APRETUDE tablet and Suspension for Injection
Professional Information

SCHEDULING STATUS:

S4

1. NAME OF MEDICINE:

APRETUDE 30 mg

Film-coated tablet

(Cabotegravir (as cabotegravir sodium))

APRETUDE 600 mg/3 mL

Prolonged-release Suspension for Injection

(Cabotegravir 200 mg/mL)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

APRETUDE 30 mg:

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

Contains sugar (lactose monohydrate 163,59 mg/tablets).

APRETUDE 600 mg\3 mL:

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

Contains sugar (mannitol 35,0 mg/mL).

3. PHARMACEUTICAL FORM:

APRETUDE 30 mg film-coated tablet, is a white, film-coated, oval tablet, debossed with ‘SV CTV’ on one face.

APRETUDE suspension for injection, is a white to light pink, free-flowing suspension.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Film-coated tablets:

APRETUDE tablets are indicated for short term pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 infection in at-risk individuals weighing at least 35 kg (see section 4.2 and section 4.4). APRETUDE tablets may be used as:

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

Suspension for Injection:

APRETUDE injection is indicated for PrEP to reduce the risk of sexually acquired HIV-1 infection in at-risk individuals weighing at least 35 kg (see section 4.2 and section 4.4).

4.2 Posology and method of administration:

Posology:

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

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

Film-coated tablets:

APRETUDE may be taken with or without food.

Suspension for Injection:

Refer to the Instructions for Use for detailed step by step injection procedure (see Section 6.6).

APRETUDE injection should be administered by a healthcare professional.

When administering APRETUDE injection, the BMI of the individual should be taken into consideration to ensure that the needle length is sufficient to reach the gluteus muscle.

Adults, adolescents weighing at least 35 kg:

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

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

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

When used for oral lead-in, APRETUDE 30 mg tablets are recommended for approximately one month (at least 28 days), prior to the initiation of APRETUDE 600mg\3 mL injection to assess tolerability to cabotegravir.

Table 1 Oral Lead-in Dosing Schedule

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

Suspension for Injection:

Initiation Injections:

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

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

Continuation Injections:

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

Table 2 Recommended Intramuscular Dosing Schedule

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

Missed dose:

Film-coated Tablet:

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

Suspension for Injection:

Adherence to the injection dosing schedule is strongly recommended.

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

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

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

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

Adolescents and Children:

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

Elderly:

No dose adjustment is required in elderly patients. There are limited data available on the use of APRETUDE in patients aged 65 years and over (see section 5.2 – Special Patient Populations).

Renal impairment:

No dosage adjustment is required in patients with mild to severe renal impairment and not on dialysis (see section 5.2 – Special Patient Populations).

Hepatic impairment:

No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). APRETUDE has not been studied in patients with severe hepatic impairment (Child-Pugh score C) (see section 5.2 – Special Patient Populations).

4.3 Contraindications:

APRETUDE is contraindicated in patients:

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

4.4 Special warnings and precautions for use:

Overall HIV-1 infection prevention strategy:

APRETUDE is not always effective in preventing HIV-1 acquisition. The time to onset of protection after commencing APRETUDE is unknown.

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

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

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

Potential risk of resistance:

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

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

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

Long-acting properties of APRETUDE injection:

Residual concentrations of APRETUDE injection may remain in the systemic circulation of individuals for prolonged periods (up to 12 months or longer), therefore, medical practitioners should take the prolonged release characteristics of APRETUDE into consideration when the medicinal product is discontinued (see section 4.5, section 4.6 and section 4.9).

Importance of adherence:

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

Hypersensitivity reactions:

Hypersensitivity reactions have been reported in association with other integrase inhibitors. These reactions were characterised by rash, constitutional findings and sometimes organ dysfunction, including liver injury. Administration of APRETUDE oral lead-in was used in clinical studies to help identify participants who may be at risk of a hypersensitivity reaction. While no such reactions have been observed to date in association with APRETUDE, medical practitioners should remain vigilant and should discontinue APRETUDE and other suspected agents immediately, should signs or symptoms of hypersensitivity develop (including, but not limited to, severe rash, or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia or angioedema). Clinical status, including liver aminotransferases should be monitored and appropriate therapy initiated. Administration of oral lead-in is recommended to help identify patients who may be at risk of a hypersensitivity reaction (see section 4.2, section 4.3 and Long-acting properties of APRETUDE injection below).

Hepatotoxicity:

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

Monitoring of liver chemistries is recommended and treatment with APRETUDE should be discontinued if hepatotoxicity is suspected (see Long-acting properties of APRETUDE injection).

Interactions with medicinal products:

Caution should be given to prescribing APRETUDE with medicines that may reduce its exposure (see section 4.5).

APRETUDE tablets contain lactose:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take APRETUDE tablets.

APRETUDE suspension for injections contain mannitol: mannitol may have a laxative effect.

4.5 Interactions with other medicines and other forms of interaction:

Effect of cabotegravir on the pharmacokinetics of other medicines:

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

Cabotegravir inhibited the organic anion transporters (OAT) 1 (IC50 = 0,81 µM) and OAT3 (IC50 = 0,41 µM) *in vitro*, however, based on physiologically based pharmacokinetic (PBPK) modelling no interaction with OAT substrates is expected at clinically relevant concentrations.

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

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

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

Effect of other medicines on the pharmacokinetics of cabotegravir:

Cabotegravir is primarily metabolised by UGT1A1 with some contribution from UGT1A9. Medicines which are strong inducers of UGT1A1 or UGT1A9 are expected to decrease cabotegravir plasma concentrations leading to lack of efficacy (see section 4.3).

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

In vitro, cabotegravir was not a substrate of OATP1B1, OATP1B3, OATP2B1 or OCT1. Cabotegravir is a substrate of P-gp and BCRP, however, because of its high permeability, no alteration in absorption is expected when co-administered with either P-gp or BCRP inhibitors.

No interaction studies have been performed with APRETUDE injection. The interaction data provided in Table 5 is obtained from studies with oral APRETUDE.

Table 5: Interactions

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

Concomitant Medicine Class: Medicine Name	Effect on Concentration of Cabotegravir or Concomitant Medicine	Clinical Comment
Rifabutin	Cabotegravir ↓ AUC ↓ 21 % C_{max} ↓ 17 % C_T ↓ 8 %	*APRETUDE tablets:* Rifabutin did not significantly change cabotegravir plasma concentration. No dose adjustment is required. *APRETUDE injection:* When rifabutin is started before or concomitantly with the first APRETUDE initiation injection the recommended APRETUDE dosing schedule is one 3 mL (600 mg) injection followed 2 weeks later by a second 3 mL (600 mg) initiation injection and monthly, thereafter, while on rifabutin. When rifabutin is started at the time of the second initiation injection or later, the recommended dosing schedule is 3 mL (600 mg), monthly, while on rifabutin. After stopping rifabutin, the recommended APRETUDE dosing schedule is 3 mL (600 mg) every 2 months.
Anticonvulsants: Carbamazepine Oxcarbazepine Phenytoin Phenobarbitone	Cabotegravir ↓	Metabolic inducers may significantly decrease cabotegravir plasma concentrations. Concomitant use is contraindicated.
Antacids (e.g., magnesium, calcium or aluminium)	Cabotegravir ↓	*APRETUDE tablets:* Co-administration of antacid supplements has the potential to decrease oral cabotegravir absorption and has not been studied. Antacid products containing polyvalent cations are recommended to be administered at least 2 hours before or 4 hours after oral APRETUDE. *APRETUDE injection:* Interaction is not relevant following parenteral administration.
Oral contraceptives (Ethinyl estradiol (EE) and levonorgestrel	EE ↔ AUC ↑ 2 % C_{max} ↓ 8 % C_T ↔ 0 % LNG ↔	Cabotegravir did not significantly change ethinyl estradiol and levonorgestrel plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with APRETUDE.

4.6 Fertility, pregnancy and lactation:

Pregnancy:

Safety in pregnancy has not been established.

There are no studies of cabotegravir in pregnant women. The effect on human pregnancy is unknown.

Cabotegravir was not teratogenic when studied in pregnant rats and rabbits but caused a delay in delivery that was associated with reduced survival and viability of rat offspring at exposures higher than for therapeutic doses (see section 5.3). The relevance to human pregnancy is unknown.

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).

Breastfeeding:

Safety in lactation has not been established.

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.

Fertility:

Animal studies indicate no effects of cabotegravir on male or female fertility (see section 5.3).

4.7 Effects on ability to drive or use machines:

APRETUDE may cause dizziness. Patients experiencing dizziness should avoid driving and operation of machinery.

4.8 Undesirable effects:

Clinical trial data:

Adverse reactions for APRETUDE were identified from the Phase III clinical studies, HPTN 083 and HPTN 084. In HPTN 083, the median time on blinded study product was 65 weeks and 2 days (1 day to 156 weeks and 1 day), with a total exposure on APRETUDE of 3 270 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 APRETUDE of 1 920 person years.

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

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

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

The AEs identified in these studies are listed below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1000 and < 1/100), rare (≥ 1/10 000 and < 1/1000) and very rare (< 1/10 000), including isolated reports.

Table 6: Adverse Events[1]

MedDRA System Organ Class (SOC)	Frequency Category	Adverse Reactions
Psychiatric disorders	Common	Depression, abnormal dreams, insomnia
Nervous system disorders	Very common Common Uncommon	Headache Dizziness Vasovagal reactions (in response to injections)
Gastrointestinal disorders	Very common Common	Diarrhoea Nausea, vomiting, abdominal pain[2], flatulence
Hepatobiliary Disorders	Very common Uncommon	Transaminase increased [3] Hepatotoxicity
Skin and subcutaneous tissue disorders	Common	Rash[3]

MedDRA System Organ Class (SOC)	Frequency Category	Adverse Reactions
Musculoskeletal and connective tissue disorders	Common	Myalgia
General disorders and administrative site conditions	Very common	Pyrexia [4], injection site reactions[5] (pain and tenderness, site nodule, induration)
	Common	Injection site reactions[5] (swelling, bruising, erythema, warmth, pruritis, anaesthesia), fatigue, malaise
	Uncommon	Injection site reactions (ISRs)[5] (haematoma, discolouration, abscess)
Investigations	Uncommon	Weight increased

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

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

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

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

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

Local Injection Site Reactions (ISRs):

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

Out of 20 286 injections, 8 900 ISRs were reported.

A total of 2 117 participants received at least one injection. Of the 1 740 (82 %) participants who experienced at least one ISR, the maximum severity of ISRs reported was mild (Grade 1, 34 % of participants), moderate (Grade 2, 46 % of participants) or severe (Grade 3, 3 % of participants). No participants experienced Grade 4 ISRs. The median duration of overall ISR events was 4 days. The proportion of participants reporting ISRs at each visit and the severity of the ISRs decreased over time.

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

Out of 13 068 injections, 1 171 ISRs were reported.

A total of 1 519 participants received at least one injection. Of the 578 (38 %) participants who experienced at least one ISR, the maximum severity of ISRs reported was mild (Grade 1, 25 % of participants), moderate (Grade 2, 13 % of participants) or severe (Grade 3, < 1 % of participants). No participants experienced Grade 4 ISRs. The median duration of overall ISR events was 8 days. The proportion of participants reporting ISRs at each visit and the severity of the ISRs generally decreased over time.

Weight increased:

At the Week 41 and 97 timepoints in HPTN 083, participants who received cabotegravir gained a median of 1,2 kg (IQR -1,0, 3,5; n=1 623) and 2,1 kg (IQR; -0,9, 5,9 n = 601) in weight from baseline, respectively.

At the Week 41 and 97 timepoints in HPTN 084, participants who received cabotegravir gained a median of 2,0 kg (IQR 0,0, 5,0; n = 1151) and 4,0 kg (IQR; 0,0, 8,0, n = 216) in weight from baseline, respectively.

Changes in laboratory Chemistries:

In both HPTN 083 and HPTN 084, elevated hepatic transaminases (ALT/AST) levels were observed in participants treated with cabotegravir. In HPTN 083, 40 (2 %) participants in the cabotegravir group experienced maximum post baseline Grade 3 or 4 ALT levels and 68 (3 %) Grade 3 or 4 AST levels respectively. In HPTN 084, 12 (< 1 %) participants in the cabotegravir group experienced maximum post baseline Grade 3 or 4 ALT levels and 15 (< 1 %) Grade 3 and 4 AST levels, respectively.

A few participants in the cabotegravir groups had adverse events of AST or ALT increased which resulted in discontinuation of study product. In HPTN 083, 29 (1 %) participants in the cabotegravir group discontinued due to ALT increase and 7 (< 1 %) discontinued due to AST increase. In HPTN 084, 12 (< 1 %) participants in the cabotegravir group discontinued treatment due to ALT increase and there were no discontinuations due to AST increase.

Paediatric population:

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

Post-marketing data:

No data available.

Reporting of adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form', found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

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

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

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

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Category A 20.2.8 Antiviral agents

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:

Clinical studies:

The efficacy of cabotegravir for PrEP has been evaluated in two randomised (1:1), double blind, multi-site, two-arm, controlled studies.

In HPTN 083, following extended retrospective virologic testing, cisgender men and transgender women who have sex with men in the cabotegravir arm had a 69% reduction in the risk of acquiring incident HIV infection, hazard ratio (95 % CI) 0,31 (0,16, 0,58).

In HPTN 084, following extended retrospective virologic testing, cisgender women in the cabotegravir arm had a 90% reduction in the risk of acquiring incident HIV infection, hazard ratio (95 % CI) 0,10 (0,04, 0.27).

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) were noted. As noted above, the detection of T124A is selection of a pre-existing minority variant that does not have differential susceptibility to cabotegravir. No amino acid substitutions in the integrase region were selected when passaging the wild-type HIV-1 NL-432 in the presence of 6,4 nM of cabotegravir through Day 56.

Among the multiple mutants, the highest fold-change was observed with mutants containing Q148K or Q148R. E138K/Q148H resulted in a 0,92-fold decrease in susceptibility to cabotegravir but E138K/Q148K resulted in an 81-fold decrease in susceptibility to cabotegravir. G140C/Q148R and G140S/Q148R resulted in a 22- and 12-fold decrease in susceptibility to cabotegravir, respectively. While N155H did not alter susceptibility to cabotegravir, N155H/Q148R resulted in a 61-fold decrease in susceptibility to cabotegravir.

Resistance in vivo:

HPTN 083:

In the primary analysis of the HPTN 083 study, there were 13 incident infections on the cabotegravir arm, five incident infections occurred when receiving cabotegravir PrEP injections, of which 4 participants received on-time injections and 1 participant had one injection off-schedule.

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.

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).

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 cabotegravir (fold-change = 2,32). The fourth participant had INSTI resistance mutations G140A and Q148R. Phenotype showed resistance to cabotegravir (fold-change=13). The fifth participant had no INSTI resistance mutations.

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.

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.

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.

Effects on Electrocardiogram:

In a randomised, placebo-controlled, three-period cross-over trial, oral cabotegravir 150 mg every 12 hours, for three doses (n = 42), did not prolong the QTc interval over 24 hours post dose. After baseline and placebo adjustment, the maximum time-matched mean QTc change based on Fridericia's correction method (QTcF) for cabotegravir was 2,62 msec (1-side 90 % upper CI:5,26 msec). The geometric mean CAB Cmax observed with the supratherapeutic dose is approximately 2,8-fold and 5,6-fold above the 30 mg oral once-daily dose and the CAB LA 600 mg every 2 months dose, respectively.

5.2 Pharmacokinetic properties:

Oral:

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

Suspension for Injection:

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

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

Dosing Phase	Dosage Regimen	Geometric Mean (5th, 95th Percentile)[a]		
		$AUC_{(0\text{-}tau)}$[b] (µ•h/mL)	C_{max} (µ/mL)	C_{tau} (µ/mL)
Oral lead-in[c]	30 mg once daily	145 (93,5, 224)	8.0 (5,3, 11.9)	4.6 (2,8, 7,5)
Initial injection[d]	600 mg IM Initial Dose	1591 (714, 3245)	8,0 (5,3, 11.9)	1,5 (0,65, 2,9)
Every 2-month injection[e]	600 mg IM Every 2-month	3764 (2431, 5857)	4,0 (2,3, 6,8)	1,6 (0,8, 3,0)

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

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

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

[d] Initial injection C_{max} values primarily reflect oral dosing because the initial injection was administered on the same day as the last oral dose; however, the $AUC_{(0\text{-}tau)}$ and C_{tau} values reflect the initial injection. When administered without oral lead-in to HIV infected recipients (n = 110), the observed cabotegravir geometric mean (5th, 95th percentile) C_{max} (1-week post-initial injection) was 1,89 mcg/mL (0,438, 5,69) and C_{tau} was 1,43 mcg/mL (0,403, 3,90).

[e] Pharmacokinetic parameter values represent steady state

Absorption:

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

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

The absolute bioavailability of cabotegravir has not been established.

Suspension for Injection: Cabotegravir injection exhibits absorption-limited pharmacokinetics because cabotegravir is slowly absorbed into the systemic circulation from the gluteal muscle resulting in sustained plasma concentrations. Following a single 600 mg intramuscular dose, plasma cabotegravir concentrations are detectable on the first day with median cabotegravir concentrations at 4 hours post dose of 0,290 µg/mL, which is above in-vitro PA-IC90 of 0,166 µg/mL and reach maximum plasma concentration with a median T_{max} of 7 days. Target concentrations are achieved following the initial IM injection (see Table 6). Cabotegravir has been detected in plasma up to 52 weeks or longer after administration of a single injection.

Plasma CAB exposure increases in proportion or slightly less than in proportion to dose following single and repeat IM injection of doses ranging from 100 to 800 mg.

Distribution:

Cabotegravir is highly bound (approximately > 99 %) to human plasma proteins, based on *in vitro* data. Following administration of oral tablets, the mean apparent oral volume of distribution (Vz/F) in plasma was 12,3 L. In humans, the estimate of plasma cabotegravir Vc/F was 5,27 L and Vp/F was 2,43 L. These volume estimates, along with the assumption of high F, suggest some distribution of cabotegravir to the extracellular space.

Cabotegravir is present in the female and male genital tract, following a single 3 mL (600 mg) IM injection, as observed in a study in healthy participants (n = 15). Median cabotegravir concentrations at Day 3 (the earliest tissue PK sample) were 0,49 µg/mL in cervical tissue, 0,29 µg/mL in cervicovaginal fluid, 0,37 µg/mL in vaginal tissue, 0,32 µg/mL in rectal tissue, and 0,69 µg/mL in rectal fluid, which are above the *in vitro* PA-IC90.

Metabolism:

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

Elimination:

Oral: Cabotegravir has a mean terminal half-life of 41 hours and an apparent clearance (CL/F) of 0,21 L per hour based on population pharmacokinetic analyses.

Suspension for Injection: Cabotegravir mean apparent terminal phase half-life is absorption-rate limited and is estimated to be 5,6 to 11,5 weeks after a single dose IM injection. The significantly longer apparent half-life compared to oral administration reflects absorption from the injection site into the systemic circulation. The apparent CL/F was 0,151 L/h.

Special patient populations:

Gender:

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

Race:

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

BMI:

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

Adolescents:

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

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

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

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

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

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

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

[e] Pharmacokinetic parameter values represent steady state.

Children:

The pharmacokinetics and dosing recommendations of APRETUDE in children 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 dosage adjustment is necessary for patients with mild to severe renal impairment (not on dialysis). Cabotegravir has not been studied in patients on dialysis.

Hepatic impairment:

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

HBV and HCV Co-infected Patients:

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

Polymorphisms in Medicine Metabolising Enzymes:

In a meta-analysis of healthy and HIV-infected subjects, HIV-infected subjects with UGT1A1 genotypes conferring poor cabotegravir metabolism had a 1,2-fold increase in mean steady-state cabotegravir AUC, C_{max}, and C_{tau} following cabotegravir injection vs. 1,38-fold mean increase following oral cabotegravir administration. This was similar to 1,3- to 1,5-fold mean increase in steady-state cabotegravir, AUC, C_{max}, and C_{tau} observed following oral cabotegravir in healthy and HIV infected subjects combined. These differences are not considered clinically relevant. Polymorphisms in UGT1A9 were not associated with differences in the pharmacokinetics of cabotegravir, therefore, no dose adjustment is required in subjects with either UGT1A1 or UGT1A9 polymorphisms.

5.3 Preclinical safety data:

Carcinogenesis/mutagenesis:

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

Reproductive Toxicology:

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

Pregnancy: In an embryo-foetal development study, there were no adverse developmental outcomes following oral administration of cabotegravir to pregnant rabbits at doses up to 2 000 mg/kg/day (0,66 times the exposure in humans at the MRHD of 30 mg oral or approximately 1 times 400 mg IM dose) or to pregnant rats at doses up to 1000 mg/kg/day (> 30 times the exposure in humans at the MRHD of 30 mg oral or 400 mg IM dose). In rats, alterations in foetal growth (decreased body weights) in the absence of maternal toxicity were observed at 1 000 mg/kg/day. Studies in pregnant rats showed that cabotegravir crosses the placenta and can be detected in foetal tissue.

Non-clinical data from rat pre- and post-natal (PPN) studies at 1 000 mg/kg/day (> 30 times the exposure in humans at the MRHD of 30 mg oral or 400 mg IM dose) cabotegravir delayed the onset of parturition, and in some rats, this delay was associated with an increased number of stillbirths and neonatal mortalities immediately after birth. A lower dose of 5 mg/kg/day cabotegravir (> 10 times the exposure in humans at the MRHD of 30 mg oral or 400 mg IM dose) was not associated with delayed parturition or neonatal mortality in rats. In rabbit and rat studies there was no effect on survival when foetuses were delivered by caesarean section. When rat pups born to cabotegravir-treated dams were cross-fostered at birth and nursed by control mothers, similar incidences of neonatal mortalities were observed.

Animal toxicology and/or pharmacology:

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

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

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

In a 3-month study in rats, when cabotegravir was administered by monthly sub-cutaneous (SC) injection (up to 100 mg/kg/dose); monthly IM injection (up to 75 mg/kg/dose) or weekly SC injection (100 mg/kg/dose), there were no adverse effects noted and no new target organ toxicities (at exposures > 30 times the exposure in humans at the MRHD of 400 mg IM dose).

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Film-coated tablets:

Tablet core: lactose monohydrate, microcrystalline cellulose, hypromellose, sodium starch glycolate, magnesium stearate.

Tablet coating: hypromellose, titanium dioxide (E171), macrogol.

Suspension for injection:

Mannitol (E421), polysorbate 20, macrogol 3350, water for injections.

6.2 Incompatibilities:

In the absence of compatibility studies, APRETUDE injections must not be mixed with other medicines.

6.3 Shelf life:

APRETUDE 600 mg\3 mL: 60 months

APRETUDE 30 mg: 36 months

6.4 Special precautions for storage:

APRETUDE tablets:

Store at or below 30 ºC.

APRETUDE injections:

Unopened packs: Store at or below 30 ºC. Do not freeze.

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

6.5 Nature and contents of container:

Film-coated tablets:

A carton containing 30 tablets which are packed into opaque, white HDPE (high density polyethylene) bottles with child-resistant closures that include a polyethylene faced induction heat seal liner.

Suspension for Injection:

A carton containing a single-use Type I clear glass vials,

and sealed with bromobutyl rubber stoppers. The stopper is secured with an aluminum overseal with a removeable orange plastic cap. The vial in the carton is a brown colour after terminal sterilization.

Pack sizes: Single vial or multipacks of 25 vials.

6.6 Special precautions for disposal and or handling:

Overview

At each visit, one injection is required. APRETUDE 600 mg\3 mL.

APRETUDE 600 mg\3 mL is a suspension that does not need further dilution or reconstitution.

APRETUDE 600 mg\3 mL is for intramuscular use only. It must be administered to the gluteal sites.

Note: The ventrogluteal site is recommended.

Your pack contains:

- 1 vial of APRETUDE 600 mg/3mL

To prepare the injection:

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

To administer the injection:

- 1 additional luer-lock needle (use safety needle if available) of 23 gauge, 1,5 inches.

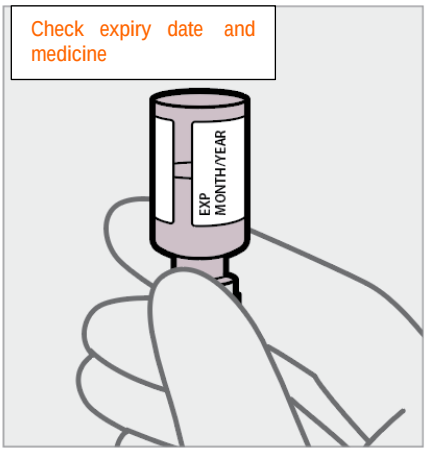
Consider the patient's build and use medical judgment to select an appropriate injection needle length.

You will also need:

- non-sterile gloves
- 2 alcohol swabs
- 1 gauze pad
- a suitable sharps container.

PREPARATION

1. Inspect vial.

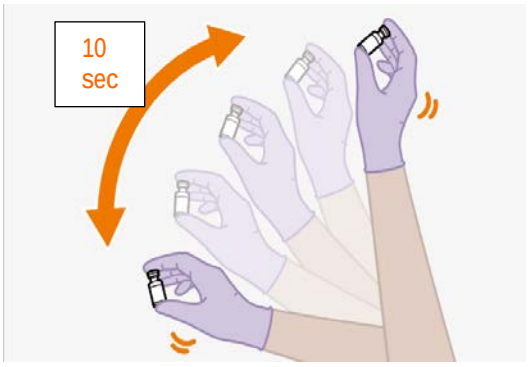


- Check that the expiry date has not passed.
- Inspect the vial immediately. If you can see foreign matter, do not use the product.

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

Do not use if the expiry date has passed.

2. Shake vigorously



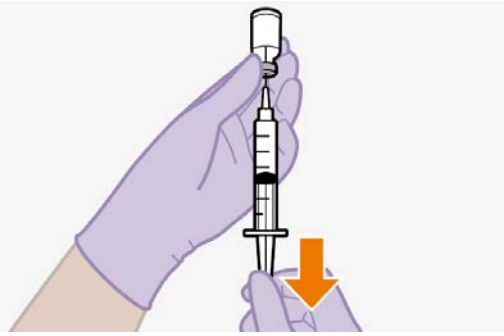
- Hold the vial firmly and vigorously shake for a full 10 seconds as shown.
- Invert the vial and check the resuspension. It should look uniform. If the suspension is not uniform, shake the vial again.
- It is also normal to see small air bubbles.
- Remove the cap from the vial.
- Wipe the rubber stopper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

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

3. Prepare syringe and needle

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

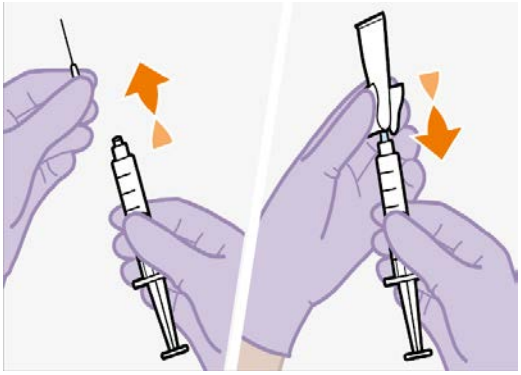
4. Slowly draw up dose



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

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

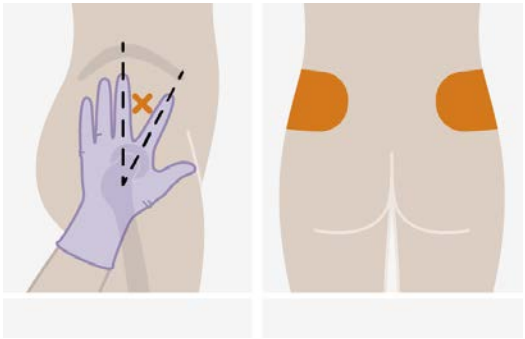
5. Attach injection needle



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

INJECTION

6. Prepare injection site



Injections must be administered to the gluteal sites.

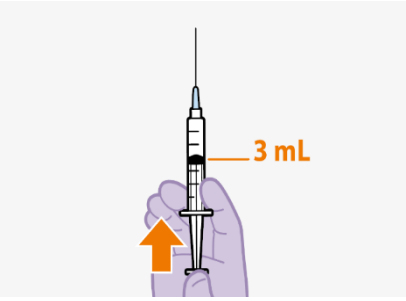
Select from the following areas for the injection:

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

Note: For gluteal intramuscular use only.

Do not inject intravenously.

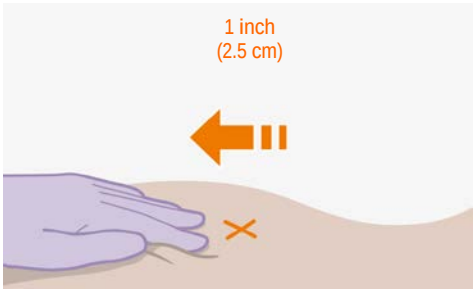
7. Remove extra liquid



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

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

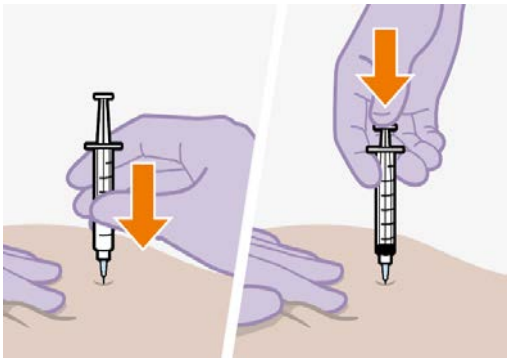
8. Stretch skin



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

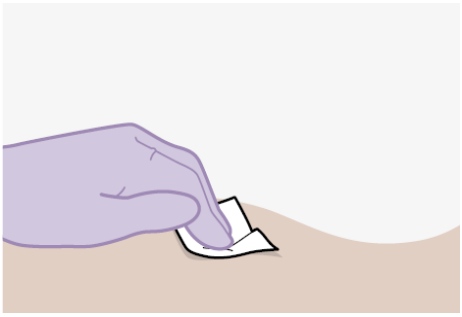
- Firmly drag the skin covering the injection site, displacing it by about an inch (2,5 cm).
- Keep it held in this position for the injection.

9. Inject



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

10. Assess the injection site



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

Do not massage the area.

Questions and Answers

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

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

   It is best to let the vial come to room temperature naturally. However, you can use the warmth of your hands to speed up the warm-up time, but make sure the vial does not get above 30 °C. 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 healthcare professional. The injection should not be administered in any other site.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBER(S):

APRETUDE 600 mg\3 mL: 56/20.2.8/0979

APRETUDE 30 mg: 56/20.2.8/0980

9. DATE OF FIRST AUTHORISATION:

22 November 2022

GDSv2