analysis demonstrated the superiority (p< 0.0001) of cabotegravir compared to TDF/FTC with an 88% reduction in the risk of acquiring incident HIV-1 infection hazard ratio (95% CI) 0.12 (0.05, 0.31); further testing revealed 1 of the infections on cabotegravir to be prevalent then yielding a 90% reduction in the risk of HIV-1 incident infection relative to TDF/FTC (see Table 7).

Table 7 Primary Efficacy Endpoint in HPTN 084: Comparison of Rates of Incident HIV Infections during Randomised Phase (mITT, extended retrospective virologic testing)

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

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

Findings from pre-planned subgroup analyses were consistent with the overall protective effect, with a lower rate of incident HIV-1 infections observed for participants randomised to the cabotegravir group compared with participants randomised to the TDF/FTC group (see Table 8).

Table 8 Rate of incident HIV-1 infection by subgroup in HPTN 084 (mITT, extended retrospective virologic testing)

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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Apretude injections in children under the age of 12 years, in the prevention of HIV-1 infection.

5.2 Pharmacokinetic properties

Cabotegravir pharmacokinetics is similar between healthy and HIV-infected subjects. The pharmacokinetic 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 9 Pharmacokinetic parameters following cabotegravir orally once daily, and initiation and every 2 month continuation intramuscular injections in adults

Dosing Phase	Dose Regimen	Geometric Mean (5th, 95th Percentile)[1]		
		$AUC_{(0\text{-}tau)}$[2] (µg•h/mL)	C_{max} (µg/mL)	C_{tau} (µg/mL)
Oral lead-in[3] (Optional)	30 mg once daily	145 (93.5, 224)	8.0 (5.3, 11.9)	4.6 (2.8, 7.5)
Initial injection[4]	600 mg IM Initial Dose	1591 (714, 3245)	8.0 (5.3, 11.9)	1.5 (0.65, 2.9)
Every 2-month injection[5]	600 mg IM Every 2-month	3764 (2431, 5857)	4.0 (2.3, 6.8)	1.6 (0.8, 3.0)

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

[2] 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.

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

[4] 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).

[5] Pharmacokinetic parameter values represent steady state.

Absorption

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 intramuscular (IM) injection (see Table 9). Cabotegravir has been detected in plasma up to 52 weeks or longer after administration of a single injection.

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 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.

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

Biotransformation

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 medicinal product 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 glucuronide 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).

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

Elimination

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 reflects elimination from the injection site into the systemic circulation. The apparent CL/F was 0.151 L/h.

Linearity/non-linearity

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.

Polymorphisms

In a meta-analysis of healthy and HIV-infected participant trials, HIV-infected participants with UGT1A1 genotypes conferring poor cabotegravir metabolism had a 1.2-fold mean increase in steady-state cabotegravir AUC, C_{max}, and C_{tau} following long-acting injection administration compared with participants with genotypes associated with normal metabolism via UGT1A1. These differences are not considered clinically relevant. No dose adjustment is required in individuals with UGT1A1 polymorphisms.

Special 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 dose adjustment is required on the basis of race.

Body Mass Index (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 dose adjustment is needed for adolescents weighing ≥ 35 kg.

Table 10 Predicted pharmacokinetic parameters following cabotegravir orally once daily, and initiation and every 2 month continuation intramuscular injections in adolescents Participants aged 12 to less than 18 years (≥ 35 kg)

Dosing Phase	Dose Regimen	Geometric Mean (5th, 95th Percentile)[1]		
		$AUC_{(0\text{-}tau)}$[2] (µg•h/mL)	C_{max} (µg/mL)	C_{tau} (µg/mL)
Oral lead-in[3] (Optional)	30 mg once daily	193 (106, 346)	14.4 (8.02,25.5)	5.79 (2.48,12.6)
Initial injection[4]	600 mg IM Initial Dose	2123 (881, 4938)	11.2 (5.63,21.5)	1.84 (0.64,4.52)
Every 2-month injection[5]	600 mg IM Every 2-month	4871 (2827, 8232)	7.23 (3.76,14.1)	2.01 (0.64,4.73)

[1] Pharmacokinetic (PK) parameter values were based on population PK model simulations in a virtual HIV-1 infected adolescent population weighing 35-156 kg.
[2] 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.
[3] Oral lead-in pharmacokinetic parameter values represent steady-state.
[4] 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.
[5] Pharmacokinetic parameter values represent steady state.

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 dose 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 dose 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.

5.3 Preclinical safety data

Carcinogenesis and 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 studies

No effect on male or female fertility was observed in rats treated with cabotegravir at oral doses up to 1000 mg/kg/day (> 20 times the exposure in humans at the maximum recommended dose (MRHD) of 30 mg/day orally).

In an embryo-foetal development study there were no adverse developmental outcomes following oral administration of cabotegravir to pregnant rabbits up to a maternal toxic dose of 2,000 mg/kg/day

(0.66 times the exposure in humans at the oral MRHD) or to pregnant rats at doses up to 1000 mg/kg/day (> 30 times the exposure in humans at the oral MRHD). In rats, alterations in foetal growth (decreased body weights) were observed at oral dose of 1,000 mg/kg/day. Studies in pregnant rats showed that cabotegravir crosses the placenta and can be detected in foetal tissue.

In rat pre- and post-natal (PPN) studies cabotegravir reproducibly induced a delayed onset of parturition, and an increase in the number of stillbirths and neonatal mortalities at oral dose of 1,000 mg/kg/day (> 30 times the exposure in humans at the oral MRHD). At a lower dose of 5 mg/kg/day (approximately 10 times the exposure in humans at the oral MRHD) cabotegravir was not associated with delayed parturition or neonatal mortality. In rabbit and rat studies there was no effect on survival when foetuses were delivered by caesarean section. Given the exposure ratio, the relevance to humans is unknown.

Repeated dose toxicity

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 reactions in rats or monkeys given cabotegravir orally at doses up to 1,000 mg/kg/day or 500 mg/kg/day, respectively.

In a 14 day and 28 day monkey toxicity study, gastro-intestinal (GI) effects (body weight loss, emesis, loose/watery faeces, and moderate to severe dehydration) were observed and were the result of local medicinal product administration (oral) 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 reactions noted and no new target organ toxicities (at exposures > 49 times the exposure in humans at the MRHD of 600 mg IM dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

3 years

Shelf life of suspension in syringe

Chemical and physical in-use stability has been demonstrated for 2 hours at 25°C.
Once the suspension has been drawn into the syringe, the injection should be used as soon as possible, but may be stored for up to 2 hours. If 2 hours are exceeded, the medicinal product, syringe and needle must be discarded. From a microbiological point of view, the product should be used immediately. If

not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Unopened vial

Do not freeze.

Suspension in syringe

Do not store above 25°C (see section 6.3).

6.5 Nature and contents of container and special equipment for use, administration

Brown 3 mL type I glass vial, with bromobutyl rubber stopper and a grey aluminium overseal with an orange plastic flip-cap.

Pack sizes of 1 vial or 25 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Hold the vial firmly and vigorously shake for a full 10 seconds. Invert the vial and check the resuspension. It should look uniform. If the suspension is not uniform, shake the vial again. It is normal to see small air bubbles.

Full instructions for use and handling of Apretude injection are provided in the package leaflet (see Instructions for Use).

7. MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H,
3811 LP Amersfoort
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1760/002
EU/1/23/1760/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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

1. NAME OF THE MEDICINAL PRODUCT

Apretude 30 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains cabotegravir sodium equivalent to 30 mg cabotegravir.

Excipient with known effect

Each film-coated tablet contains 155 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

White, oval, film-coated tablets (approximately 8.0 mm by 14.3 mm), debossed with 'SV CTV' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Apretude is indicated in combination with safer sex practices for short term pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in high-risk adults and adolescents, weighing at least 35 kg (see section 4.2 and section 4.4). Apretude tablets may be used as:

- oral lead-in to assess tolerability of Apretude prior to administration of long acting cabotegravir injection.
- oral PrEP for individuals who will miss planned dosing with cabotegravir injection.

4.2 Posology and method of administration

Apretude should be prescribed by a healthcare professional experienced in the management of HIV PrEP.

Individuals must be tested for HIV-1 prior to initiating cabotegravir (see section 4.3). A combined antigen/antibody test as well as an HIV-RNA-based test should both be negative. Prescribers are advised to perform both tests, even if the result of the HIV-RNA-based test will become available after oral administration. If a combined testing strategy including both tests is not available, testing should follow local guidelines.

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.

The healthcare provider and individual may decide to use cabotegravir tablets as an oral lead-in prior to the initiation of Apretude injection to assess tolerability (see Table 1) or may proceed directly to Apretude injections (see Apretude injection SmPC).

Posology

Oral lead-in
When used for oral lead-in, cabotegravir tablets should be taken for approximately one month (at least 28 days) to assess tolerability to cabotegravir (see section 4.4). One Apretude 30 mg tablet should be taken, once daily with or without food.

Table 1 Recommended dosing schedule

	Oral lead-in
Medicinal product	**During month 1**
Apretude	30 mg once daily

Oral dosing for missed injections of cabotegravir.
If a delay of more than 7 days from a scheduled injection visit cannot be avoided, Apretude 30 mg tablets may be used once daily to replace one scheduled injection visit. The first dose of oral therapy should be taken two months (+/- 7 days) after the last injection of cabotegravir. For oral PrEP durations greater than two months, an alternative PrEP regimen is recommended.

Injection dosing should be resumed on the day oral dosing completes or within 3 days, thereafter (see Apretude injection SmPC).

Missed doses
If the individual misses a dose of Apretude tablets, the individual should take the missed dose as soon as possible, providing the next dose is not due within 12 hours. If the next dose is due within 12 hours, the individual should not take the missed dose and simply resume the usual dosing schedule.

Vomiting
If an individual vomits within 4 hours of taking Apretude tablets, another Apretude tablet should be taken. If an individual vomits more than 4 hours after taking Apretude tablets, the individual does not need to take another tablet until the next regularly scheduled dose.

Special populations

Elderly
No dose adjustment is required in elderly individuals. There are limited data available on the use of cabotegravir in individuals aged 65 years and over (see section 5.2).

Hepatic impairment
No dose adjustment is required in individuals with mild or moderate hepatic impairment (Child-Pugh score A or B). Cabotegravir has not been studied in individuals with severe hepatic impairment (Child-Pugh score C [see section 5.2]).
If administered in an individual with severe hepatic impairment, cabotegravir should be used with caution.

Renal impairment
No dose adjustment is required in individuals with mild to severe renal impairment (CrCL < 30 mL/min and not on dialysis [see section 5.2]). Cabotegravir has not been studied in individuals with end-stage renal disease on renal replacement therapy. As cabotegravir is greater than 99% protein bound, dialysis is not expected to alter exposures of cabotegravir. If administered in an individual on renal replacement therapy, cabotegravir should be used with caution.

Paediatric population
The safety and efficacy of cabotegravir in children and adolescents weighing less than 35 kg have not been established. No data are available.

Method of administration

Oral use.

4.3 Contraindications

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

Individuals with an unknown or positive HIV-1 status (see sections 4.2 and 4.4).

Concomitant use with rifampicin, rifapentine, carbamazepine, oxcarbazepine, phenytoin or phenobarbital (see section 4.5).

4.4 Special warnings and precautions for use

Overall HIV-1 infection prevention strategy

Apretude may not always be effective in preventing HIV-1 infection (see section 5.1). Cabotegravir concentrations associated with significant antiviral activity (> 4x Protein Adjusted-Inhibitory Concentration, PA-IC90, see section 5.2) are achieved and maintained within hours after initiation of oral lead-in. The exact time from initiation of Apretude for HIV-1 PrEP to maximal protection against HIV-1 infection is unknown.

Apretude should be used for PrEP as part of an overall HIV-1 infection prevention strategy including the use of other HIV-1 prevention measures (e.g. knowledge of HIV1 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 section 4.3). Individuals should be re-confirmed to be HIV-negative at frequent intervals. A combined antigen/antibody test as well as an HIV-RNA-based test should both be negative. Prescribers are advised to perform both tests, even if the result of the HIV-RNA-based test will become available after oral administration. If a combined testing strategy including both tests is not available, testing should follow local guidelines while taking Apretude.

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 cabotegravir if an individual acquires HIV-1 either before, or while taking or following discontinuation of cabotegravir. To minimise this risk, it is essential to confirm HIV-1 negative status at frequent intervals. A combined antigen/antibody test as well as an HIV-RNA-based test should both be negative. Prescribers are advised to perform both tests, even if the result of the HIV-RNA-based test will become available after oral administration. If a combined testing strategy including both tests is not available, testing should follow local guidelines. Individuals who are diagnosed with HIV-1 should immediately begin anti-retroviral therapy (ART).

Apretude alone does not constitute a complete regimen for the treatment of HIV-1 and HIV-1 resistance mutations have emerged in some individuals with undetected HIV-1 infection who were only taking Apretude.

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

Importance of adherence

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

Hypersensitivity reactions

Hypersensitivity reactions have been reported in association with integrase inhibitors including cabotegravir. These reactions were characterised by rash, constitutional findings and sometimes organ dysfunction, including liver injury. Apretude and other suspected medicinal products should be discontinued 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 sections 4.2 and 4.8).

Hepatoxicity

Hepatotoxicity has been reported in a limited number of individuals receiving cabotegravir with or without known pre-existing hepatic disease (see section 4.8). Administration of cabotegravir oral lead-in was used in clinical studies to help identify individuals who may be at risk of hepatotoxicity.

Clinical and laboratory monitoring are recommended and Apretude tablets should be discontinued if hepatotoxicity is confirmed, and individuals managed as clinically indicated.

Adolescents

Suicidal ideation and suicide attempt have been reported with cabotegravir, particularly in those with pre-existing psychiatric illness (see section 4.8). Although clinical studies did not show an increased incidence of psychiatric illness in adolescents compared to adult subjects, given the vulnerability of the adolescent population, adolescents should be counselled before prescribing, and periodically while receiving Apretude, and managed as clinically indicated.

Interactions with medicinal products

Caution should be given to prescribing Apretude tablets with medicinal products that may reduce its exposure (see section 4.5).

Polyvalent cation containing antacids are recommended to be taken at least 2 hours before and 4 hours after taking Apretude tablets (see section 4.5).

Excipients

Individuals with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other agents on the pharmacokinetics of cabotegravir

Cabotegravir is primarily metabolised by uridine diphosphate glucuronosyl transferase (UGT) 1A1 and to a lesser extent by UGT1A9. Medicinal products which are strong inducers of UGT1A1 or UGT1A9 are expected to decrease cabotegravir plasma concentrations leading to lack of efficacy (see section 4.3 and table 2 below). In poor metabolizers of UGT1A1, representing a maximum clinical UGT1A1 inhibition, the mean AUC, C_{max} and C_{tau} of oral cabotegravir increased by up to 1.5-fold (see section 5.2). No dosing adjustments for Apretude are recommended in the presence of UGT1A1 inhibitors.

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

Effect of cabotegravir on the pharmacokinetics of other medicinal products

In vivo, cabotegravir did not have an effect on midazolam, a cytochrome P450 (CYP) 3A4 probe. *In vitro*, cabotegravir did not induce CYP1A2, CYP2B6, or CYP3A4.

In vitro, cabotegravir inhibited the organic anion transporters (OAT) 1 (IC_{50}=0.81 μM) and OAT3 (IC_{50}=0.41 μM). Cabotegravir may increase the AUC of OAT1/3 substrates up to approximately 80% therefore caution is advised when co-dosing with narrow therapeutic index OAT1/3 substrate medicinal products (e.g. methotrexate).

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

The drug interaction data provided in Table 2 is obtained from studies with oral cabotegravir (increase is indicated as "↑", decrease as "↓", no change as "↔", area under the concentration versus time curve as "AUC", maximum observed concentration as "C_{max}", concentration at end of dosing interval as "Cτ").

Table 2 Drug interactions

Medicinal products by therapeutic areas	**Interaction** Geometric mean change (%)	**Recommendations concerning co-administration**
HIV-1 Antiviral medicinal products		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine	Cabotegravir ↔ AUC ↑ 1% C_{max} ↑ 4% Cτ ↔ 0%	Etravirine did not significantly change cabotegravir plasma concentration. No dose adjustment of Apretude tablets is necessary.
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 Apretude or rilpivirine is necessary when co-administered.
Anticonvulsants		
Carbamazepine Oxcarbazepine	Cabotegravir ↓	Metabolic inducers may significantly decrease cabotegravir plasma concentrations, concomitant use is contraindicated (see section 4.3).

Phenytoin Phenobarbital		
Antacids		
Antacids (e.g. magnesium, aluminium, or calcium)	Cabotegravir ↓	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 (see section 4.4).
Antimycobacterials		
Rifampicin	Cabotegravir ↓ AUC ↓ 59% C_{max} ↓ 6%	Rifampicin significantly decreased cabotegravir plasma concentration which is likely to result in loss of therapeutic effect. Dosing recommendations for co-administration of Apretude with rifampicin have not been established and co-administration of Apretude with rifampicin is contraindicated (see section 4.3).
Rifapentine	Cabotegravir ↓	Rifapentine may significantly decrease cabotegravir plasma concentrations, concomitant use is contraindicated (see section 4.3).
Rifabutin	Cabotegravir ↓ AUC ↓ 21% C_{max} ↓ 17% Cτ ↓ 26%	Rifabutin did not significantly change cabotegravir plasma concentration. No dose adjustment is required.
Oral Contraceptives		
Ethinyl estradiol (EE) and Levonorgestrel (LNG)	EE ↔ AUC ↑ 2% C_{max} ↓ 8% Cτ ↔ 0% LNG ↔ AUC ↑ 12% C_{max} ↑ 5% Cτ ↑ 7%	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 tablets.

Paediatric population
Interaction studies have only been performed in adults

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

If a woman plans a pregnancy, the benefits and the risks of starting/continuing PrEP with Apretude should be discussed.

Pregnancy

There are a limited amount of data from the use of cabotegravir in pregnant women. The effect of cabotegravir on pregnancy is unknown.

Cabotegravir was not teratogenic when studied in pregnant rats and rabbits but exposures higher than the therapeutic dose showed reproductive toxicity in animals (see section 5.3). The relevance to human pregnancy is unknown.

Apretude tablets are not recommended during pregnancy unless the expected benefit justifies the potential risk to the foetus.

Breast-feeding

It is expected that cabotegravir will be secreted into human milk based on animal data, although this has not been confirmed in humans.

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

Fertility

There are no data on the effects of cabotegravir on human male or female fertility. Animal studies indicate no effects of cabotegravir on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Individuals should be informed that dizziness, somnolence and fatigue have been reported during treatment with Apretude tablets. The clinical status of the individual and the adverse reaction profile of Apretude tablets should be borne in mind when considering the individual's ability to drive or operate machinery.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions in HPTN 083 were: headache (17%) and diarrhoea (14%).

The most frequently reported adverse reactions in HPTN 084 were: headache (23%) and transaminase increased (19%).

Tabulated list of adverse reactions

Adverse reactions for cabotegravir were identified from the Phase III clinical studies; HPTN 083 and HPTN 084; and post-marketing data. 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 3231 person years. In HPTN 084, the median time on blinded study product was 64 weeks and 1 day (1 day to 153 weeks and 1 day), with a total exposure on cabotegravir of 2009 person years.

The adverse reactions identified for cabotegravir in adults and adolescents are listed in Table 3 by system organ class and frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000).

Table 3 Tabulated list of adverse reactions

MedDRA System organ class (SOC)	Frequency category	Adverse reactions
Immune system disorders	Uncommon	Hypersensitivity*[4]
Psychiatric disorders	Common	Abnormal dreams Insomnia Depression

		Anxiety
	Uncommon	Suicide attempt[4]; Suicidal ideation[4] (particularly in individuals with a pre-existing psychiatric illness)
Nervous system disorders	Very common	Headache
	Common	Dizziness
	Uncommon	Somnolence
Gastrointestinal disorders	Very common	Diarrhoea
	Common	Nausea Abdominal pain[1] Flatulence Vomiting
Hepatobiliary Disorders	Uncommon	Hepatotoxicity
Skin and subcutaneous tissue disorders	Common	Rash[2]
	Uncommon	Urticaria*[4] Angioedema*[4]
Musculoskeletal and connective tissue disorders	Common	Myalgia
General disorders and administrative site conditions	Very common	Pyrexia[3]
	Common	Fatigue Malaise
Investigations	Very common	Transaminase increased
	Uncommon	Weight increased Blood bilirubin increased

[1]Abdominal pain includes the following grouped MedDRA preferred terms: upper abdominal pain and abdominal pain.
[2]Rash includes the following grouped MedDRA preferred terms: rash, rash erythematous, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic.
[3]Pyrexia includes the following grouped MedDRA preferred terms: pyrexia and feeling hot.
[4]This adverse reaction was identified through post-marketing reporting. The frequency category is based on individuals exposed to cabotegravir in randomised clinical studies.
*Please refer to section 4.4

Description of selected adverse reactions

Weight increased
At the week 41 and week 97 timepoints in HPTN 083, participants who received cabotegravir gained a median of 1.2 kg (Interquartile Range [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 Week 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 reactions 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.

Adolescents

Based on data from two open-label multicenter clinical trials in 64 HIV-uninfected, at-risk adolescents (below 18 years of age and weighing ≥ 35 kg at enrolment) receiving cabotegravir, no new safety issues were identified in adolescents compared with the safety profile established in adults receiving cabotegravir for HIV-1 PrEP in HPTN 083 and HPTN 084.

Based on data from the Week 16 analysis of the MOCHA study in 23 HIV-infected adolescents (aged at least 12 years and weighing ≥ 35 kg) receiving background combination anti-retroviral therapy, no new safety concerns were identified in adolescents with the addition of oral cabotegravir followed by injectable cabotegravir (n=8) when compared with the safety profile established with cabotegravir in adults (see section 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific treatment for Apretude overdose. If overdose occurs, the individual should be treated supportively with appropriate monitoring as necessary.

Cabotegravir is known to be highly protein bound in plasma; therefore, dialysis is unlikely to be helpful in removal of medicinal product from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 nM in 293T cells and 0.57 nM in MT-4 cells. Cabotegravir demonstrated antiviral activity in cell culture against a panel of 24 HIV-1 clinical isolates (three in each group of M clades A, B, C, D, E, F, and G, and 3 in group O) with EC_{50} values ranging from 0.02 nM to 1.06 nM for HIV-1. Cabotegravir EC_{50} values against three HIV-2 clinical isolates ranged from 0.10 nM to 0.14 nM.

Antiviral Activity in combination with other antiviral medicinal products
No medicinal products 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).

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/Q148R resulted in a 12-fold decrease in susceptibility and 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. Other multiple mutants, which resulted in a FC between 5 and 10, are: T66K/L74M (FC=6.3), G140S/Q148K (FC=5.6), G140S/Q148H (FC=6.1) and E92Q/N155H (FC=5.3).

Resistance in vivo

HPTN 083
In the primary analysis of the HPTN 083 study, there were 13 incident infections on the cabotegravir arm and 39 incident infections on the tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) arm. In the cabotegravir arm, 5 incident infections occurred when receiving cabotegravir PrEP injections, of which 4 participants received on-time injections and 1 participant had one injection off-schedule. Five incident infections occurred ≥ 6 months after the last dose of cabotegravir PrEP. Three incident infections occurred during the oral lead-in period.

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

None of the 5 participants who were infected after prolonged interruption from cabotegravir administration had INSTI resistance mutations. Neither genotype nor phenotype could be generated

for one of the 5 participants, with just 770 copies/mL HIV-1 RNA. Integrase phenotype could not be generated for one of the remaining 4 participants. The remaining 3 participants retained susceptibility to all INSTIs.

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

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

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

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

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

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

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

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

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

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

<u>Clinical efficacy and safety</u>

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 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 medicinal products up to Week 153.

At baseline, the median age of participants was 26 years, 12% were transgender women, 72% were non-white, 67% were < 30 years and < 1% were over 60 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 (corrected for early stopping). The primary analysis demonstrated the superiority of cabotegravir compared to TDF/FTC with a 66% reduction in the risk of acquiring incident HIV infection, hazard ratio (95% CI) 0.34 (0.18, 0.62); further testing revealed one of the infections on cabotegravir to be prevalent then yielding a 69% reduction in the risk of incident infection relative to TDF/FTC (see Table 4).

Table 4 Primary Efficacy Endpoint: Comparison of Rates of Incident HIV Infections during Randomized Phase in HPTN 083 (mITT, extended retrospective virologic testing)

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

[1]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 on cabotegravir was determined to be a prevalent infection. The original hazard ratio (95% CI) from the primary analysis is 0.34 (0.18, 0.62).

Findings from all subgroup analyses were consistent with the overall protective effect, with a lower rate of incident HIV-1 infections observed for participants randomised to the cabotegravir group compared with participants randomised to the TDF/FTC group (see Table 5).

Table 5 Rate of incident HIV-1infection by subgroup in HPTN 083 (mITT, extended retrospective virologic testing)

Subgroup	**Cabotegravir incidence per 100 person years**	**Cabotegravir person years**	**TDF/FTC incidence per 100 person years**	**TDF/FTC person years)**	**HR (95% CI)**
Age					

< 30 years	0.47	2110	1.66	1987	0.29 (0.15, 0.59)
≥ 30 years	0.18	1101	0.50	1206	0.39 (0.08, 1.84)
Gender					
MSM	0.35	2836	1.14	2803	0.32 (0.16, 0.64)
TGW	0.54	371	1.80	389	0.34 (0.08, 1.56)
Race (US)					
Black	0.58	691	2.28	703	0.26 (0.09, 0.76)
Non-Black	0.00	836	0.50	801	0.11 (0.00, 2.80)
Region					
US	0.26	1528	1.33	1504	0.21 (0.07, 0.60)
Latin America	0.49	1021	1.09	1011	0.47 (0.17, 1.35)
Asia	0.35	570	1.03	581	0.39 (0.08, 1.82)
Africa	1.08	93	2.07	97	0.63 (0.06, 6.50)

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

HPTN 084

In HPTN 084, a superiority study, 3224 cisgender women were randomised 1:1 and received either cabotegravir (n=1614) or TDF/FTC (n=1610) as blinded study medicinal products 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, with a maximum age of 45 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 (corrected for early stopping). The primary analysis demonstrated the superiority of cabotegravir compared to TDF/FTC with an 88% reduction in the risk of acquiring incident HIV-1 infection hazard ratio (95% CI) 0.12 (0.05, 0.31); further testing revealed 1 of the infections on cabotegravir to be prevalent then yielding a 90% reduction in the risk of HIV-1 incident infection relative to TDF/FTC (see Table 6).

Table 6 Primary Efficacy Endpoint in HPTN 084: Comparison of Rates of Incident HIV Infections during Randomised Phase (mITT, extended retrospective virologic testing)

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

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

Findings from pre-planned subgroup analyses were consistent with the overall protective effect, with a lower rate of incident HIV-1 infections observed for participants randomised to the cabotegravir group compared with participants randomised to the TDF/FTC group (see Table 7).

Table 7 Rate of incident HIV-1infection by subgroup in HPTN 084 (mITT, extended retrospective virologic testing)

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

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Apretude tablets in children under the age of 12 years, in the prevention of HIV-1 infection.

5.2 Pharmacokinetic properties

Cabotegravir pharmacokinetics is comparable between healthy and HIV-infected subjects, with the same ADME observed across all populations. The PK variability of cabotegravir is moderate. In Phase I studies in healthy subjects, between-subject CVb% for AUC, C_{max}, and C_{tau} ranged from 26 to 34% across healthy subject studies. Within-subject variability (CVw%) is lower than between-subject variability.

Table 8 Pharmacokinetic parameters following cabotegravir orally once daily in adults

Dosing Phase	Dose Regimen	Geometric Mean (5th, 95th Percentile)[1]		
		$AUC_{(0\text{-}tau)}$[2] (mcg•h/mL)	C_{max} (mcg/mL)	C_{tau} (mcg/mL)
Oral lead-in[3]	30 mg once daily	145 (93.5, 224)	8.0 (5.3, 11.9)	4.6 (2.8, 7.5)

[1] a Pharmacokinetic (PK) parameter values were based on individual post-hoc estimates from population PK models for subjects in Phase III treatment studies.
[2] tau is dosing interval: 24 hours for oral administration.
[3] Oral lead-in pharmacokinetic parameter values represent steady-state.

Absorption

Cabotegravir is rapidly absorbed following oral administration, with median T_{max} at 3 hours post dose for tablet formulation. With once daily dosing, pharmacokinetic steady-state is achieved by 7 days. Cabotegravir may be administered with or without food. Bioavailability of cabotegravir is independent of meal content: high fat meals increased cabotegravir $AUC_{(0\text{-}\infty)}$ by 14% and increased C_{max} by 14% relative to fasted conditions. These increases are not clinically significant.

The absolute bioavailability of cabotegravir has not been established.

Distribution

Cabotegravir is highly bound (> 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 bioavailability, suggest some distribution of cabotegravir to the extracellular space.

Cabotegravir is present in the female and male genital tract, following a single 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.

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

Biotransformation

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 medicinal product 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 glucuronide 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).

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

Elimination

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

Polymorphisms
In a meta-analysis of healthy and HIV-infected subject trials, subjects with UGT1A1 genotypes conferring poor cabotegravir metabolism had a 1.3- to 1.5-fold mean increase in steady-state cabotegravir AUC, C_{max}, and C_{tau} compared with subjects with genotypes associated with normal metabolism via UGT1A1. These differences are not considered clinically relevant. No dose adjustment is required in subjects with UGT1A1 polymorphisms.

Special populations

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

Body Mass Index (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 dose adjustment is needed for adolescents weighing ≥ 35 kg.

Table 9 Predicted pharmacokinetic parameters following cabotegravir orally once daily in adolescents aged 12 to less than 18 years (≥ 35 kg)

Dosing Phase	Dose 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)

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

The pharmacokinetics and dosing recommendations of cabotegravir in paediatric individuals less than 12 years of age or weighing less than 35 kg 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 dose 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 dose 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.

5.3 Preclinical safety data

Carcinogenesis and 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 studies

No effect on male or female fertility was observed in rats treated with cabotegravir at oral doses up to 1000 mg/kg/day (> 20 times the exposure in humans at the maximum recommended dose (MRHD) of 30 mg/day orally).

In an embryo-foetal development study there were no adverse developmental outcomes following oral administration of cabotegravir to pregnant rabbits up to a maternal toxic dose of 2,000 mg/kg/day (0.66 times the exposure in humans at the oral MRHD) or to pregnant rats at doses up to 1000 mg/kg/day (> 30 times the exposure in humans at the oral MRHD). In rats, alterations in foetal growth (decreased body weights) were observed at oral dose of 1,000 mg/kg/day. Studies in pregnant rats showed that cabotegravir crosses the placenta and can be detected in foetal tissue.

In rat pre- and post-natal (PPN) studies cabotegravir reproducibly induced a delayed onset of parturition, and an increase in the number of stillbirths and neonatal mortalities at oral dose of 1,000 mg/kg/day (> 30 times the exposure in humans at the oral MRHD). A lower dose of 5 mg/kg/day (approximately 10 times the exposure in humans at the oral MRHD) cabotegravir was not associated with delayed parturition or neonatal mortality. In rabbit and rat studies there was no effect on survival when foetuses were delivered by caesarean section. Given the exposure ratio, the relevance to humans is unknown.

Repeated dose toxicity

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 reactions in rats or monkeys given cabotegravir orally at doses up to 1,000 mg/kg/day or 500 mg/kg/day, respectively.

In a 14 day and 28 day monkey toxicity study, gastro-intestinal (GI) effects (body weight loss, emesis, loose/watery faeces, and moderate to severe dehydration) were observed and was the result of local medicinal product administration (oral) 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 reactions noted and no new target organ toxicities (at exposures > 49 times the exposure in humans at the MRHD of 600 mg IM dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose Monohydrate
Microcrystalline cellulose (E460)
Hypromellose (E464)
Sodium starch glycolate
Magnesium stearate

Tablet coating
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol (E1521)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

White HDPE (high density polyethylene) bottles closed with polypropylene child-resistant closure, with a polyethylene faced induction heat seal liner. Each bottle contains 30 film-coated tablets.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H,
3811 LP Amersfoort
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1760/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Prolonged-release suspension for injection
GlaxoSmithKline Manufacturing S.p.A.
Strada Provinciale Asolana 90
Torrile
PR
43056
Italy

Film-coated tablets
Glaxo Wellcome S.A.
Avenida De Extremadura 3
Aranda De Duero
Burgos
09400
Spain

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of APRETUDE in a Member State, the Marketing Authorization Holder (MAH) must agree the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority.

To supplement routine risk minimisation activities, the educational materials are aimed at mitigating the risks of HIV seroconversion, the development of resistance and medication errors, including treatment noncompliance in individuals taking APRETUDE by increasing awareness of these risks and providing guidance information for prescribers and individuals at risk.

The MAH shall ensure that in each Member State where APRETUDE is marketed, all healthcare professionals and individuals at risk who are expected to prescribe and/or use APRETUDE have access to/are provided with the following educational package, which comprises of the following:

  - Guide for prescribers
  - Guide for individuals at risk
  - Prescribers' checklist
  - Reminder Card for individuals at risk

Key messages of the additional risk minimization measures for APRETUDE for Pre Exposure Prophylaxis (PrEP) are outlined below.

Guide for prescribers shall contain the following elements:

- Details on use of APRETUDE for pre-exposure prophylaxis as part of an overall HIV-1 infection prevention strategy including the use of other HIV-1 prevention measures (such as e. g. knowledge of HIV-1 status, regular testing for other sexually transmitted infections, condom use).
- Reminder that APRETUDE should only be used to reduce the risk of acquiring HIV-1 in individuals confirmed to be HIV negative.
- Individuals should be re-confirmed to be HIV-negative at each injection visit 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.
- Details on the potential risk of developing resistance to APRETUDE if an individual acquires HIV-1 either before, or while taking APRETUDE, or following discontinuation of APRETUDE.
- Importance of commencing antiretroviral therapy (ART) in instances of HIV-1 acquisition in individuals who are suspected or confirmed with a diagnosis of HIV-1.
- APRETUDE does not constitute a complete ART regimen for the treatment of HIV 1 and HIV resistance mutations have emerged in individuals with undetected HIV 1 infection who were only taking APRETUDE.
- Consideration of alternative forms of non-long-acting PrEP following discontinuation of APRETUDE injection for those individuals that remain at risk of HIV acquisition, which should be initiated within 2 months of the final APRETUDE injection.

- Importance of counselling individuals at risk periodically to strictly adhere to the recommended APRETUDE dosing schedule/appointments to reduce the risk of HIV-1 acquisition and the potential development of resistance.

Prescriber checklist shall provide reminders for evaluations and counselling at initial and follow up visit, including:

- Test to re-confirm HIV-1 negative status at each injection visit to minimise the risk of developing resistance to APRETUDE.
- To reconfirm HIV-1 status, if clinical symptoms consistent with acute viral infection are present and recent (< 1 month) exposures to HIV-1 are suspected.
- To commence antiretroviral therapy (ART) in instances of HIV-1 acquisition in individuals who are suspected or confirmed with a diagnosis of HIV-1.
- To discuss and reiterate the importance of adherence to the recommended APRETUDE dosing schedule/appointments to reduce the risk of HIV-1 acquisition and the potential development of resistance.
- To summarise and restate that APRETUDE for pre-exposure prophylaxis is part of an overall HIV-1 infection prevention strategy including the use of other HIV-1 prevention measures (such as e. g. knowledge of HIV-1 status, regular testing for other sexually transmitted infections, condom use).
- To consider alternative forms of non-long-acting PrEP following discontinuation of APRETUDE injection for those individuals that remain at risk of HIV acquisition, which should be initiated within 2 months of the final APRETUDE injection.

Guide for Individuals at risk shall contain the following elements:
Important information individuals at risk need to know before, while taking and after stopping APRETUDE including:

- Requirements that APRETUDE for pre-exposure prophylaxis is part of an overall HIV-1 infection prevention strategy including the use of other HIV-1 prevention measures (such as e. g. knowledge of HIV-1 status, regular testing for other sexually transmitted infections, condom use).
- Reminder that APRETUDE should only be used to reduce the risk of acquiring HIV-1 in individuals confirmed to be HIV negative.
- Individuals should be re-confirmed to be HIV-negative at each injection visit while taking APRETUDE for pre-exposure prophylaxis.
- Importance of informing physician if recent (< 1 month) exposures to HIV-1 are suspected.
- APRETUDE alone does not constitute a complete regimen for the treatment of HIV-1
- Ensure strict adherence to dosing regimen/appointment to reduce the risk of HIV 1 acquisition and the potential development of resistance.
- Consideration of alternative forms of non long-acting PrEP following discontinuation of APRETUDE if they remain at risk of HIV acquisition.

Reminder card for Individuals at risk shall contain the following elements:

- The date of the individuals next APRETUDE injection visit.
- Reminder of the importance of strict adherence to dosing regimen/appointment to reduce the risk of HIV 1 acquisition and the potential development of resistance.
- Reminder that APRETUDE pre-exposure prophylaxis is part of an overall HIV-1 infection prevention strategy including the use of other HIV-1 prevention measures (such as e. g. knowledge of HIV-1 status, regular testing for other sexually transmitted infections, condom use).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – 600 MG INJECTION

1. NAME OF THE MEDICINAL PRODUCT

Apretude 600 mg prolonged-release suspension for injection
cabotegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 600 mg cabotegravir.

3. LIST OF EXCIPIENTS

Also contains: mannitol, polysorbate 20, macrogol and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release suspension for injection
Contents: 1 vial
Contents: 25 vials
3 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Open here
For intramuscular use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not freeze

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H,
3811 LP Amersfoort
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1760/002
EU/1/23/1760/003

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL – 600 MG INJECTION

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Apretude 600 mg prolonged-release suspension for injection
cabotegravir
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON - TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Apretude 30 mg film-coated tablets
cabotegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose monohydrate (see package leaflet for further information)

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV
Van Asch van Wijckstraat 55H,
3811 LP Amersfoort
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1760/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

apretude

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL - TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Apretude 30 mg film-coated tablets
cabotegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1760/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Apretude 600 mg prolonged-release suspension for injection
cabotegravir

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

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

1. What Apretude is and what it is used for

Apretude contains the active ingredient cabotegravir. Cabotegravir belongs to a group of anti-retroviral medicines called integrase inhibitors (INIs).

Apretude is used to help prevent HIV-1 infection in adults and adolescents weighing at least 35kg who are at an increased risk of infection. This is called **pre-exposure prophylaxis: PrEP** (see section 2). It should be used in combination with safer sex practices, such as use of condoms.

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

Do not use Apretude:
- if you are **allergic** *(hypersensitive)* to cabotegravir or any of the other ingredients of this medicine (listed in section 6).
- If you are **HIV positive** or you do not know if you are HIV positive**.** Apretude can only help reduce your risk of getting HIV before you are infected. **You must get tested** to make sure you are HIV negative before taking Apretude.
- if you are **taking any of the following medicines**:
  - *carbamazepine, oxcarbazepine, phenytoin, phenobarbital* (medicines to treat epilepsy and prevent fits).
  - *rifampicin* or *rifapentine* (medicines to treat some bacterial infections such as tuberculosis).

These medicines reduce the effectiveness of Apretude by decreasing the amount of Apretude in the blood.
➔ If you think these apply to you, or if you are not sure, **tell your doctor**.

Warnings and precautions

Just taking Apretude may not prevent HIV infection.

HIV infection is spread by sexual contact with someone who is HIV positive or by transfer of infected blood. Although Apretude lowers the risk of becoming infected, you can still get HIV when taking this medicine.
Other measures should be taken to further reduce your risk of getting HIV:

- **Get tested** for other sexually transmitted infections when your doctor tells you to. These infections make it easier for HIV to infect you.
- **Use a condom** when you have oral or penetrative sex.
- Do not share or re-use needles or other injection or drug equipment.
- Do not share personal items that may have blood or body fluids on them (such as razor blades or toothbrushes).

Discuss with your doctor the additional precautions needed to further decrease the risk of getting HIV.

Reduce the risk of getting HIV:

There is a risk of resistance to this medicine if you get infected with HIV. This means that the medicine will not prevent HIV infection. To minimise this risk and to prevent infection with HIV, it is important that you:

- **attend your planned appointments** to receive your Apretude injection. Talk to your doctor if you are thinking about stopping injections, as this may increase your risk of getting a HIV infection. If you do stop, or are late receiving your Apretude injection, you will need to take other medicines or precautions to reduce your risk of getting HIV and possibly developing viral resistance.

- **get tested for HIV** when your doctor tells you. You must be regularly tested to make sure that you remain HIV-1 negative while taking Apretude.

- **tell your doctor straight away** if you think you have been infected with HIV (you may get a flu-like illness). They may want to do more tests to make sure you are still HIV negative.

Apretude injection is a long-acting medicine
If you stop Apretude injections, cabotegravir will remain in your system for up to a year or more after your last injection, **but this will not be enough to protect you from becoming infected.**

It is important that you attend your planned appointments to receive Apretude injection. Talk to your doctor if you are thinking about stopping PrEP.

Once you stop Apretude injections you may need to take other medicines to reduce the risk of getting HIV infection or use other safe sex precautions.

Liver problems
Let your doctor know if you have liver problems. You may need to be more closely monitored. *(See also 'Uncommon side effects' in section 4).*

Adolescents
Your doctor will discuss your mental health with you before and while receiving Apretude. Let your doctor know if you have mental health problems. You may need to be more closely monitored *(See also section 4).*

Allergic reaction
Apretude contains cabotegravir, which is an integrase inhibitor. Integrase inhibitors, including cabotegravir, can cause a serious allergic reaction known as a *hypersensitivity reaction.* You need to know about important signs and symptoms to look out for while you're receiving Apretude.

➔ **Read the information** in 'Possible side effects' in section 4 of this leaflet.

Children and adolescents
This medicine should not be used in children or adolescents weighing less than 35 kg, because it has not been studied in these individuals.

Other medicines and Apretude
Tell your doctor if you are taking, have recently taken or might take any other medicines, including other medicines bought without a prescription.

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

Apretude must not be given with some other medicines that may affect how well the medicine works . (see 'Do not use Apretude' in section 2). These include:
- *carbamazepine, oxcarbazepine, phenytoin, phenobarbital* (medicines to treat epilepsy and prevent fits).
- *rifampicin* or *rifapentine* (medicines to treat some bacterial infections such as tuberculosis).

Tell your doctor if you are taking:
- **rifabutin** (to treat some bacterial infections such as tuberculosis). You may need to receive Apretude injections more often.

➔ **Tell your doctor or pharmacist** if you are taking this medicine. Your doctor may decide that you need extra check-ups.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant**,** or are planning to have a baby, ask your doctor for advice before receiving this medicine.

Pregnancy
Apretude is not recommended during pregnancy. The effect of Apretude on pregnancy is unknown. Talk to your doctor: if you could get pregnant, if you are planning to have a baby or if you become pregnant. Do not stop attending your appointments to receive Apretude without consulting your doctor. Your doctor will consider the benefit to you and the risk to your baby of starting/continuing Apretude.

Breast-feeding
It is not known whether the ingredients of Apretude can pass into breast milk. However, cabotegravir, may pass into breast milk for up to 12 months after the last injection of Apretude. If you are breast-feeding, or thinking about breast-feeding, check with your doctor. Your doctor will consider the benefit and risks of breast-feeding for you and your baby.

Driving and using machines

Apretude can make you dizzy and have other side effects that make you less alert.
➔ **Don't drive or use machines** unless you are sure you're not affected.

3. How Apretude is given

This medicine is given as a 600 mg injection. A nurse or doctor will give you Apretude in the muscle of your buttock.

You must have a HIV-negative test before being given Apretude.

You will be given your first and second dose of Apretude one month apart. After the second dose, you will be given Apretude as a single injection once every 2 months.

Before starting treatment with Apretude injections, you and your doctor may decide first take cabotegravir tablets (called *oral lead-in* period). The lead-in period allows you and your doctor to assess whether it's appropriate to proceed with injections.
If you decide to start treatment with tablets:

- You should take one 30 mg Apretude tablet once a day, for approximately one month.
- You should have your first injection on the same day as your last tablet or no later than 3 days after.
- You will then receive an injection every 2 months

Injection Schedule for every 2 month dosing

When	Which medicine
First and second injection one month apart	Apretude 600 mg
Third injection onwards, every two months	Apretude 600 mg

If you are given too much Apretude injection
A doctor or nurse will give this medicine to you, so it is unlikely that you will be given too much. If you are worried, tell the doctor or nurse and you will be treated as needed.

If you miss a Apretude injection
Contact your doctor immediately to make a new appointment.
It is important that you keep your regular planned appointments to receive your injection and reduce the risk of getting HIV (see section 2). Talk to your doctor if you are thinking about stopping Apretude.

Talk to your doctor if you think you will not be able to receive your Apretude injection at the usual time. Your doctor may recommend you take cabotegravir tablets instead, until you are able to receive an Apretude injection again.

Don't stop receiving Apretude injections without advice from your doctor.
Keep receiving Apretude injections for as long as your doctor recommends. Don't stop unless your doctor advises you to. If you stop and you are still at risk of getting HIV your doctor must start you on another PrEP medicine within 2 months of your last Apretude injection.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

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

Allergic reactions

Apretude contains cabotegravir, which is an integrase inhibitor. Integrase inhibitors including cabotegravir can cause a serious allergic reaction known as a hypersensitivity reaction.

If you get any of the following symptoms:
- skin rash
- a high temperature (*fever*)
- lack of energy (*fatigue*)
- swelling, sometimes of the face or mouth (*angioedema*), causing difficulty in breathing
- muscle or joint aches.

➔ **See a doctor straight away.** Your doctor may decide to carry out tests to check your liver, kidneys or blood, and may tell you to stop taking Apretude.

Very common side effects (may affect more than 1 in 10 people)
- headache
- diarrhoea
- injection site reactions:
    - very common: pain and discomfort, a hardened mass (induration), or lump (nodule)
    - common: redness (erythema), itching (pruritus), swelling, warmth, numbness (aneasthesia) or bruising, (which may include discolouration or a collection of blood under the skin)
    - uncommon: collection of pus (abscess)
- feeling hot (pyrexia)
- changes in liver function (transaminase increased), as measured in blood tests

Common side effects (may affect up to 1 in 10 people)
- depression
- anxiety
- abnormal dreams
- difficulty in sleeping (insomnia)
- dizziness
- feeling sick (nausea)
- vomiting
- stomach pain (abdominal pain)
- wind (flatulence)
- rash
- muscle pain (myalgia)
- lack of energy (fatigue)
- generally feeling unwell (malaise)

Uncommon side effects (may affect up to 1 in 100 people)
- suicide attempt
- suicidal thoughts (particularly in individuals who have had depression or mental health problems before)
- allergic reaction (hypersensitivity)
- hives (urticaria)
- swelling (angioedema), sometimes of the face or mouth, which can cause difficulty in breathing
- feeling drowsy *(*somnolence*)*
- weight gain.
- feeling lightheaded, during or following an injection (vasovagal reactions). This may lead to fainting.

- liver damage (hepatotoxicity). Signs may include yellowing of the skin and the whites of the eyes, loss of appetite, itching, tenderness of the stomach, light-coloured stools or unusually dark urine.
- Increase in blood bilirubin, a breakdown product of red blood cells, as measured in blood tests.

Reporting of side effects
If you get any side effects, **talk to your doctor or nurse.** This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Apretude

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

The doctor or nurse is responsible for storing this medicine correctly.

Do not freeze.

6. Contents of the pack and other information

What Apretude contains
The active substance is cabotegravir.

Each 3 ml vial contains 600 mg cabotegravir.

The other ingredients are:
Mannitol (E421)
Polysorbate 20 (E432)
Macrogol (E1521)
Water for injections

What Apretude looks like and contents of the pack
Cabotegravir is a white to light pink suspension, presented in a brown glass vial with a rubber stopper and an aluminium overseal with a plastic flip-cap.

Marketing Authorisation Holder
ViiV Healthcare BV
Van Asch van Wijckstraat 55H,
3811 LP Amersfoort
Netherlands

Manufacturer
GlaxoSmithKline Manufacturing S.p.A.
Strada Provinciale Asolana 90
Torrile
PR
43056
Italy

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

België/Belgique/Belgien
ViiV Healthcare srl/bv
Tél/Tel: + 32 (0) 10 85 65 00

България
ViiV Healthcare BV
Тел.: + 359 80018205

Česká republika
GlaxoSmithKline, s.r.o.
Tel: + 420 222 001 111
cz.info@gsk.com

Danmark
GlaxoSmithKline Pharma A/S
Tlf: + 45 36 35 91 00
dk-info@gsk.com

Deutschland
ViiV Healthcare GmbH
Tel.: + 49 (0)89 203 0038-10
viiv.med.info@viivhealthcare.com

Eesti
ViiV Healthcare BV
Tel: + 372 8002640

Ελλάδα
GlaxoSmithKline Μονοπρόσωπη A.E.B.E.
Τηλ: + 30 210 68 82 100

España
Laboratorios ViiV Healthcare, S.L.
Tel: + 34 900 923 501
es-ci@viivhealthcare.com

France
ViiV Healthcare SAS
Tél.: + 33 (0)1 39 17 69 69
Infomed@viivhealthcare.com

Hrvatska
ViiV Healthcare BV
Tel: + 385 800787089

Ireland
GlaxoSmithKline (Ireland) Limited
Tel: + 353 (0)1 4955000

Ísland
Vistor hf.

Lietuva
ViiV Healthcare BV
Tel: + 370 80000334

Luxembourg/Luxemburg
ViiV Healthcare srl/bv
Belgique/Belgien
Tél/Tel: + 32 (0) 10 85 65 00

Magyarország
ViiV Healthcare BV
Tel.: + 36 80088309

Malta
ViiV Healthcare BV
Tel: + 356 80065004

Nederland
ViiV Healthcare BV
Tel: + 31 (0) 33 2081199

Norge
GlaxoSmithKline AS
Tlf: + 47 22 70 20 00

Österreich
GlaxoSmithKline Pharma GmbH
Tel: + 43 (0)1 97075 0
at.info@gsk.com

Polska
GSK Services Sp. z o.o.
Tel.: + 48 (0)22 576 9000

Portugal
VIIVHIV HEALTHCARE, UNIPESSOAL, LDA
Tel: + 351 21 094 08 01
viiv.fi.pt@viivhealthcare.com

România
ViiV Healthcare BV
Tel: + 40 800672524

Slovenija
ViiV Healthcare BV
Tel: + 386 80688869

Slovenská republika
ViiV Healthcare BV

Sími: +354 535 7000

Italia
ViiV Healthcare S.r.l
Tel: + 39 (0)45 7741600

Κύπρος
ViiV Healthcare BV Τηλ: + 357 80070017

Latvija
ViiV Healthcare BV
Tel: + 371 80205045

Tel: + 421 800500589

Suomi/Finland
GlaxoSmithKline Oy
Puh/Tel: + 358 (0)10 30 30 30

Sverige
GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

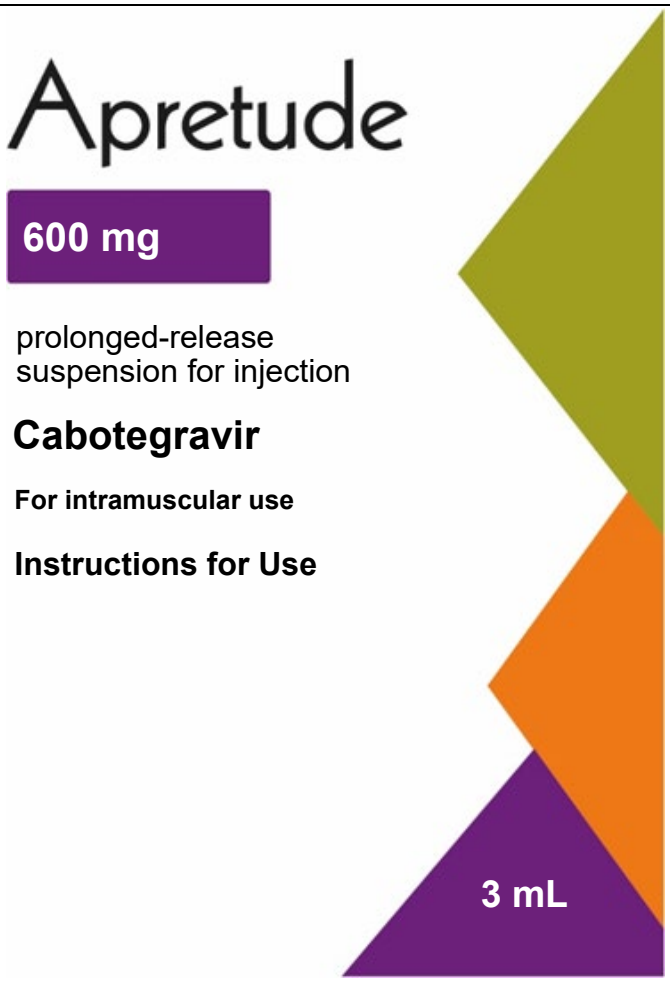
United Kingdom (Northern Ireland)
ViiV Healthcare BV
Tel: + 44 (0)800 221441
customercontactuk@gsk.com

This leaflet was last revised in {**MM/YYYY**}

Other sources of information

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

The following information is intended for healthcare professionals only:



Overview

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

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

Cabotegravir 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.

To prepare the injection

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

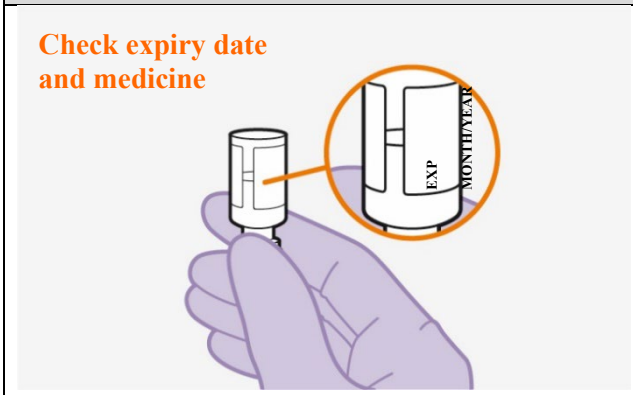
To administer the injection
• 1 additional Luer-Lock needle (use safety needle if available) of 23 gauge, 1.5 inches Consider the patient's build and use medical judgment to select an appropriate injection needle length.

You will also need

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

Preparation

1. Inspect vial



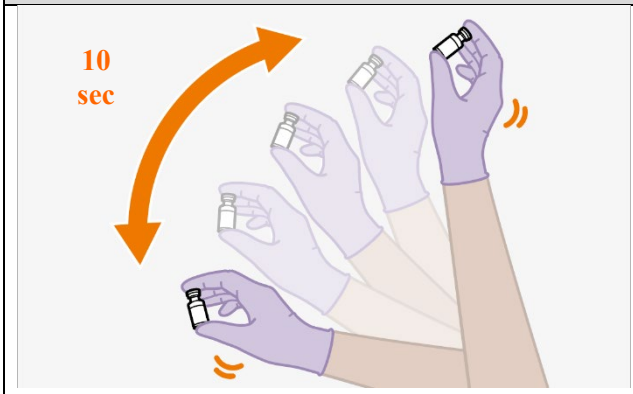
- Check that the expiry date

  Do not use if the expiry date has passed

- Inspect the vial . If you can see foreign matter, do not use the product.

Note: The cabotegravir vial has a brown tint to the glass.

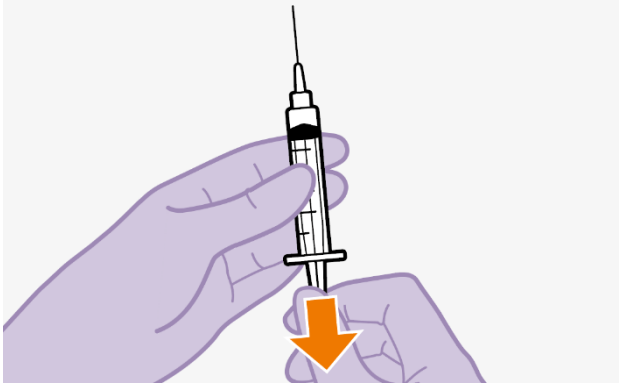
2. Shake vigorously



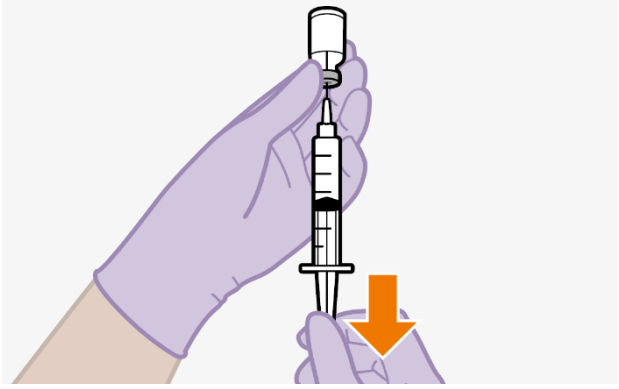
- Hold the vial firmly and vigorously shake for a full 10 seconds as shown.
- Invert the vial and check the resuspension. It should look uniform. If the suspension is not uniform, shake the vial again.
- It is normal to see small air bubbles.
- Remove the cap from the vial.
- Wipe the rubber stopper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

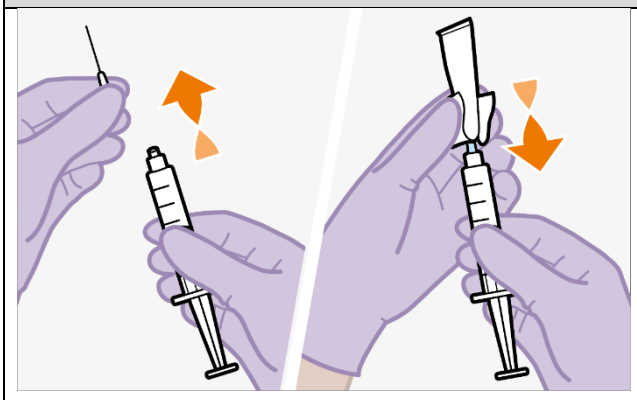
4. Slowly draw up dose



- 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.

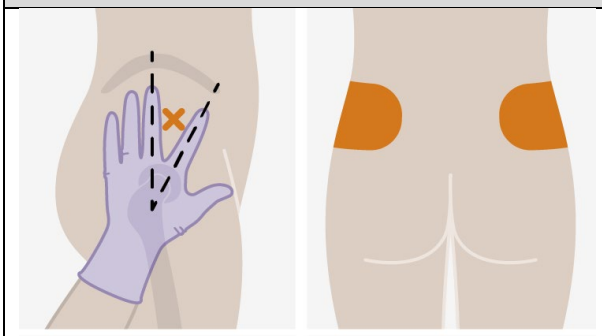
5. Attach injection needle



- 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



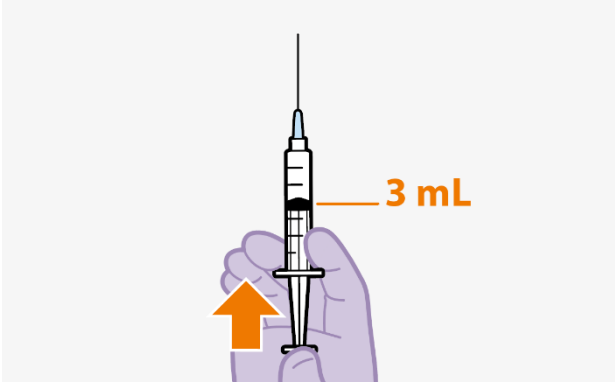
Ventrogluteal **Dorsogluteal**

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.

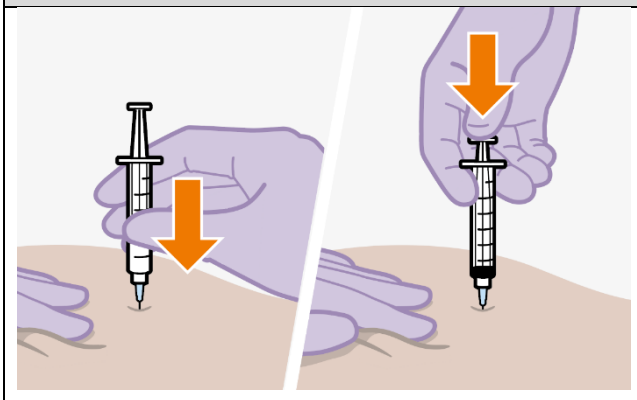
Note: Clean the injection site with an alcohol swab. Allow the skin to air dry before continuing.

8. Stretch skin

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

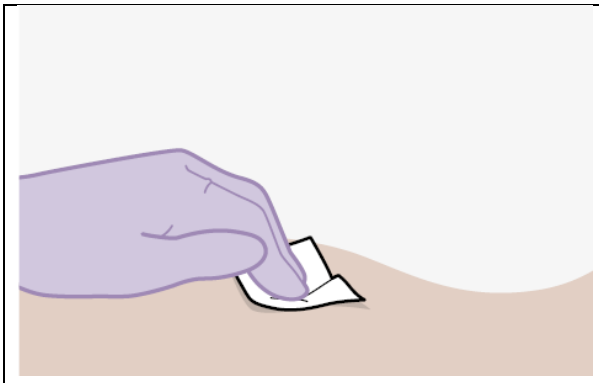
- Firmly drag the skin covering the injection site, displacing it by about an inch (2.5 cm).
- Keep it held in this position for the injection.

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 medicine to reach 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.

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.

Package leaflet: Information for the patient

Apretude 30 mg film-coated tablets
cabotegravir

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

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

1. What Apretude is and what it is used for

Apretude contains the active ingredient cabotegravir. Cabotegravir belongs to a group of anti-retroviral medicines called integrase inhibitors (INIs).

Apretude is used to help prevent HIV-1 infection in adults and adolescents weighing at least 35kg who are at an increased risk of infection. This is called **pre-exposure prophylaxis: PrEP** (see section 2). It should be used in combination with safer sex practices, such as use of condoms.

Your doctor may advise you to take Apretude tablets before you are given a Apretude injection for the first time (called *oral lead-in* period, see section 3).

If you are being given Apretude injections, but you are not able to receive your injection, your doctor may also recommend that you take Apretude tablets instead, until you can receive the injection again (see section 3).

2. What you need to know before you take Apretude

Do not use Apretude:
- if you are **allergic** *(hypersensitive)* to cabotegravir or any of the other ingredients of this medicine (listed in section 6).
- If you are **HIV positive** or you do not know if you are HIV positive. Apretude can only help reduce your risk of getting HIV before you are infected. **You must get tested** to make sure you are HIV negative before taking Apretude.
- if you are **taking any of the following medicines**:
  - *carbamazepine, oxcarbazepine, phenytoin, phenobarbital* (medicines to treat epilepsy and prevent fits).
  - *rifampicin or rifapentine* (medicines to treat some bacterial infections such as tuberculosis).

These medicines reduce the effectiveness of Apretude by decreasing the amount of Apretude in the blood

➔ If you think these apply to you, or if you are not sure, **tell your doctor**.

Warnings and precautions

Just taking Apretude may not prevent HIV infection.

HIV infection is spread by sexual contact with someone who is HIV positive or by transfer of infected blood. Although Apretude lowers the risk of becoming infected, you can still get HIV when taking this medicine.
Other measures should be taken to further reduce your risk of getting HIV:

- **Get tested** for other sexually transmitted infections when your doctor tells you to. These infections make it easier for HIV to infect you.
- **Use a condom** when you have oral or penetrative sex.
- Do not share or re-use needles or other injection or drug equipment.
- Do not share personal items that may have blood or body fluids on them (such as razor blades or toothbrushes).

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

Reduce the risk of getting HIV:

There is a risk of resistance to this medicine if you get infected with HIV. This means that the medicine will not prevent HIV infection. To minimise this risk and to prevent infection with HIV, it is important that you:

- **take Apretude tablets every day** to reduce your risk, not just when you think you have been at risk of HIV infection. Do not miss any doses of Apretude or stop taking it. Missing doses may increase your risk of getting HIV infection.

- **get tested for HIV** when your doctor tells you. You must be regularly tested to make sure that you remain HIV-1 negative while taking Apretude.

- **tell your doctor straight away** if you think you may have been infected with HIV (you may get a flu-like illness). They may want to do more tests to make sure you are still HIV negative.

Liver problems
Let your doctor know if you have liver problems. You may need to be more closely monitored. *(See also 'Uncommon side effects' in section 4).*

Adolescents
Your doctor will discuss your mental health with you before and while receiving Apretude. Let your doctor know if you have mental health problems. You may need to be more closely monitored *(See also section 4).*

Allergic reaction
Apretude contains cabotegravir, which is an integrase inhibitor. Integrase inhibitors, including cabotegravir, can cause a serious allergic reaction known as a *hypersensitivity reaction.* You need to know about important signs and symptoms to look out for while you're receiving Apretude.

➔ **Read the information** in 'Possible side effects' in section 4 of this leaflet.

Children and adolescents

This medicine should not be used in children or adolescents less than 12 years of age or weighing less than 35 kg, because it has not been studied in these individuals.

Other medicines and Apretude
Tell your doctor if you are taking, have recently taken or might take any other medicines including other medicines bought without a prescription.

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

Apretude must not be given with some other medicines that may affect how well the medicine works (see 'Do not use Apretude' in section 2). These include:

- *carbamazepine, oxcarbazepine, phenobarbital, or phenytoin* (medicines used to treat epilepsy and prevent fits).
- *rifampicin or rifapentine* (medicines to treat some bacterial infections such as tuberculosis).

Tell your doctor if you are taking:

- **antacids (**medicines to treat indigestion and heartburn**).** Antacids can stop the medicine in Apretude tablets from being absorbed into your body. **Do not take these medicines** in the 2 hours before you take Apretude or for at least 4 hours after you take it.

➔ **Tell your doctor or pharmacist** if you are taking this medicine. Your doctor may decide that you need extra check-ups.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant**,** or are planning to have a baby, ask your doctor for advice before receiving this medicine.

Pregnancy
Apretude is not recommended during pregnancy. The effect of Apretude on pregnancy is unknown. Talk to your doctor: if you could get pregnant, if you are planning to have a baby or if you become pregnant. Your doctor will consider the benefit to you and the risk to your baby of starting/continuing Apretude.

Breast-feeding
It is not known whether the ingredients of Apretude can pass into breast milk.
If you are breast-feeding, or thinking about breast-feeding, check with your doctor. Your doctor will consider the benefit and risks of breast-feeding for you and your baby.

Driving and using machines

Apretude can make you dizzy and have other side effects that make you less alert.

➔ **Don't drive or use machines** unless you are sure you're not affected.

Apretude contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Apretude contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Apretude

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

You must have a HIV-negative test before taking Apretude.

When you start treatment with Apretude injections, you and your doctor may decide to first start treatment with cabotegravir tablets in an oral lead-in period.
This allows your doctor to assess whether it's appropriate to proceed with injections.

If you decide to start treatment with tablets for the oral lead-in:
- You should take one 30 mg Apretude tablet once a day, for approximately one month.
- **After one month of tablets,** you should receive your first injection on the same day as your last tablet or no later than 3 days after.
- You will then receive an injection every 2 months

Oral lead-in schedule

When	What medicine
Month 1	30 mg Apretude tablet once a day
At month 2 and month 3	600 mg Apretude injection each month
Month 5 onwards	600 mg Apretude injection every two months

If you are not able to receive your Apretude injection, your doctor may recommend you take Apretude tablets instead, until you can receive an injection again.

How to take the tablets
Apretude tablets should be swallowed with a small amount of water. They can be taken with or without food.
Do not take antacids (medicines to treat indigestion and heartburn) during the 2 hours before you take a Apretude tablet or for at least 4 hours after you take it, as this can stop Apretude tablets being absorbed into your body and make it less effective.

If you take more Apretude than you should
If you take too many tablets of Apretude, **contact your doctor or pharmacist for advice** and you will be treated as needed. If possible, show them the Apretude tablet bottle.

If you forget to take Apretude
If you notice within 12 hours of the time you usually take Apretude, take the missed tablet as soon as possible. If you notice after 12 hours, then skip that dose and take the next dose as usual.
Do not take a double dose to make up for a forgotten tablet.

If you vomit less than 4 hours after taking Apretude, take another tablet. If you vomit more than 4 hours after taking Apretude you should not take another tablet until your next scheduled dose.

Don't stop taking Apretude without advice from your doctor
Take Apretude for as long as your doctor recommends. Don't stop unless your doctor advises you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

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

Allergic reactions

Apretude contains cabotegravir, which is an integrase inhibitor. Integrase inhibitors including cabotegravir can cause a serious allergic reaction known as a hypersensitivity reaction.

If you get any of the following symptoms:
- skin rash
- a high temperature (*fever*)
- lack of energy (*fatigue*)
- swelling, sometimes of the face or mouth (*angioedema*), causing difficulty in breathing
- muscle or joint aches.

➔ **See a doctor straight away.** Your doctor may decide to carry out tests to check your liver, kidneys or blood, and may tell you to stop taking Apretude.

Very common side effects
(may affect more than 1 in 10 people)
- headache
- diarrhoea
- feeling hot (*pyrexia*)
- changes in liver function (transaminases increased), as measured in blood tests

Common side effects
(may affect up to 1 in 10 people)
- depression
- anxiety
- abnormal dreams
- difficulty in sleeping (insomnia)
- dizziness
- feeling sick (nausea)
- vomiting
- stomach pain (abdominal pain)
- wind (flatulence)
- rash
- muscle pain (myalgia)
- lack of energy (fatigue)
- generally feeling unwell (malaise)

Uncommon side effects
(may affect up to 1 in 100 people)
- suicide attempt and suicidal thoughts (particularly in individuals who have had depression or mental health problems before)
- allergic reaction (hypersensitivity)
- hives (urticaria)
- swelling (angioedema), sometimes of the face or mouth, which can cause difficulty in breathing
- feeling drowsy (somnolence)
- weight gain.

- liver damage (hepatotoxicity). Signs may include yellowing of the skin and the whites of the eyes, loss of appetite, itching, tenderness of the stomach, light-coloured stools or unusually dark urine
- Increase in blood bilirubin, a breakdown product of red blood cells, as measured in blood tests.

Reporting of side effects
If you get any side effects, **talk to your doctor or nurse.** This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Apretude

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Apretude contains

The active substance is cabotegravir. Each tablet contains 30 mg cabotegravir.

The other ingredients are:

Tablet core
Lactose Monohydrate
Microcrystalline Cellulose (E460)
Hypromellose (E464)
Sodium Starch Glycolate
Magnesium Stearate

Tablet coating
Hypromellose (E464)
Titanium Dioxide (E171)
Macrogol (E1521)

What Apretude looks like and contents of the pack
Apretude film-coated tablets are white, oval, film-coated tablets, debossed with ‘SV CTV’ on one side.

The film-coated tablets are provided in bottles closed with child-resistant closures.

Each bottle contains 30 film-coated tablets.

Marketing Authorisation Holder

ViiV Healthcare BV
Van Asch van Wijckstraat 55H,
3811 LP Amersfoort
Netherlands

Manufacturer
Glaxo Wellcome S.A.
Avenida De Extremadura 3
Aranda De Duero
Burgos
09400
Spain

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

België/Belgique/Belgien
ViiV Healthcare srl/bv
Tél/Tel: + 32 (0) 10 85 65 00

България
ViiV Healthcare BV
Тел.: + 359 80018205

Česká republika
GlaxoSmithKline, s.r.o.
Tel: + 420 222 001 111
cz.info@gsk.com

Danmark
GlaxoSmithKline Pharma A/S
Tlf: + 45 36 35 91 00
dk-info@gsk.com

Deutschland
ViiV Healthcare GmbH
Tel.: + 49 (0)89 203 0038-10
viiv.med.info@viivhealthcare.com

Eesti
ViiV Healthcare BV
Tel: + 372 8002640

Ελλάδα
GlaxoSmithKline Μονοπρόσωπη A.E.B.E.
Τηλ: + 30 210 68 82 100

España
Laboratorios ViiV Healthcare, S.L.
Tel: + 34 900 923 501
es-ci@viivhealthcare.com

France
ViiV Healthcare SAS

Lietuva
ViiV Healthcare BV
Tel: + 370 80000334

Luxembourg/Luxemburg
ViiV Healthcare srl/bv
Belgique/Belgien
Tél/Tel: + 32 (0) 10 85 65 00

Magyarország
ViiV Healthcare BV
Tel.: + 36 80088309

Malta
ViiV Healthcare BV
Tel: + 356 80065004

Nederland
ViiV Healthcare BV
Tel: + 31 (0) 33 2081199

Norge
GlaxoSmithKline AS
Tlf: + 47 22 70 20 00

Österreich
GlaxoSmithKline Pharma GmbH
Tel: + 43 (0)1 97075 0
at.info@gsk.com

Polska
GSK Services Sp. z o.o.
Tel.: + 48 (0)22 576 9000

Portugal
VIIVHIV HEALTHCARE, UNIPESSOAL, LDA

Tél.: + 33 (0)1 39 17 69 69
Infomed@viivhealthcare.com

Hrvatska
ViiV Healthcare BV
Tel: + 385 800787089

Ireland
GlaxoSmithKline (Ireland) Limited
Tel: + 353 (0)1 4955000

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
ViiV Healthcare S.r.l
Tel: + 39 (0)45 7741600

Κύπρος
ViiV Healthcare BV Τηλ: + 357 80070017

Latvija
ViiV Healthcare BV
Tel: + 371 80205045

Tel: + 351 21 094 08 01
viiv.fi.pt@viivhealthcare.com

România
ViiV Healthcare BV
Tel: + 40 800672524

Slovenija
ViiV Healthcare BV
Tel: + 386 80688869

Slovenská republika
ViiV Healthcare BV
Tel: + 421 800500589

Suomi/Finland
GlaxoSmithKline Oy
Puh/Tel: + 358 (0)10 30 30 30

Sverige
GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

United Kingdom (Northern Ireland)
ViiV Healthcare BV
Tel: + 44 (0)800 221441
customercontactuk@gsk.com

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Other sources of information

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