VOCABRIA tablet and Suspension for Injections

SCHEDULING STATUS:

S4

1. NAME OF MEDICINE:

VOCABRIA 30 mg

Film-coated tablet

(Cabotegravir sodium)

VOCABRIA 400 mg (2 mL)

VOCABRIA 600 mg (3 mL)

Prolonged-release Suspensions for Injection

(Cabotegravir 200 mg/mL)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

VOCABRIA 30 mg:

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

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

For the full list of excipients, see section 6.1.

VOCABRIA 400 mg:

Each single dose 2 mL vial contains 400 mg cabotegravir (as cabotegravir free acid).

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

VOCABRIA 600 mg:

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

VOCABRIA 30 mg film coated tablet, is a white, film-coated, oval tablet, debossed with SV CT on one face.

VOCABRIA suspension for Injection, is a white to light pink, free-flowing suspension.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Film-coated tablets:

VOCABRIA tablets are indicated in combination with rilpivirine tablets for short-term (see section 4.2) treatment of human immunodeficiency virus (HIV)-1 infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/mL) and have no known or suspected resistance to either cabotegravir or rilpivirine for:

- oral lead-in to assess tolerability of cabotegravir prior to administration of long-acting (LA) VOCABRIA injection.
- oral therapy for adults who will miss planned dosing with VOCABRIA injection.

Suspension for Injection:

Cabotegravir injection is indicated in combination with rilpivirine injection for treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/mL) and have no known or suspected resistance to either cabotegravir or rilpivirine.

4.2 Posology and method of administration:

Posology:

Therapy should be initiated by a medical practitioner experienced in the management of HIV infection.

VOCABRIA is indicated for the treatment of HIV in combination with rilpivirine, therefore, the prescribing information for rilpivirine should be consulted for recommended dosing.

Prior to starting VOCABRIA, healthcare professionals should have carefully selected patients who agree to the required injection schedule and counsel patients about the importance of adherence to scheduled dosing visits to help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance with missed doses.

Film-coated tablets:

VOCABRIA may be taken with or without food. When taken at the same time as rilpivirine, VOCABRIA should be taken with a meal.

Suspension for Injection:

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

VOCABRIA injection should be administered by a healthcare professional.

When administering the VOCABRIA injection, healthcare professionals should take into consideration the BMI of the patient to ensure that the needle length is sufficient to reach the gluteus muscle.

VOCABRIA and rilpivirine injections should be administered at separate gluteal injection sites during the same visit.

Adults:

The healthcare provider and patient may proceed directly to LA injectable therapy (see Tables 2 and 3, for monthly and every 2-month dosing recommendations, respectively).

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

Oral lead-in (film-coated tablets):

When used for oral lead-in, VOCABRIA oral tablets are recommended for approximately one month (at least 28 days) in virologically suppressed patients prior to the initiation of cabotegravir injection to assess tolerability to cabotegravir. VOCABRIA tablets should be taken together with rilpivirine tablets.

Table 1 Oral Lead-in Dosing Schedule in Adults

	ORAL LEAD-IN
Medicine	For 1 month (at least 28 days), followed by the Initiation Injection[a]
VOCABRIA	30 mg once daily
Rilpivirine	25 mg once daily
[a] see Table 2 for monthly injection dosing schedule and Table 3 for every 2-month dosing schedule.	

Monthly dosing (suspension for injection):

Initiation injection:

On the final day of prior antiretroviral therapy or oral lead-in, the recommended initial VOCABRIA injection dose in adults is a single 3 mL (600 mg) intramuscular injection.

Continuous injections:

After the initiation injection, the recommended VOCABRIA continuation injection dose in adults is a single 2 mL (400 mg) intramuscular injection, administered monthly. Patients may be given injections up to 7 days before or after the date of the monthly 2 mL dosing schedule.

Table 2 Recommended Oral Lead-in and Monthly Intramuscular Dosing Schedule in Adults

	INITIATION INJECTION	CONTINUATION INJECTIONS
Medicine	Direct to Injection (month 1) OR Following oral lead-in (month 2)	One month after initiation injection and monthly onwards
VOCABRIA	3 mL (600 mg)	2 mL (400 mg)
Rilpivirine	3 mL (900 mg)	2 mL (600 mg)

Every 2-month dosing (suspension for injection):

Initiation injections:

On the final day of prior antiretroviral therapy or oral lead-in, the recommended initial VOCABRIA injection dose in adults is a single 3 mL (600 mg) intramuscular injection. One month later, a second 3 mL (600 mg) intramuscular injection should be administered. Patients 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 VOCABRIA continuation injection dose in adults is a single 3 mL (600 mg) intramuscular injection administered every 2-months. Patients may be given injections up to 7 days before or after the date of the 'every 2-month,' 3 mL dosing schedule.

Table 3 Recommended Every 2-Month Intramuscular Dosing Schedule in Adults

	INITIATION INJECTIONS	CONTINUATION INJECTIONS
Medicine	Direct to injection: months 1 and 2 OR Following oral lead-in (month 2)	Month 5 onwards
VOCABRIA	3 mL (600 mg)	3 mL (600 mg)
Rilpivirine	3 mL (900 mg)	3 mL (900 mg)

Change in Dosing Frequency:

Dosing Recommendations when Switching from Monthly to Every 2-Month Injections:

Patients switching from a monthly continuation injection schedule to an every 2-month continuation injection dosing schedule should receive a single 3 mL (600 mg) intramuscular injection of cabotegravir one month after the last 2 mL (400 mg) continuation injection dose and then 3 mL (600 mg) every 2 months thereafter.

Dosing Recommendations when Switching from Every 2-Month to Monthly Injections:

Patients switching from an every 2-month continuation injection schedule to a monthly continuation dosing schedule should receive a single 400 mg intramuscular injection of VOCABRIA 2 months after the last 600 mg continuation injection dose and then 400 mg monthly thereafter.

Missed dose:

Film-coated tablet:

If the patient misses a dose of oral VOCABRIA, the patient should take the missed dose as soon as possible.

Suspension for injection:

Adherence to the injection dosing schedule is strongly recommended. Patients who miss a scheduled injection visit should be clinically reassessed to ensure resumption of therapy remains appropriate (see Tables 4 and 5).

Missed monthly Injection:

If a delay of more than 7 days from a scheduled injection visit cannot be avoided, VOCABRIA tablets (30 mg) may be used in combination with rilpivirine tablets (25 mg) once daily to replace up to 2 consecutive monthly injection visits. For oral therapy durations greater than 2 months, an alternative oral regimen is recommended.

The first dose of oral therapy should be taken one month (± 7 days) after the last injection dose of VOCABRIA or rilpivirine. Injection dosing should be resumed on the day oral dosing completes, as recommended in Table 4.

Table 4 Injection Dosing Recommendations After Missed Injections or Oral Therapy for patients on monthly injection dosing

Time since last injection	Recommendation
≤ 2 months:	Continue with the monthly 2 mL injections dosing schedule as soon as possible

> 2 months:	Re-initiate the patient on the 3 mL dose, and then continue to follow the monthly 2 mL injection dosing schedule.

Missed 2-month injection:

If a delay of more than 7 days from a scheduled injection visit cannot be avoided, VOCABRIA tablets (30 mg) may be used in combination with rilpivirine tablets (25 mg) once daily to replace one 2-monthly injection visit. For oral therapy durations greater than 2 months, an alternative oral regimen is recommended.

The first dose of oral therapy should be taken two months (± 7 days) after the last injection dose of VOCABRIA or rilpivirine. Injection dosing should be resumed on the day oral dosing completes, as recommended in Table 5.

Table 5 Injection Dosing Recommendations After Missed Injections or Oral Therapy for patients on every 2-month injection dosing

Missed Injection Visit	Time since last injection	Recommendation (all injections are 3 mL)
Injection 2	≤ 2 months	Resume with 3 mL (600 mg) injection as soon as possible and continue with 2-month injection dosing schedule.
	> 2 months	Re-initiate the patient on the 3 mL (600 mg) dose, followed by a second 3 mL (600 mg) initiation injection one month later. Then follow the every 2-month injection dosing schedule.
Injection 3 or later	≤ 3 months	Resume with 3 mL (600 mg) injection as soon as possible and continue with 2-month injection dosing schedule.
	> 3 months	Re-initiate the patient on the 3 mL (600 mg) dose, followed by a second 3 mL initiation injection one month later. Then follow the every 2-month injection dosing schedule.

Adolescents and Children:

The safety and efficacy of VOCABRIA in children and adolescents aged under 18 years have not been established.

Special populations:

Elderly:

No dose adjustment is required in elderly patients. There are limited data available on the use of cabotegravir 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). VOCABRIA has not been studied in patients with severe hepatic impairment (Child-Pugh score C) (see section 5.2 – Special Patient Populations).

4.3 Contraindications:

VOCABRIA 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.

VOCABRIA is only indicated for treatment of HIV in combination with rilpivirine, therefore, the prescribing information for rilpivirine should also be consulted.

4.4 Special warnings and precautions for use:

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 VOCABRIA oral lead-in was used in clinical studies to help identify patients who may be at risk of a hypersensitivity reaction.

While no such reactions have been observed to date in association with VOCABRIA, medical practitioners should remain vigilant and should discontinue VOCABRIA and other suspected agents immediately, should signs or symptoms of hypersensitivity develop (including, but not limited to, severe rash, or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia or angioedema). Clinical status, including liver aminotransferases should be monitored and appropriate therapy initiated. (See section 4.2, section 4.3 and Long-acting properties of VOCABRIA injection below and section 5.1 clinical efficacy and safety).

Hepatotoxicity:

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

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

Long-acting properties of cabotegravir injection:

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

Risk of resistance following treatment discontinuation:

To minimise the risk of developing viral resistance it is essential to adopt an alternative, fully suppressive antiretroviral regimen no later than one month after the final injection of cabotegravir when dosed monthly and no later than two months after the final injection of VOCABRIA when dosed every 2 months.

If virologic failure is suspected, an alternative regimen should be adopted as soon as possible.

Interactions with medicinal products:

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

Lipodystrophy and metabolic abnormalities:

Combination antiretroviral therapy has been associated with the redistribution/accumulation of body fat, including central obesity, dorso-cervical fat, enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and elevated serum lipid and glucose levels in HIV patients. Clinical examination should include evaluation for physical signs of fat redistribution. Patients with evidence of lipodystrophy should have a thorough cardiovascular risk assessment.

Immune Reconstitution Inflammatory Syndrome:

Immune reconstitution inflammatory syndrome (IRIS) is an immunopathological response resulting from the rapid restoration of pathogen-specific immune responses to pre-existing antigens combined with immune dysregulation, which occurs shortly after starting combination Anti-Retroviral Therapy (cART). Typically, such reaction presents by paradoxical deterioration of opportunistic infections being treated or with unmasking of an asymptomatic opportunistic disease, often with an atypical inflammatory presentation. IRIS usually develops within the first three months of initiation of ART and occurs more commonly in patients with low CD4 counts. Common examples of IRIS reactions to opportunistic diseases are tuberculosis, cytomegalovirus retinitis, and cryptococcal meningitis. Appropriate treatment of the opportunistic disease should be instituted or continued and ART continued. Inflammatory manifestations generally subside after a few weeks. Severe cases may respond to glucocorticoids, but there is only limited evidence for this in patients with tuberculosis IRIS. Autoimmune disorders (such as Graves' disease) have also been reported as IRIS reactions; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Osteonecrosis:

Although the aetiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index), cases of osteonecrosis have been reported, particularly in patients with advanced HIV-disease and/or long-term exposure to combination antiretroviral therapy (cART). Patients should be advised to seek medical advice if they experience joint aches and pain, joint stiffness or difficulty in movement.

Opportunistic infections:

Patients receiving VOCABRIA should be advised that they may continue to develop opportunistic infections and other complications of HIV infection, and therefore they should remain under close observation by healthcare professionals experienced in the treatment of patients with associated HIV disease. Regular monitoring of viral load and CD4 counts needs to be done.

Transmission of infection:

While effective viral suppression with antiviral suppression, including VOCABRIA, has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

Concomitant treatment with rilpivirine:

VOCABRIA is indicated for the treatment of HIV in combination with rilpivirine, therefore, the prescribing information for rilpivirine should be consulted.

VOCABRIA tablets contain lactose:

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

VOCABRIA tablets contain less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free.'

VOCABRIA Suspension for injections contain mannitol: mannitol may have a mild laxative effect.

4.5 Interactions with other medicines and other forms of interaction:

VOCABRIA is indicated for the treatment of HIV in combination with rilpivirine, therefore, the prescribing information for rilpivirine should be consulted for associated interactions.

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 VOCABRIA 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 VOCABRIA injection. The interaction data provided in Table 6 is obtained from studies with oral VOCABRIA.

Table 6 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 VOCABRIA is necessary when co-administered with rilpivirine.
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 VOCABRIA with rifampicin is contraindicated. Dosing recommendations for co-administration of VOCABRIA (oral and injection) with rifampicin have not been established.
Rifapentine	Cabotegravir ↓	Rifapentine may significantly decrease cabotegravir plasma concentrations, concomitant use is contraindicated.
Rifabutin	Cabotegravir ↓ AUC ↓ 21 % C_{max} ↓ 17 % C_T ↓ 8 %	*VOCABRIA tablets:* Rifabutin did not significantly change cabotegravir plasma concentration. No dose adjustment is required. Prior to initiation of oral VOCABRIA therapy, the prescribing information for VOCABRIA injection should be consulted regarding concomitant use with rifabutin. *VOCABRIA injection:* Rifabutin may decrease cabotegravir plasma concentrations, concomitant use should be avoided.
Anticonvulsants: Carbamazepine Oxcarbazepine Phenytoin Phenobarbitone	Cabotegravir ↓	Metabolic inducers 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
Antacids (e.g., magnesium, calcium or aluminium)	Cabotegravir ↓	*VOCABRIA 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 VOCABRIA. *VOCABRIA injection:* Interaction is not relevant following parenteral administration.
Oral contraceptives (Ethinyl estradiol (EE) and levonorgestrel	EE ↔ AUC ↑ 2 % C_{max} ↓ 8 % Cт ↔ 0 % LNG ↔	Cabotegravir did not significantly change EE and levonorgestrel plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with VOCABRIA.

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).

Lactation:

Safety in lactation has not been established.

Health experts recommend that where possible HIV infected women do not breast feed their infants in order to avoid transmission of HIV. In settings where formula feeding is not feasible, local official lactation and treatment guidelines should be followed when considering breast feeding during antiretroviral therapy.

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

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:

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

4.8 Undesirable effects:

Clinical trial data:

VOCABRIA + rilpivirine were administered as a combination regimen (monthly and every 2-month dosing) and associated adverse events (AEs) are listed in Table 6. AEs listed include those attributable to both the oral and injectable formulations of VOCABRIA and rilpivirine. When frequencies differed between phase III studies, the highest frequency category is quoted in Table 7.

The most frequently reported AEs from monthly dosing studies were injection site reactions (up to 84 %), headache (up to 12 %) and pyrexia[3] (10 %).

The most frequently reported AERs from the 2-month dosing were injection site reactions (76 %), headache (7 %) and pyrexia[3] (7 %).

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 7: Adverse Events

MedDRA System Organ Class (SOC)	Frequency Category	AEs for cabotegravir + rilpivirine regimen
Psychiatric disorders	Common	Depression, anxiety, abnormal dreams, insomnia
Nervous system disorders	Very common	Headache
	Common	Dizziness
	Uncommon	Somnolence, vasovagal reactions (in response to injections)
Gastrointestinal disorders	Common	Nausea, vomiting, abdominal pain[1], flatulence, diarrhoea
Hepatobiliary Disorders	Uncommon	Hepatotoxicity
Skin and subcutaneous tissue disorders	Common	Rash[2]
Musculoskeletal and connective tissue disorders	Common	Myalgia
General disorders and administrative site conditions	Very common	Injection site reactions[4] (pain and discomfort, site nodule, induration), pyrexia[3]
	Common	Injection site reactions[4] (swelling, erythema, pruritus, bruising, warmth, haematoma), fatigue, asthenia, malaise
	Uncommon	Injection site reactions[4] (cellulitis, abscess, anaesthesia, haemorrhage, discolouration)
Investigations	Common	Weight increased
	Uncommon	Transaminase increased

[1] Abdominal pain includes the following grouped MedDRA preferred terms: abdominal pain, upper abdominal pain.

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

[3] Pyrexia includes the following grouped MedDRA preferred terms: pyrexia, body temperature increased, feeling hot. Some events of pyrexia had a close temporal association with injection.

[4] Injection site reactions listed in the table have been reported in 2 subjects or more.

Local Injection Site Reactions (ISRs):

In each of the three Phase III studies, approximately ≤ 1 % of subjects discontinued treatment with cabotegravir + rilpivirine because of ISRs.

When dosing monthly, out of 30 393 injections, 6 815 ISRs were reported. When dosing every 2 months, out of 8 470 injections, 2 507 ISRs were reported.

The severity of reactions was generally mild (Grade 1, 70 % - 75 % of subjects) or moderate (Grade 2, 27 % - 36 % of subjects). 3-4 % of subjects experienced severe (Grade 3) ISRs, and no subjects experienced Grade 4 ISRs. The median duration of overall ISR events was 3 days. The percentage of subjects reporting ISRs decreased over time.

Weight increased:

At the Week 48 time point, subjects in FLAIR and ATLAS, who received VOCABRIA + rilpivirine gained a median of 1,5 kg in weight (pooled analysis). In the individual studies FLAIR and ATLAS, the median weight gains in the VOCABRIA + rilpivirine arms were 1,3 kg and 1,8 kg respectively. At the 48-week timepoint, in ATLAS-2M the median weight gain in both the monthly and 2-monthly CAB+RPV dosing arms was 1,0 kg.

Changes in laboratory chemistries:

Small, non-progressive increases in total bilirubin (without clinical jaundice) were observed with treatment with cabotegravir + rilpivirine. These changes are not considered clinically relevant as they likely reflect competition between CAB and unconjugated bilirubin for a common clearance pathway (UGT1A1).

Elevated transaminases (ALT/AST) were observed in subjects receiving VOCABRIA + rilpivirine during the clinical trials. These elevations were primarily attributed to acute viral hepatitis. A few subjects had transaminase elevations attributed to suspected drug-related hepatotoxicity.

Elevated lipases were observed during clinical trials with VOCABRIA + rilpivirine; Grade 3 and 4 lipase increases occurred with cabotegravir + rilpivirine. These elevations were generally asymptomatic and did not lead to discontinuation.

Asymptomatic creatine phosphokinase (CPK) elevations, mainly in association with exercise, have also been reported with VOCABRIA + rilpivirine treatment.

For other AEs associated with rilpivirine, the relevant prescribing information should be consulted.

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 VOCABRIA. 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 VOCABRIA 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:

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.

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:

The number of subjects who met Confirmed Virologic Failure (CVF) criteria was low across the pooled FLAIR and ATLAS trials. In the pooled analysis, there were 7 CVFs on cabotegravir plus rilpivirine (7/591, 1,2 %). The CVFs on cabotegravir + rilpivirine in 201584 (FLAIR) with resistance data had Subtype A1 with IN substitution L74I, treatment-emergent INI resistance associated substitution Q148R or G140R; rilpivirine resistance-associated substitution K101E, E138E/A/K/T or E138K. The three CVFs in 201585 (ATLAS) had subtype A, A1 and AG.

The following mutations were noted: rilpivirine resistance-associated substitution E138A, E138E/K, or E138K; IN substitution L74I; INI resistance-associated substitution N155H.

In the ATLAS-2M study, the following RPV resistance-associated mutations of, K101E, E138A, E138E/K, Y188L, K101E+M230L or K101E+E138A; IN substitution L74I; INI resistance-associated substitutions (N155H; N155N/H, Q148R; Q148Q/R+N155N/H, or Q148R+E138E/K; were observed.

In the Q4W arm, neither subject had any RPV or INSTI resistance-associated substitutions at Baseline. One subject had the NNRTI substitution, G190Q, in combination with the NNRTI polymorphism, V189I. At SVF timepoint, one subject had on-treatment rilpivirine resistance-associated mutations, K101E + M230L and the other retained the G190Q + V189I NNRTI substitutions with the addition of V179V/I. Both subjects showed reduced phenotypic susceptibility to RPV. Both subjects also had INSTI resistance-associated mutations, either Q148R + E138E/K or N155N/H at SVF and 1 subject had reduced susceptibility to CAB. Neither subject had the INSTI substitution, L74I. Fold-changes for the Q4W subjects were 1,8 and 4,6 for cabotegravir, 1,0 and 1,4 for dolutegravir and 1,1 and 1,5 for bictegravir.

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.

Clinical efficacy and safety:

Monthly Dosing:

The efficacy of cabotegravir has been evaluated in two Phase III randomised, multicentre, active-controlled, parallel-arm, open-label, non-inferiority studies, FLAIR (201584) and ATLAS (201585).

In a pooled analysis of the two pivotal studies, cabotegravir + rilpivirine was non-inferior to CAR on the proportion of subjects having plasma HIV-1 RNA ≥ 50 c/mL (1,9 % and 1,7 % respectively) at Week 48.

In the FLAIR study at 96 Weeks, the results remained consistent with the results at 48 Weeks. The proportion of subjects having plasma HIV-1 RNA ≥ 50 c/mL in cabotegravir plus rilpivirine (n = 283) was 3,2 %. The proportion of subjects having plasma HIV-1 RNA < 50 c/mL in cabotegravir plus rilpivirine and CAR was 87 %.

In the FLAIR study, an evaluation of safety and efficacy was performed at Week 124 for patients electing to switch (at Week 100) from abacavir/dolutegravir/lamivudine to cabotegravir plus rilpivirine in the Extension Phase. Subjects were given the option to switch with or without an oral lead-in phase, creating an oral lead-in (OLI) group (n = 121) and a direct to injection (DTI) group (n = 111). At Week 124, the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL was 0,8 % and 0,9 % for the oral lead-in and direct to injection groups, respectively. The rates of virologic suppression (HIV-1 RNA < 50 c/mL) were similar in both OLI (93,4 %) and DTI (99,1 %) groups.

Every 2-month Dosing:

In ATLAS-2M, cabotegravir + rilpivirine administered every 2 months was non-inferior to cabotegravir and rilpivirine administered every month on the proportion of subjects having plasma HIV-1 RNA ≥ 50 c/mL (1,7 % and 1,0 % respectively) at Week 48. The adjusted treatment difference between cabotegravir + rilpivirine administered every 2 months and every month (0,8; 95 % CI: -0,6, 2,2) met the non-inferiority criterion (upper bound of the 95 % CI below 4 %). Furthermore, cabotegravir + rilpivirine dosed every 2 months was non-inferior to CAB+RPV dosed every month on the proportion of subjects having plasma HIV-1 RNA < 50 c/mL (94 % and 93 %, respectively) at Week 48. The adjusted treatment difference between cabotegravir + rilpivirine dosed every 2 months and monthly (0,8; 95 % CI: -2,1, 3,7) met the non-inferiority criteria (lower bound of the 95 % CI greater than -10 %.

In the ATLAS-2M study, treatment differences on the primary endpoint across baseline characteristics (CD4+ lymphocyte count, gender, race, BMI, age and prior exposure to cabotegravir/rilpivirine) were not clinically meaningful.

5.2 Pharmacokinetic properties:

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 $AUC_{(0-\infty)}$ 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 intramuscular dose, plasma cabotegravir concentrations are detectable on the first day and gradually rise to reach maximum plasma concentration with a median T_{max} of 7 days. Cabotegravir has been detected in plasma up to 52 weeks or longer after administration of a single injection. Pharmacokinetic steady state is achieved by 44 weeks.

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. Median cervical and vaginal tissue:plasma ratios ranged from 0,16 to 0,28 and median rectal tissue:plasma ratios were ≤ 0,08 following a single 400 mg IM injection at 4, 8, and 12 weeks after dosing.

Cabotegravir is present in cerebrospinal fluid (CSF). In HIV-infected subjects receiving a regimen of cabotegravir injection + rilpivirine injection, the cabotegravir CSF to plasma concentration ratio [median (range)] (n = 16) was 0,003 (0,002 to 0,004), one week following a steady-state cabotegravir (Q4W or Q8W) injection.

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). 47 % 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. 27 % 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 0,151 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 0,197 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.

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 limited data for the use of cabotegravir in subjects with HCV co-infection. There are no data for the use of cabotegravir in subjects with HBV co-infection.

Polymorphisms in Drug Metabolising Enzymes:

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

5.3 Preclinical safety data:

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: Non-clinical data from rat pre- and post-natal (PPN) studies at 1000 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 glycollate, 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, VOCABRIA injections must not be mixed with other medicines.

6.3 Shelf life:

VOCABRIA 30 mg: 36 months

VOCABRIA 400 mg (2 mL): 36 months

VOCABRIA 600 mg (3 mL): 36 months

6.4 Special precautions for storage:

VOCABRIA tablets:

Store at or below 30 ºC.

VOCABRIA 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 white HDPE (high density polyethylene) bottles with child-resistant closures.

Suspension for Injection:

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

and sealed with bromobutyl rubber stoppers in two nominal fill presentations, 2 mL and 3mL. The stopper is secured with an aluminum overseal with a removeable plastic cap. The 2 mL fill presentation has a dark gray cap and the 3 mL fill presentation has an orange cap. The vial in the carton is a brown colour after terminal sterilization.

Not all presentations are available in the market.

6.6 Special precautions for disposal and or handling:

A complete dose requires two injections:

- 2 mL of VOCABRIA + 2 mL of rilpivirine OR
- 3 mL of VOACABRIA + 3 mL of rilpivirine.

VOCABRIA and Rilpivirine injections are suspensions that do not need further dilution or reconstitution.

VOCABRIA and Rilpivirine are for intramuscular use.

Both injections should be administered at separate gluteal injection sites.

VOCABRIA and Rilpivirine injections are for intramuscular use only.

The administration order is not important.

You will also need:

- 1 luer-lock syringe (5 mL)
- 1 aspiration needle

  1 luer-lock needle size (1½ inch* (21G – 23G) (Use safety injection needle if available).

  *Consider the patient's build and use medical judgement to select an appropriate injection length
- Gloves

- 2 alcohol swabs
- 2 gauze swabs
- A suitable sharpe container
- 1 rilpivirine 2 mL/3mL pack

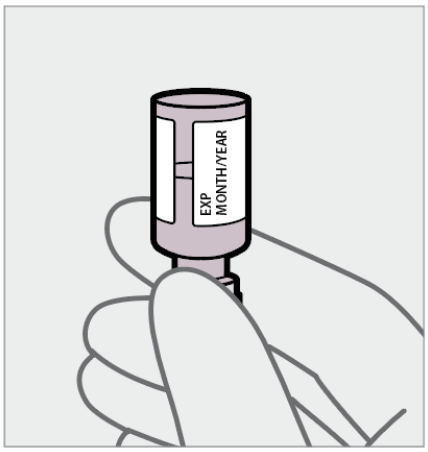
1. Prepare vial:

Inspect vial.

Obtain 1 vial pack. Take the vial out of the carton.

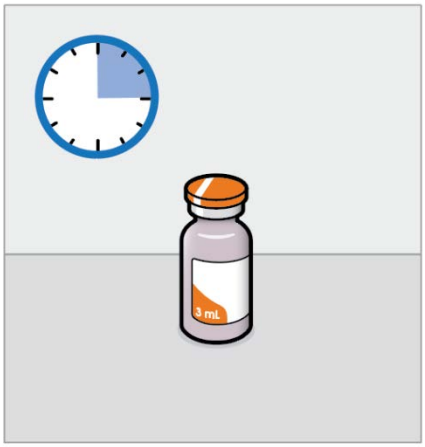
Check the expiry date (EXP) on the vials.

Do not use if the expiry date has passed.



Leave vial at room temperature for 15 minutes.

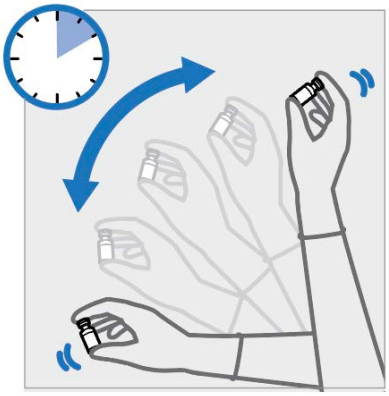
If the vial has been stored in a refrigerator, place the vial on a flat surface and let it sit at room temperature for at least **15 minutes** before use.



2. Prepared medication for injection:

Shake vigorously.

Hold one vial firmly and shake vigorously with a loose wrist and a long arm motion for at least **10 seconds**.

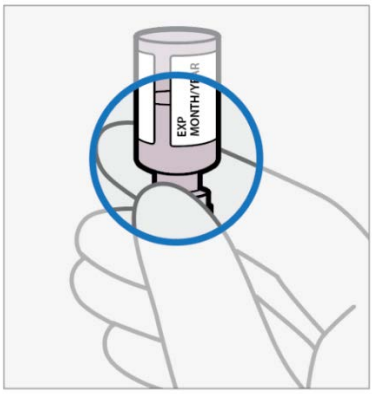


Check liquid.

Check the resuspension through the brown tinted glass with the cap pointing down. You may see small air bubbles. This is normal.

If the resuspension is not uniform,

shake the vial vigorously again.

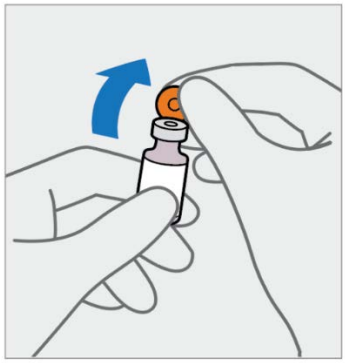


Remove vial cap:

Remove the cap from vial.

Wipe the rubber stopper with an alcohol swab.

Do not let anything touch the rubber stopper after wiping it.

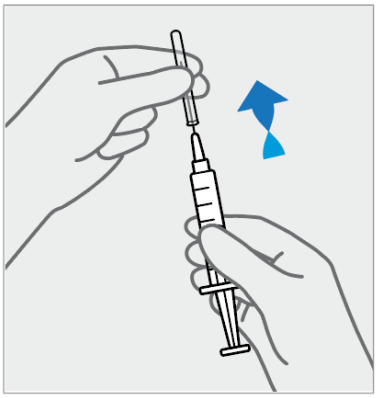


3. Prepare the Syringe:

Attach aspiration needle.

Hold the syringe upright and firmly twist the syringe onto the needle base.

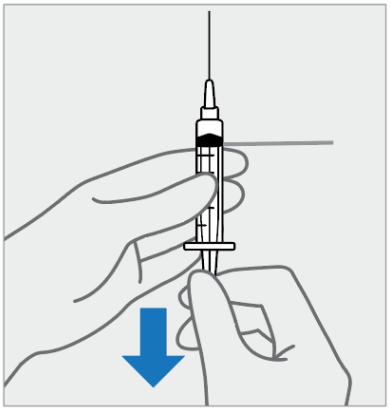
Remove the needle cover.



Draw air into syringe.

Pull the plunger and draw **1 ml** of air into the syringe.

Doing so makes it easier to draw up liquid later.

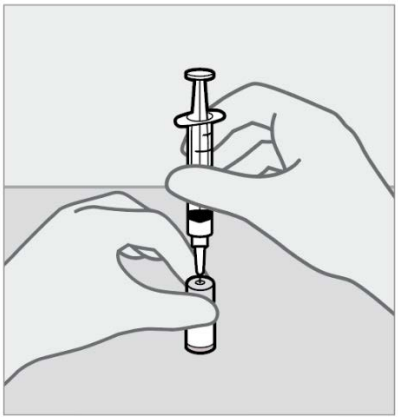


4. Draw and adjust the dose:

Insert aspiration needle into vial.

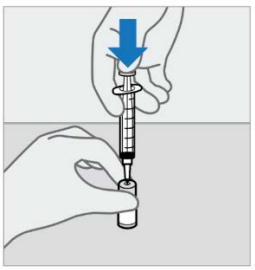
Place the vial on a flat surface.

Insert the needle into the stopper.



Push air into vial.

Press plunger all the way down to push the air into the vial.

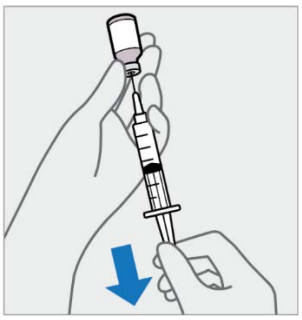


Draw up liquid.

Invert the syringe and vial.

Firmly hold the barrel of the syringe. Slowly pull the plunger to **withdraw as much liquid as possible** into the syringe.

There may be more liquid in the syringe than the dose amount. This is normal.



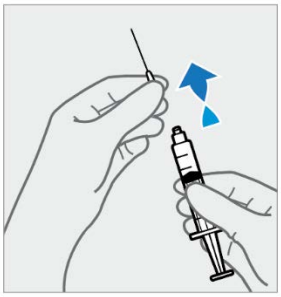
Remove aspiration needle.

Pull the needle out of the vial stopper.

Twist the needle off the syringe.

NOTE: Keep the syringe upright to avoid leakage.

Check that the suspension looks uniform and white to pink.

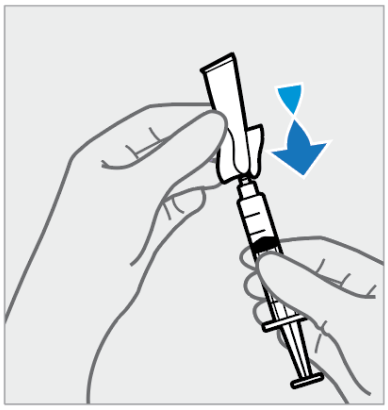


Attach injection needle.

Peel the needle packaging halfway.

Attach injection needle.

Remove the needle packaging from the needle.

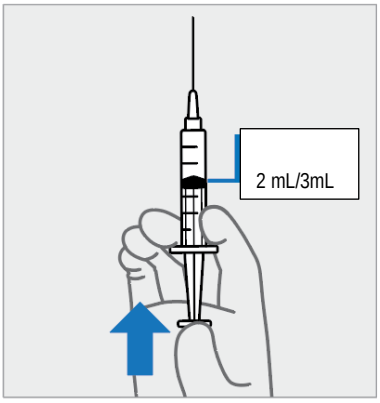


The medication can be in the syringe for up to 2 hours. If more than 2 hours pass, dispose of the syringe

Adjust dose.

Hold the syringe with the needle pointing up.

Press the plunger to the **2 mL/3 mL** line to remove extra liquid and any air bubbles.



5. Inject VOCABRIA in a gluteal site:

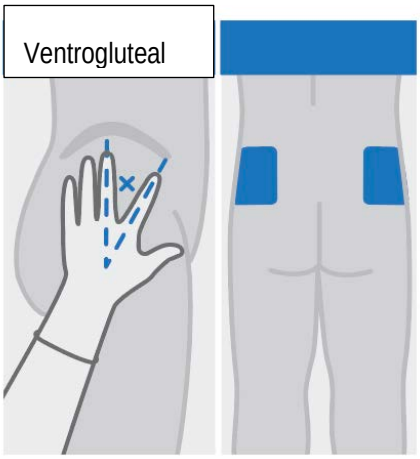
Prepare injection site.

Administer the injection to one of the following sites:

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

Clean the injection site with an alcohol swab.

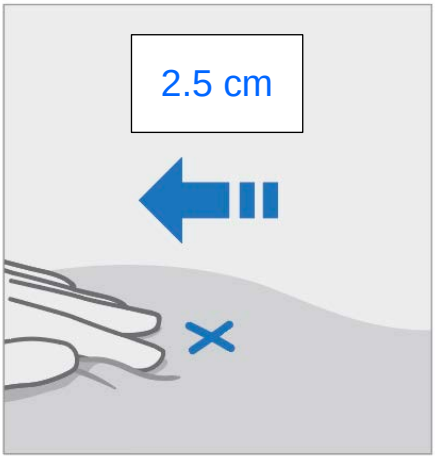
Allow the skin to air dry.



Stretch skin.

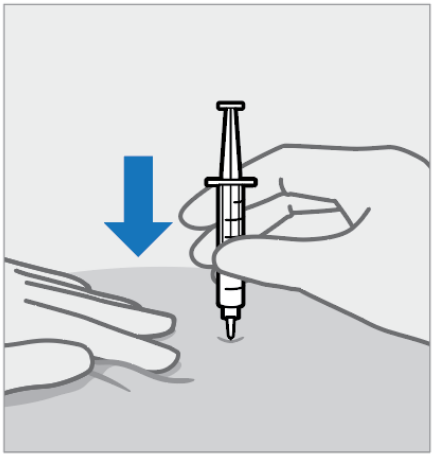
Firmly drag the skin covering the injection site, displacing it by about 2,5 cm. This technique minimizes medicine leakage from the injection site.

Keep the skin held in this position for the entire injection.



Insert needle.

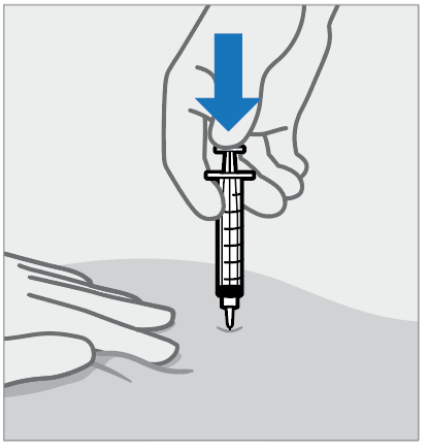
Insert the needle to its full depth or deep enough to reach the muscle.



Inject medication.

Keeping the skin stretched, slowly press the plunger all the way down until it stops.

Remove the needle and immediately let go of the skin.



Check injection site.

There may be a small amount of blood or liquid at the injection site.

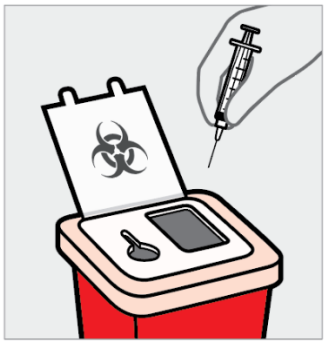
Hold pressure over the skin with a gauze pad until any bleeding stops.

Do not rub the injection site. If needed, cover the injection site with a bandage.

6. After the Injection:

Dispose.

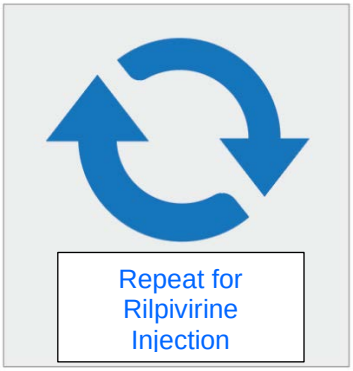
Dispose of the used syringe and vial according to your local health and safety regulations.



Repeat for rilpivirine injection.

If you have not yet injected rilpivirine, refer to the Instructions for Use that come with rilpivirine to complete the treatment.

Inject rilpivirine into a separate ventrogluteal site from the cabotegravir injection site.



7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBER(S):

VOCABRIA 400 mg (2 mL): 56/20.2.8/0124

VOCABRIA 600 mg (3 mL): 56/20.2.8/0125

VOCABRIA 30 mg: 56/20.2.8/0126

9. DATE OF FIRST AUTHORISATION:

4 July 2023

PDS-4