VOCABRIA

Cabotegravir

QUALITATIVE AND QUANTITATIVE COMPOSITION:

Film-coated Tablet:
White, film-coated, oval tablet marked with "SV CTV" one side.
Each film-coated tablet contains 30 mg of cabotegravir (as cabotegravir sodium).

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

Suspension for Injection:
White to light pink, prolonged-release suspension for injection.
Each 2 mL vial contains 400 mg cabotegravir (as cabotegravir free acid).
Each 3 mL vial contains 600 mg cabotegravir (as cabotegravir free acid).

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

CLINICAL INFORMATION:

Indications:

Film-coated Tablets:

VOCABRIA tablets are indicated in combination with rilpivirine tablets for short term (*see Dosage and Administration)* 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:

VOCABRIA 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 (*see Clinical studies*).

Dosage and Administration:

Pharmaceutical Form:

Film-coated tablet and suspension for injection.

Posology:

Therapy should be initiated by a physician 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.

Method of Administration:

Film-coated Tablet:

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 Instructions for Use & Handling*).

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.

Cabotegravir 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

VOCABRIA injection to assess tolerability to cabotegravir. *VOCABRIA* tablets should be taken with together rilpivirine tablets.

Table 1 Oral Lead-in Dosing Schedule in Adults

	ORAL LEAD-IN
Drug	**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.

Continuation Injection:

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 Monthly Intramuscular Dosing Schedule in Adults

	INITIATION INJECTION	**CONTINUATION INJECTION**
Drug	**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**
Drug	**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**
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 *VOCABRIA* 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 two 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 (400 mg) injections dosing schedule as soon as possible
>2 months:	Re-initiate the patient on the 3 mL (600 mg) dose, and then continue to follow the monthly 2 mL (400 mg) 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 two 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 has not been established.

Elderly:

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

Renal impairment:

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

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, phenobarbital, 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.

Warnings and Precautions:

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 cabotegravir 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 cabotegravir, physicians 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 Dosage and Administration, Contraindications and Long acting properties of VOCABRIA injection, Clinical Studies).*

Hepatotoxicity:

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

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

Long-acting properties of VOCABRIA injection:

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

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 *VOCABRIA* 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 medicinal products that may reduce its exposure (*see Interactions*).

Opportunistic infections:

Patients receiving *VOCABRIA* or any other antiretroviral therapy may still develop opportunistic infections and other complications of HIV infection. Therefore, patients should remain under close clinical observation by physicians experienced in the treatment of these associated HIV diseases.

Transmission of infection:

While effective viral suppression with antiretroviral therapy 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.

Interactions:

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 agents:

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

Cabotegravir inhibited the organic anion transporters (OAT) 1 (IC50=0.81 μM) and OAT3 (IC50=0.41 μM) *in vitro*, however, based on physiologically based

pharmacokinetic (PBPK) modelling no interaction with OAT substrates is expected at clinically relevant concentrations.

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

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

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

Effect of other agents on the pharmacokinetics of cabotegravir:

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

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

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

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

No drug interaction studies have been performed with cabotegravir injection. The drug interaction data provided in Table 6 is obtained from studies with oral cabotegravir.

Table 6 Drug interactions

Concomitant Drug Class: Drug Name	**Effect on Concentration of Cabotegravir or Concomitant Drug**	**Clinical Comment**
HIV-1 Antiviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine	Cabotegravir ↔ AUC ↑ 1% C_{max} ↑ 4% Cτ ↔ 0%	Etravirine did not significantly change cabotegravir plasma concentration. No dosage adjustment is required.
Non-nucleoside Reverse	Cabotegravir ↔ AUC ↑ 12%	Rilpivirine did not significantly change cabotegravir plasma

Transcriptase Inhibitor: Rilpivirine	C_{max} ↑ 5% Cτ ↑ 14% Rilpivirine ↔ AUC ↓ 1% C_{max} ↓ 4% Cτ ↓ 8%	concentration. No dose adjustment of *VOCABRIA* is necessary when co-administered with rilpivirine.
Other Agents		
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% Cτ ↓ 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 Phenobarbital	Cabotegravir ↓	Metabolic inducers may significantly decrease cabotegravir plasma concentrations. Concomitant use is contraindicated.
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% Cτ ↔ 0% LNG ↔	Cabotegravir did not significantly change ethinyl estradiol and levonorgestrel plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with *VOCABRIA*.

Pregnancy and Lactation:

Fertility:

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

Pregnancy:

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

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

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

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

Lactation:

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 *VOCABRIA* injection.

Effects on Ability to Drive and Use Machines:

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

Adverse Reactions:

Clinical trial data:

Adverse drug reactions (ADRs) for cabotegravir + rilpivirine were identified from Phase III clinical trials; 201584 (FLAIR) and 201585 (ATLAS) (pooled analysis) and 207966 ATLAS-2M at Week 48.

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

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

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

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

Table 7 Adverse reactions

MedDRA System Organ Class (SOC)	Frequency Category	ADRs for cabotegravir + rilpivirine regimen
Psychiatric disorders	Common	Depression Anxiety Abnormal dreams Insomnia
Nervous system disorders	Very common	Headache
	Common	Dizziness
	Uncommon	Somnolence Vasovagal reactions[4] (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. The majority of pyrexia events were reported within one week of injections.
[4] Associated with injection formulation only. Injection site reactions listed in the table have been reported in 2 subjects or more.

The overall safety profile at Week 96 and Week 124 in FLAIR study were consistent with that observed at Week 48, with no new safety findings identified. In the extension phase of FLAIR study, initiating the CAB LA + RPV LA regimen with Direct to Injection did not identify any new safety concerns related to omitting the Oral Lead-in phase (*see Clinical Studies*).

Local Injection Site Reactions:
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 30393 injections, 6815 ISRs were reported. When dosing every 2 months, out of 8470 injections, 2507 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 cabotegravir + rilpivirine gained a median of 1.5 kg in weight; those in the CAR group gained a median of 1.0 kg (pooled analysis). In the individual studies FLAIR and ATLAS, the median weight gains in the cabotegravir + rilpivirine arms were 1.3 kg and 1.8 kg respectively, compared to 1.5 kg and 0.3 kg in the CAR arms. 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 cabotegravir and unconjugated bilirubin for a common clearance pathway (UGT1A1).

Elevated transaminases (ALT/AST) were observed in subjects receiving cabotegravir + 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 at a higher incidence with *VOCABRIA* + rilpivirine compared with the CAR group. 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 cabotegravir + rilpivirine treatment.

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

Post-marketing data:

No data

Overdose:

Symptoms and signs:

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

Treatment:

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 drug following an injection (*see Warnings and Precautions*).

PHARMACOLOGICAL PROPERTIES:

Pharmacodynamics:

ATC code:

Pharmacotherapeutic group: Antivirals for systemic use, Integrase inhibitors.

ATC code: J05AJ04

Mechanism of action:

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

Pharmacodynamic effects:

Antiviral Activity in cell culture:
Cabotegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean concentration of cabotegravir necessary to reduce viral replication by 50 percent (EC_{50}) values of 0.22 nM in peripheral blood mononuclear cells (PBMCs), 0.74nM in 293T cells and 0.57 nM in MT-4 cells. Cabotegravir demonstrated antiviral activity in cell culture against a panel of 24 HIV-1 clinical isolates (three in each group of M clades A, B, C, D, E, F, and G, and 3 in group O) with EC_{50} values ranging from 0.02 nM to 1.06 nM for HIV-1. Cabotegravir EC_{50} values against three HIV-2 clinical isolates ranged from 0.10 nM to 0.14 nM. No clinical data is available in patients with HIV-2.

Antiviral Activity in combination with other antiviral agents:
No drugs with inherent anti-HIV activity were antagonistic to cabotegravir's antiretroviral activity (*in vitro* assessments were conducted in combination with rilpivirine, lamivudine, tenofovir and emtricitabine).

Effect of Human Serum and Serum Proteins*:*
In vitro studies suggested a 408-fold shift in IC_{50} of cabotegravir in the presence of 100% human serum (by method of extrapolation), and the protein adjusted IC_{50} (PA-IC_{50}) was estimated to be 102 nM in MT4 cells.

Resistance in vitro:
Isolation from wild-type HIV-1 and activity against resistant strains: Viruses with >10-fold increase in cabotegravir EC50 were not observed during the 112-day passage of strain IIIB. The following integrase (IN) mutations emerged after passaging wild type HIV-1 (with T124A polymorphism) in the presence of cabotegravir: Q146L (fold-change range 1.3-4.6), S153Y (fold-change range 2.8-8.4), and I162M (fold-change = 2.8). As noted above, the detection of T124A is selection of a pre-existing minority variant that does not have differential susceptibility to cabotegravir. No amino acid substitutions in the integrase region were selected when passaging the wild-type HIV-1 NL-432 in the presence of 6.4 nM of cabotegravir through Day 56.

Among the multiple mutants, the highest fold-change was observed with mutants containing Q148K or Q148R. E138K/Q148H resulted in a 0.92-fold decrease in susceptibility to cabotegravir but E138K/Q148K resulted in an 81-fold decrease in susceptibility to cabotegravir. G140C/Q148R and G140S/Q148R resulted in a 22- and 12-fold decrease in susceptibility to cabotegravir, respectively. While N155H did not alter susceptibility to cabotegravir, N155H/Q148R resulted in a 61-fold decrease in susceptibility to cabotegravir.

Resistance in vivo:
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%) and 7 CVFs on current antiretroviral regimen (7/591, 1.2%). The three CVFs on cabotegravir + rilpivirine in 201584 (FLAIR) with resistance data had Subtype A1 with IN substitution L74I (which by itself does not cause resistance to any INI) detected at Baseline and suspected virologic failure (SVF). In addition, 2/3 CVFs had treatment emergent INI resistance associated substitution Q148R while 1/3 had G140R with reduced phenotypic susceptibility to cabotegravir. All 3 CVFs

carried one rilpivirine resistance-associated substitution: K101E, E138E/A/K/T or E138K, and 2/3 showed reduced phenotypic susceptibility to rilpivirine. The 3 CVFs in 201585 (ATLAS) had subtype A, A1 and AG. The 2 CVFs with subtype A and A1 both carried IN substitution L74I in Baseline PBMC HIV-1 DNA and at SVF in HIV-1 RNA. In addition, 1/3 CVFs carried the INI resistance-associated substitution N155H at SVF. All 3 CVFs had treatment-emergent rilpivirine resistance-associated substitutions: E138A, E138E/K or E138K, and showed reduced phenotypic susceptibility to RPV while 1/3 also showed reduced cabotegravir phenotypic susceptibility. In 2/3 CVFs the RPV resistance-associated substitutions observed at SVF were also observed at Baseline in PBMC HIV-1 DNA. The seventh CVF (FLAIR) never received an injection.

The substitutions associated with resistance to long-acting cabotegravir injection, observed in the pooled ATLAS and FLAIR trials, are G140R (n=1), Q148R (n=2), and N155H (n=1).

In the ATLAS-2M study 10 subjects met CVF criteria through Week 48: 8 subjects (1.5%) in the Q8W arm and 2 subjects (0.4%) in the Q4W arm. Eight subjects met CVF criteria at or before the Week 24 timepoint. At SVF, the 10 CVFs had HIV-1 subtype A (n=2), A1 (n=2), B (n=4), C (n=1), or Complex (n=1).

At Baseline in the Q8W arm, 5 subjects had RPV resistance-associated mutations of Y181Y/C + H221H/Y, Y188Y/F/H/L, Y188L, E138A or E138E/A and 1 subject contained cabotegravir resistance mutation, G140G/R (in addition to the above Y188Y/F/H/L RPV resistance-associated mutation). At the SVF timepoint in the Q8W arm, 6 subjects had rilpivirine resistance-associated mutations with 2 subjects having an addition of K101E and 1 subject having an addition of E138E/K from Baseline to SVF timepoint. Rilpivirine fold-change (FC) was above the biological cut-off for 7 subjects and ranged from 2.4 to 15. Five of the 6 subjects with rilpivirine resistance-associated substitution, also had INSTI resistance-associated substitutions, N155H (2); Q148R; Q148Q/R+N155N/H (2). INSTI substitution, L74I, was seen in 4/7 subjects. The Integrase genotype and phenotype assay failed for one subject and cabotegravir phenotype was unavailable for another. Fold-changes for the Q8W subjects ranged from 0.6 to 9.1 for cabotegravir, 0.8 to 2.2 for dolutegravir and 0.8 to 1.7 for bictegravir.

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, 42 healthy subjects were randomized into 6 random sequences and received three doses of oral

administration of placebo, cabotegravir 150 mg every 12 hours (mean steady-state C_{max} was approximately 2.8-fold, 5.4-fold and 5.6-fold above the 30 mg oral once-daily dose, the 400 mg cabotegravir injection monthly dose and the 600 mg cabotegravir injection every 2 month dose, respectively), or single dose of moxifloxacin 400 mg (active control). After baseline and placebo adjustment, the maximum time-matched mean QTc change based on Fridericia's correction method (QTcF) for cabotegravir was 2.62 msec (1-side 90% upper CI:5.26 msec). Cabotegravir did not prolong the QTc interval over 24 hours postdose.

Pharmacokinetics:

Oral:

Cabotegravir pharmacokinetics is similar between healthy and HIV-infected subjects. The PK variability of cabotegravir is moderate. In Phase I studies in healthy subjects, between-subject CVb% for AUC, C_{max}, and C_{tau} ranged from 26 to 34% across healthy subject studies and 28 to 56% across HIV-1 infected subject studies. Within-subject variability (CVw%) is lower than between-subject variability.

Suspension for Injection:

Cabotegravir pharmacokinetics is similar between healthy and HIV-infected subjects. The PK variability of cabotegravir is moderate to high. In HIV-infected subjects participating in Phase III studies, between-subject CVb% for C_{tau} ranged from 39 to 48%. Higher between-subject variability ranging from 41% to 89% was observed with single dose administration of long-acting cabotegravir injection.

Table 8. Pharmacokinetic parameters following cabotegravir orally once daily, and initiation, monthly 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)
Monthly injection[e]	400 mg IM monthly	2415 (1494, 3645)	4.2 (2.5, 6.5)	2.8 (1.7, 4.6)
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 FLAIR and ATLAS for the oral, initial and monthly regimen; and in ATLAS-2M for the every 2 month regimen.

[b] tau is dosing interval: 24 hours for oral administration; 1 month for monthly 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 OLI (DTI n=110), observed geometric mean (5th, 95th percentile) CAB C_{max} (1 week post initial injection) was 1.89 μg/mL (0.438, 5.69) and CAB C_{tau} was 1.43 μg/mL (0.403, 3.90).
[e] Monthly and every 2 month injection pharmacokinetic parameter values represent Week 48 data.

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.

VOCABRIA 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:

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

Distribution:

Cabotegravir is highly bound (approximately >99%) to human plasma proteins, based on *in vitro* data. Following administration of oral tablets, the mean apparent oral volume of distribution (Vz/F) in plasma was 12.3 L. In humans, the estimate of plasma cabotegravir Vc/F was 5.27 L and Vp/F was 2.43 L. These volume estimates, along with the assumption of high F, suggest some distribution of cabotegravir to the extracellular space.

Cabotegravir is present in the female and male genital tract. 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. Consistent with therapeutic cabotegravir concentrations in the CSF, CSF HIV-1 RNA (n=16) was <50 c/mL in 100% and <2 c/mL in 15/16 (94%) of subjects. At the same time point, plasma HIV-1 RNA (n=18) was <50 c/mL in 100% and <2 c/mL in 12/18 (66.7%) of subjects.

Metabolism:

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

Elimination:

Oral:

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

Suspension for Injection:

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

Special patient populations:

Gender:

Population pharmacokinetic analyses revealed no clinically relevant effect of gender on the exposure of cabotegravir, 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.

Clinical Studies:

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). The primary analysis was conducted after all subjects completed their Week 48 visit or discontinued the study prematurely.

In FLAIR, 629 HIV-1-infected, antiretroviral treatment (ART)-naive subjects received a dolutegravir integrase strand transfer inhibitor (INSTI) containing regimen for 20 weeks (either dolutegravir/abacavir/lamivudine or dolutegravir + 2 other nucleoside reverse transcriptase inhibitors if subjects were HLA-B*5701 positive). Subjects who were virologically suppressed (HIV-1 RNA <50 copies per mL, n=566) were then randomised (1:1) to receive either a cabotegravir plus rilpivirine regimen or remain on the current antiretroviral (CAR) regimen. Subjects randomised to receive the cabotegravir plus rilpivirine regimen, initiated treatment with oral lead-in dosing with a cabotegravir 30 mg tablet plus a rilpivirine 25 mg tablet, daily, for at least 4 weeks, followed by treatment with cabotegravir injection (month 1: 600 mg injection, month 2 onwards: 400 mg injection) plus rilpivirine injection (month 1: 900 mg injection, month 2 onwards: 600 mg injection), every month, for an additional 44 weeks.

In ATLAS, 616 HIV-1-infected, ART-experienced, virologically-suppressed (for at least 6 months) subjects (HIV-1 RNA <50 copies per mL) were randomised (1:1) and received either a cabotegravir plus rilpivirine regimen or remained on the CAR regimen. Subjects randomised to receive the cabotegravir plus rilpivirine regimen, initiated treatment with oral lead-in dosing with a cabotegravir 30 mg tablet plus a rilpivirine 25 mg tablet, daily, for at least 4 weeks, followed by treatment with cabotegravir injection (month 1: 600 mg, month 2 onwards: 400 mg injection) plus rilpivirine injection (month 1: 900 mg injection, month 2 onwards: 600 mg injection), every month, for an additional 44 weeks. In ATLAS, 50%, 17%, and 33% of subjects received an NNRTI, PI, or INI (respectively) as their baseline third treatment agent class prior to randomisation and this was similar between treatment arms.

At baseline, in the pooled analysis, in the cabotegravir + rilpivirine arm the median age of subjects was 38 years, 27% were female, 27% were non-white, and 7% had CD4+ cell count less than 350 cells per mm^3; these characteristics were similar between treatment arms.

The primary endpoint of both studies was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at week 48 (snapshot algorithm for the ITT-E population).

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. The adjusted treatment difference between cabotegravir + rilpivirine and CAR (0.2; 95% CI: -1.4, 1.7) for the pooled analysis met the non-inferiority criterion (upper bound of the 95% CI below 4%). Furthermore, in the pooled analysis, cabotegravir + rilpivirine was non-inferior to CAR on the proportion of subjects having plasma HIV-1 RNA <50 c/mL (93.1% and 94.4%, respectively) at Week 48. The

adjusted treatment difference between cabotegravir + rilpivirine and CAR (-1.4; 95% CI: -4.1, 1.4) for the pooled analysis met the non-inferiority criteria (lower bound of the 95% CI greater than -10%. [See Table 9]).

The non-inferiority result established in FLAIR and ATLAS demonstrated that the length of HIV-1 RNA virologic suppression prior to initiation of cabotegravir + rilpivirine (i.e. <6 months or ≥6 months) did not impact overall response rates.

The primary endpoint and other week 48 outcomes, including outcomes by key baseline factors, for FLAIR and ATLAS are shown in Tables 9 and 10.

Table 9 Virologic outcomes of randomized treatment of FLAIR and ATLAS at 48 weeks (snapshot analysis)

	FLAIR		ATLAS		Pooled Data	
	CAB + RPV N=283	**CAR N=283**	**CAB + RPV N=308**	**CAR N=308**	**CAB+RPV N=591**	**CAR N=591**
HIV-1 RNA≥50 copies/mL†	6 (2.1)	7 (2.5)	5 (1.6)	3 (1.0)	11 (1.9)	10 (1.7)
Treatment Difference % (95% CI)*	-0.4 (-2.8,2.1)		0.7 (-1.2, 2.5)		0.2 (-1.4, 1.7)	
HIV-1 RNA <50 copies/mL	265 (93.6)	264 (93.3)	285 (92.5)	294 (95.5)	550 (93.1)	558 (94.4)
Treatment Difference % (95% CI)*	0.4 (-3.7, 4.5)		-3.0 (-6.7, 0.7)		-1.4 (-4.1, 1.4)	
No virologic data at Week 48 window	12 (4.2)	12 (4.2)	18 (5.8)	11 (3.6)	30 (5.1)	23 (3.9)
Reasons						
Discontinued study/study drug due to adverse event or death	8 (2.8)	2 (0.7)	11 (3.6)	5 (1.6)	19 (3.2)	7 (1.2)
Discontinued study/study drug for other reasons	4 (1.4)	10 (3.5)	7 (2.3)	6 (1.9)	11 (1.9)	16 (2.7)
Missing data during window but on study	0	0	0	0	0	0

* Adjusted for baseline stratification factors.
† Includes subjects who discontinued for lack of efficacy, discontinued while not supressed.
N = Number of subjects in each treatment group, CI = confidence interval, CAR = current antiviral regimen.

Table 10 Proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at week 48 for key baseline factors (snapshot outcomes).

Baseline factors		Pooled Data from FLAIR and ATLAS	
		CAB+RPV N=591 n/N (%)	CAR N=591 n/N (%)
Baseline CD4+ (cells/ mm³)	<350	0/42	2/54 (3.7)
	≥350 to <500	5/120 (4.2)	0/117
	≥500	6/429 (1.4)	8 / 420 (1.9)
Gender	Male	6/429 (1.4)	9/423 (2.1)
	Female	5/162 (3.1)	1/168 (0.6)
Race	White	9/430 (2.1)	7/408 (1.7)
	Black African/American	2/109 (1.8)	3/133 (2.3)
	Asian/Other	0/52	0/48
BMI	<30 kg/m²	6/491 (1.2)	8/488 (1.6)
	≥30 kg/m²	5/100 (5.0)	2/103 (1.9)
Age (years)	<50	9/492 (1.8)	8/466 (1.7)
	≥50	2/99 (2.0)	2/125 (1.6)
Baseline antiviral therapy at randomisation	PI	1/51 (2.0)	0/54
	INI	6/385 (1.6)	9/382 (2.4)
	NNRTIs	4/155 (2.6)	1/155 (0.6)

BMI= body mass index
PI= Protease inhibitor
INI= Integrase inhibitor
NNRTI= non-nucleoside reverse transcriptase inhibitor

In both the FLAIR and ATLAS studies, treatment differences across baseline characteristics (CD4+ count, gender, age, race, BMI, age, baseline third agent treatment class) were comparable.

Subjects in both FLAIR and ATLAS were virologically suppressed prior to Day 1 or study entry, respectively, and a clinically relevant change from baseline in CD4+ cell counts was not observed.

Week 96 FLAIR:

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) and CAR (n=283) was 3.2% and 3.2% respectively (adjusted treatment difference between cabotegravir plus rilpivirine and CAR [0.0; 95% CI: -2.9, 2.9]). The proportion of subjects having plasma HIV-1 RNA <50 c/mL in cabotegravir plus rilpivirine and CAR was 87% and 89%, respectively (adjusted treatment difference between cabotegravir plus rilpivirine and CAR [-2.8; 95% CI: -8.2, 2.5]).

Week 124 FLAIR Direct to Injection:

In the FLAIR study, an evaluation of safety and efficacy was performed at Week 124 for patients electing to switch (at Week 100) from ABC/DTG/3TC to CAB + RPV in the Extension Phase, with and without an oral lead-in phase, creating an oral lead-in (OLI) group and a direct to injection (DTI) group.

At Week 124, rates of virologic suppression (HIV-1 RNA <50 c/mL) were similar in both DTI (110/111 [99.1%]) and OLI groups (113/121 [93.4%]). Initiating the CAB LA + RPV LA regimen with DTI did not identify any new safety concerns related to omitting the OLI phase.

Every 2-month Dosing:

The efficacy and safety of cabotegravir injection given every 2 months, has been evaluated in one Phase IIIb randomised, multicentre, parallel-arm, open-label, non-inferiority study, ATLAS-2M (207966). The primary analysis was conducted after all subjects completed their Week 48 visit or discontinued the study prematurely.

In ATLAS-2M, 1045 HIV-1 infected, ART experienced, virologically suppressed subjects were randomised (1:1) and received a cabotegravir plus rilpivirine injection regimen administered either every 2 months or monthly. Subjects initially on non-CAB/RPV treatment received oral lead-in treatment comprising one cabotegravir 30 mg tablet plus one rilpivirine 25 mg tablet, daily, for at least 4 weeks. Subjects randomised to monthly cabotegravir injections (month 1: 600 mg injection, month 2 onwards: 400 mg injection) and rilpivirine injections (month 1: 900 mg injection, month 2 onwards: 600 mg injection administered) received treatment for an additional 44 weeks. Subjects randomised to every 2-month cabotegravir injections (600 mg injection at months 1, 2, 4 and every 2 months thereafter) and rilpivirine injections (900 mg injection at months 1, 2, 4 and every 2 months thereafter) received treatment for an additional 44 weeks. Prior to randomisation, 63%, 13% and 24% of subjects received CAB+RPV for 0 weeks, 1 to 24 weeks and >24 weeks, respectively.

At baseline, the median age of subjects was 42 years, 27% were female, 27% were non-white and 6% had a CD4+ cell count less than 350 cells per mm^3; these characteristics were similar between the treatment arms.

The primary endpoint in ATLAS-2M was the proportion of subjects with a plasma HIV-1 RNA ≥50 c/mL at Week 48 (snapshot algorithm for the ITT-E population).

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%. [See Table 11]).

Table 11 Virologic outcomes of randomized treatment for ATLAS-2M at 48 weeks (snapshot analysis)

	2 month Dosing (Q8W)	Monthly Dosing (Q4W)
	N=522 (%)	N=523 (%)
HIV-1 RNA≥50 copies/mL†	9 (1.7)	5 (1.0)
Treatment Difference % (95% CI)*	0.8 (-0.6, 2.2)	
HIV-1 RNA <50 copies/mL	492 (94.3)	489 (93.5)
Treatment Difference % (95% CI)*	0.8 (-2.1, 3.7)	
No virologic data at week 48 window	21 (4.0)	29 (5.5)
Reasons:		
Discontinued study due to AE or death	9 (1.7)	13 (2.5)
Discontinued study for other reasons	12 (2.3)	16 (3.1)
On study but missing data in window	0	0

* Adjusted for baseline stratification factors.
† Includes subjects who discontinued for lack of efficacy, discontinued while not suppressed.
N = Number of subjects in each treatment group, CI = confidence interval, CAR = current antiviral regimen.

Table 12 Proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at week 48 for key baseline factors (snapshot outcomes)

		Number of HIV-1 RNA ≥50 c/mL / Total Assessed (%)	
		2 Month Dosing (Q8W)	Monthly dosing (Q4W)
Baseline CD4+ cell count (cells/mm3)	<350	1/ 35 (2.9)	1/ 27 (3.7)
	350 to <500	1/ 96 (1.0)	0/ 89
	≥500	7/391 (1.8)	4/407 (1.0)
Gender	Male	4/385 (1.0)	5/380 (1.3)
	Female	5/137 (3.5)	0/143
Race	White	5/370 (1.4)	5/393 (1.3)
	Non-White	4/152 (2.6)	0/130
	Black/African American	4/101 (4.0)	0/ 90
	Non-Black/African American	5/421 (1.2)	5/421 (1.2)
BMI	<30 kg/m^2	3/409 (0.7)	3/425 (0.7)
	≥30 kg/m^2	6/113 (5.3)	2/98 (2.0)

Age (years)	<35	4/137 (2.9)	1/145 (0.7)
	35 to <50	3/242 (1.2)	2/239 (0.8)
	>50	2/143 (1.4)	2/139 (1.4)
Prior exposure CAB/RPV	None	5/327 (1.5)	5/327 (1.5)
	1-24 weeks	3/69 (4.3)	0/68
	>24 weeks	1/126 (0.8)	0/128

BMI= body mass index

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.

Post-Hoc Analysis: Baseline Factors Associated with Virologic Failure:

Multivariable analyses of pooled phase 3 studies (ATLAS, FLAIR and ATLAS-2M), including data from 1039 HIV-infected adults with no prior exposure to cabotegravir plus rilpivirine, examined the influence of baseline viral and participant characteristics, dosing regimen, and post-baseline plasma drug concentrations on confirmed virologic failure (CVF) using regression modelling with a variable selection procedure. Through Week 48 in these studies, 13/1039 (1.25%) participants had CVF while receiving cabotegravir and rilpivirine.

Four covariates were significantly associated ($P<0.05$ for each adjusted odds ratio) with increased risk of CVF: rilpivirine resistance mutations at baseline identified by proviral DNA genotypic assay, HIV-1 subtype A6/A1 (associated with integrase L74I polymorphism), rilpivirine trough concentration 4 weeks following initial injection dose, body mass index of at least 30 kg/m^2 (associated with cabotegravir pharmacokinetics). Other variables including Q4W or Q8W dosing, female gender, or other viral subtypes (non A6/A1) had no significant association with CVF. No baseline factor, when present in isolation, was predictive of virologic failure. However, a combination of at least 2 of the following baseline factors was associated with an increased risk of CVF: rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI ≥30 kg/m^2 (see Table 13).

Table 13 Week 48 Outcomes by Presence of Key Baseline Factors of Rilpivirine-Resistance Associated Mutations, Subtype A6/A1[a] and BMI ≥30 kg/m^2

Baseline Factors (number)	Virologic Successes (%)[b]	Confirmed Virologic Failure (%)[c]
0	694/732 (94.8)	3/732 (0.41)
1	261/272 (96.0)	1/272 (0.37)[d]

≥2	25/35 (71.4)	9/35 (25.7)[e]
TOTAL (95% Confidence Interval)	980/1039 (94.3) (92.74%, 95.65%)	13/1039 (1.25) (0.67%, 2.13%)

[a] HIV-1 subtype A1 or A6 classification based on Los Alamos National Library panel from HIV Sequence database (June 2020)
[b] Based on the FDA Snapshot algorithm of RNA <50 copies/mL.
[c] Defined as two consecutive measurements of HIV RNA ≥200 copies/mL.
[d] Positive Predictive Value (PPV) <1%; Negative Predictive Value (NPV) 98%; sensitivity 8%; specificity 74%
[e] PPV 26%; NPV 99.6%; sensitivity 69%; specificity 97.5%

Non-Clinical Information:

Carcinogenesis/mutagenesis:

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

Reproductive Toxicology:

Fertility:

Cabotegravir when administered orally to male and female rats at 1000 mg/kg/day (>30 times the exposure in humans at the Maximum Recommended Human Dose [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 2000mg/kg/day (0.66 times the exposure in humans at the MRHD of 30 mg oral or approximately 1 times 400 mg IM dose) or to pregnant rats at doses up to 1000 mg/kg/day (>30 times the exposure in humans at the MRHD of 30 mg oral or 400 mg IM dose). In rats, alterations in foetal growth (decreased body weights) in the absence of maternal toxicity were observed at 1,000 mg/kg/day. Studies in pregnant rats showed that cabotegravir crosses the placenta and can be detected in foetal tissue.

Non-clinical data from rat pre- and post-natal (PPN) studies at 1,000 mg/kg/day (>30 times the exposure in humans at the MRHD of 30 mg oral or 400 mg IM dose) cabotegravir delayed the onset of parturition, and in some rats, this delay was associated with an increased number of stillbirths and neonatal mortalities immediately after birth. A lower dose of 5 mg/kg/day cabotegravir (>10 times the exposure in humans at the MRHD of 30 mg oral or 400 mg IM dose) was not associated with delayed parturition or neonatal mortality in rats. In rabbit and rat studies there was no effect on survival when foetuses

were delivered by caesarean section. When rat pups born to cabotegravir-treated dams were cross-fostered at birth and nursed by control mothers, similar incidences of neonatal mortalities were observed.

Animal toxicology and/or pharmacology:

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

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

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

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

PHARMACEUTICAL INFORMATION:

List of Excipients:

Film-coated tablets:

Tablet core:

Lactose Monohydrate
Microcystalline 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

Shelf-Life:

Tablets:

The expiry date applied to the product is shown on the pack when stored at:
Store at or below 30°C.

Suspension for Injection:

The expiry date applied to the product is shown on the pack when stored at:
Store at or below 30°C. Do not freeze.

Storage:

Unopened packs:

Keep out of the sight and reach of children.

Do not take *VOCABRIA* after the expiry date shown on the pack.

Don't throw away any medicines in wastewater or household waste. Ask your pharmacist how to throw away medicines no longer required. This will help to protect the environment.

Open packs:

Suspension for Injection:

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

Nature and Contents of Container:

Film-coated tablets:

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

Each bottle contains 30 film-coated tablets.

Suspension for Injection:

Individual vial only pack (single entity vial SEV):

VOCABRIA Injection, 200 mg/mL prolonged-release suspension for injection.

Cabotegravir is presented in a glass vial.

Incompatibilities:

Film-coated tablets:

None

Suspension for Injection:

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

Use and Handling:

See the Instructions for Use leaflet for complete administration instructions with illustrations.

Name and address of the holder of the certificate of registration

GlaxoSmithKline South Africa (Pty) Ltd

Block A Nicol Main Office Park
2 Bruton Road, Bryanston, 2191

South Africa

Manufactured by:

Tablets:

Glaxo Operations UK Ltd

Priory Street, Ware, Hertfordshire SG12 0DJ, United Kingdom.

Suspension for Injection:

Glaxo Operations UK Limited (trading as Glaxo Wellcome Operations)

Harmire Road

Barnard Castle

County Durham DL12 8DT

UK

Registration details:

Vocabria 30 mg film coated tablets – Reg No BOT2203818 S2

Vocabria 400 mg (2mL) injection – Reg No BOT2203819 S2

Vocabria 600 mg (3mL) injection– Reg No BOT2203820 S2

Version number: VGDS04/IPI02

Date of issue: 15 March 2021

INSTRUCTIONS FOR USE:

The following information is intended for healthcare professionals only:

Pack 1 of 2

VOCABRIA **600 mg**

Prolonged-release suspension for injection

cabotegravir

for gluteal intramuscular use only.

Instructions for Use:

You will also need
rilpivirine
900 mg (3 mL)

Overview:

A complete dose requires two injections:
3 mL of cabotegravir and 3 mL of rilpivirine.

Cabotegravir and rilpivirine are suspensions that do not need further dilution or reconstitution.

Cabotegravir and rilpivirine are **for intramuscular use**.
Both injections should be administered at separate gluteal injection sites.

The administration order is not important.

Use appropriate aseptic technique throughout.

Storage information

Store at or below 30°C.
Do not freeze.

Supplies you need:

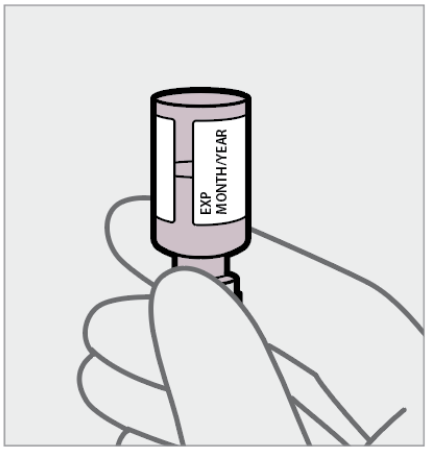
Your Pack contains

•1 vial of cabotegravir

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 judgment to select an appropriate injection needle length.
•Gloves
•2 alcohol swabs
•2 gauze pads
•A suitable sharps container
•1 rilpivirine 3 mL pack

1. Prepare vial



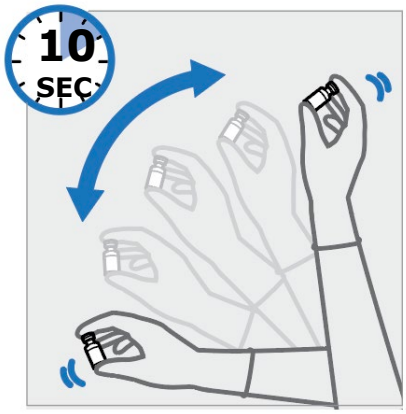
Inspect vial

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

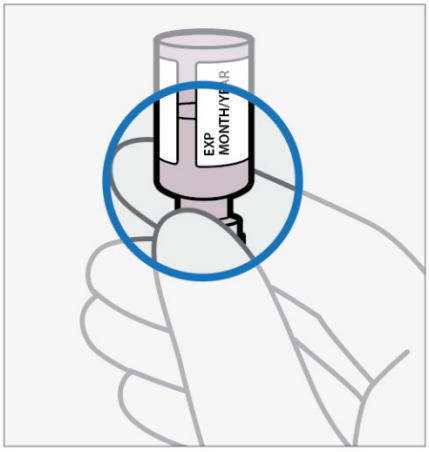
If the vial has been stored in a refrigerator, place the vial on a flat surface and let it sit at room temperature for at least **15 minutes** before use.

2. Prepare medication for injection



Shake vigorously

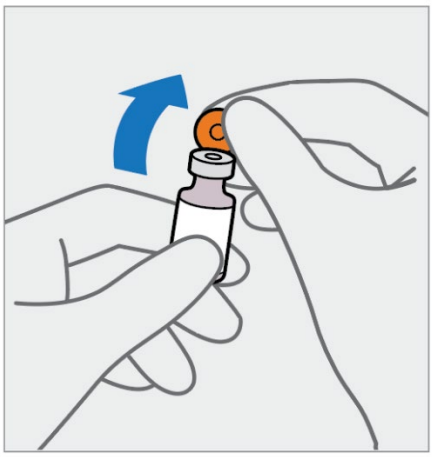
Hold one vial firmly and shake vigorously with a loose wrist and a long arm motion for at least **10 seconds**.



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.



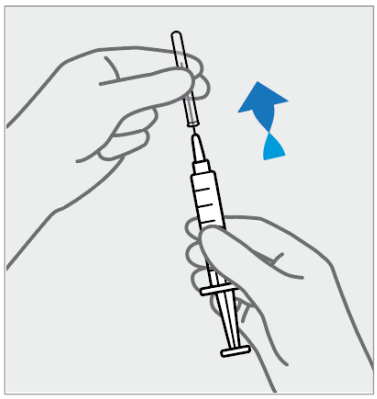
Remove vial cap

Remove the cap from vial.

Wipe the rubber stopper with an alcohol swab.

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

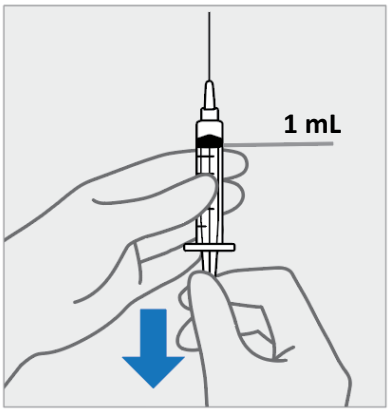
3. Prepare syringe



Attach aspiration needle

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

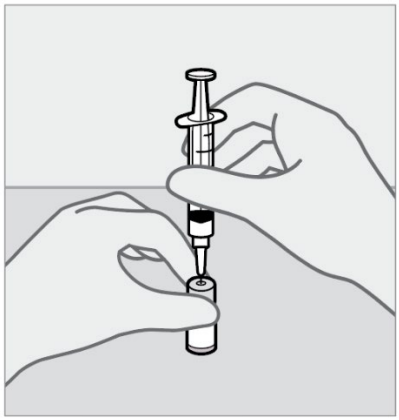
Remove the needle cover.



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.

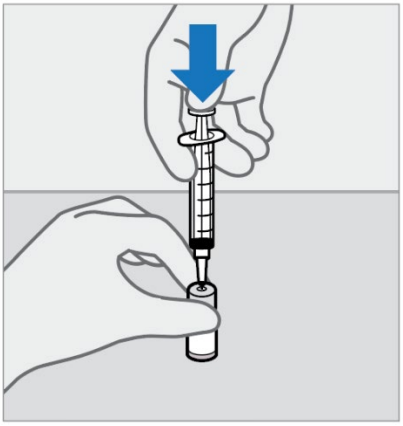
4. Draw and adjust dose



Insert aspiration needle into vial

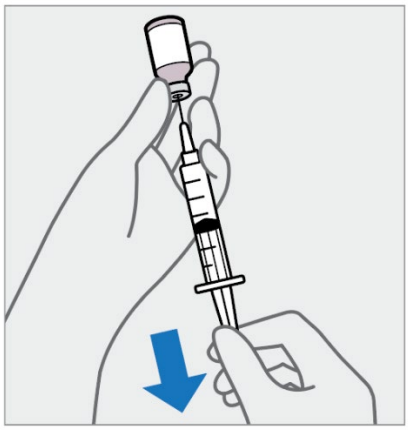
Place the vial on a flat surface.

Insert the needle into the stopper.



Push air into vial

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

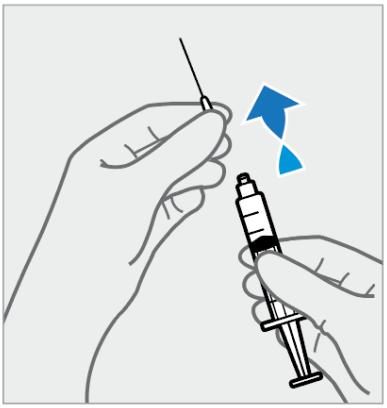


Draw up liquid

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.

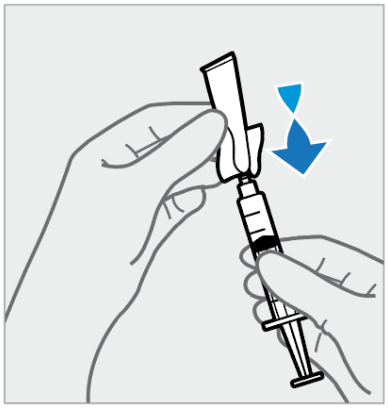


Remove aspiration needle

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.



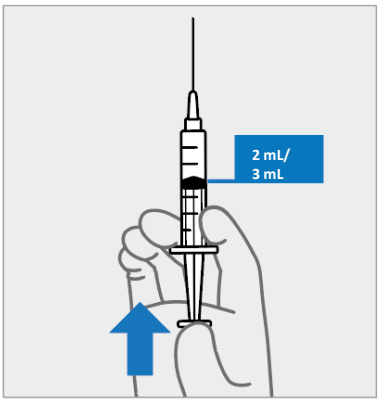
Attach injection needle

Peel the needle packaging half way.

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.

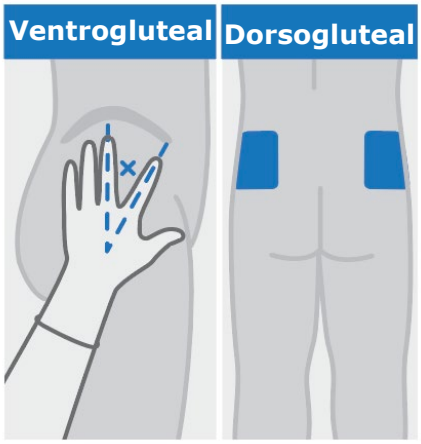


Adjust dose

Hold the syringe with the needle pointing up.

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

5. Inject cabotegravir in a gluteal site



Prepare injection site

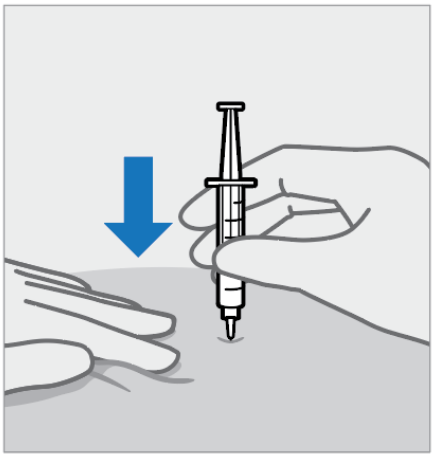
Administer the injection to one of the following sites:

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

Clean the injection site with an alcohol swab.
Allow the skin to air dry.

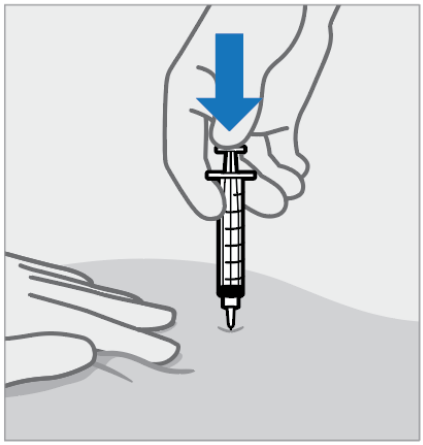
Stretch skin

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.

PATIENT INFORMATION LEAFLET

VOCABRIA 30 mg film coated tablets

cabotegravir

Read all of this leaflet carefully before you start taking this medicine.

Keep this leaflet. You may need to read it again. If you have any questions, ask your doctor or pharmacist.

This medicine has been prescribed for you personally. Don't pass it on to other people - it may harm them even if their symptoms seem to be the same as yours.

In this leaflet:

1. What VOCABRIA is and what it is used for:

VOCABRIA is used to treat HIV (human immunodeficiency virus) infection in adults.

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

VOCABRIA does not cure HIV infection; it keeps the amount of virus in your body at a low level. This helps maintain the number of CD4+ cells in your blood. CD4+ cells are a type of white blood cells that are important in helping your body to fight infection.

VOCABRIA is always given, in combination with another anti-retroviral medicine called rilpivirine to treat HIV infection. To control your HIV infection, and to stop your illness from getting worse, you must keep taking all your medicines, unless your doctor tells you to stop taking any.

2. Before you take VOCABRIA:

Don’t take VOCABRIA:

- if **you are allergic *(hypersensitive)* to cabotegravir** or to any of the other ingredients of VOCABRIA (listed in Section 6).
- If you’re taking any of these medicines:
  - **rifampicin** or **rifapentine** (to treat some bacterial infections such as tuberculosis).
  - **phenytoin, phenobarbital, carbamazepine or oxcarbazepine** (also known as anticonvulsants used to treat epilepsy and prevent seizures).

➔ **Don’t take VOCABRIA** with any of these medicines. Tell your doctor.

Conditions you need to look out for:

VOCABRIA can cause serious side effects. You must look out for certain symptoms while you are taking VOCABRIA and tell your doctor.

Allergic reaction:
Contact your doctor promptly if you develop a skin rash or other symptoms of an allergic reaction. See ‘*Conditions you need to look out for’* in **Section 4.**

Symptoms of infection:
See *‘Conditions you need to look out for’* in **Section 4**.

Take special care with VOCABRIA:

Let your doctor know if you have liver problems. Your liver function may need to be monitored. *(See also ‘Liver problems’ in section 4).*

Other medicines and VOCABRIA:

Tell your doctor or pharmacist if you're taking any other medicines, if you’ve taken any recently, or if you start taking new ones. This includes herbal medicines and other medicines bought without a prescription.

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

Don't take VOCABRIA with these medicines:

- **carbamazepine, oxcarbazepine, phenobarbital,** or **phenytoin** (also known as anticonvulsants used to treat epilepsy and prevent seizures).

- **rifampicin** or **rifapentine** (to treat some bacterial infections such as tuberculosis).

Tell your doctor if you are taking any of the medicines *in the following list*:

- medicines called **antacids**, to treat **indigestion** and **heartburn** *(see also Section 3)*
- ***rifabutin*** *(to treat some bacterial infections such as tuberculosis).*

Tell your doctor or pharmacist if you are taking any of these. Your doctor may decide that you need extra check-ups.

Pregnancy and breast-feeding:

If you are **pregnant**, or **think you could be,** or if you are **planning to have a baby**, **don't take VOCABRIA** without checking with your doctor. **Your doctor** will consider the benefit to you and the risk to your baby of taking VOCABRIA while you're pregnant.

Where possible, women who are HIV-positive should not breast feed, because HIV infection can be passed on to the baby in breast milk.

It is not known whether the ingredients of VOCABRIA can pass into breast milk and harm your baby.

➔ **Talk to your doctor immediately,** if you're breast-feeding, or thinking about breast-feeding.

Driving and using machines:

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

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

While you're taking VOCABRIA:

You will need regular blood tests:
For as long as you are taking VOCABRIA, your doctor will arrange regular blood tests to check for side effects. There is more information about these side effects in **Section 4** of this leaflet.

Stay in regular contact with your doctor:
VOCABRIA helps to control your condition, but it is not a cure for HIV infection. You need to keep taking it every day to stop your illness from getting worse. Because VOCABRIA does not cure HIV infection, you may still develop other infections and illnesses linked to HIV infection.

➔ **Keep in touch with your doctor, and don't stop taking VOCABRIA** without your doctor's advice.

Protect other people:
HIV infection is spread by sexual contact with someone who has the infection, or by transfer of infected blood (for example, by sharing injection needles). VOCABRIA will not stop you passing HIV infection on to other people. To protect other people from becoming infected with HIV:

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

3. How to take VOCABRIA:

Always take VOCABRIA exactly as your doctor has told you to. Check with your doctor or pharmacist if you're not sure.

As VOCABRIA must always be taken with another HIV medicine (rilpivirine), you should also follow the instructions for rilpivirine carefully. The leaflet is supplied in the rilpivirine carton.

When you first start treatment with VOCABRIA, you and your doctor may decide to start directly with VOCABRIA injection.

The other option is that your doctor may advise you to take one VOCABRIA tablet once a day for one month (lead-in period) before your first VOCABRIA injection. Taking VOCABRIA for one month before you receive VOCABRIA injections will allow your doctor to test how well you tolerate these medicines.

How much to take:

Adults:

Oral dosing with VOCABRIA:

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

VOCABRIA tablets are always given with another HIV medicine tablet called rilpivirine.

How to take:

VOCABRIA tablets should be swallowed whole with some liquid. VOCABRIA tablets can be taken with or without food, however, if you take VOCABRIA at the same time as rilpivirine tablets, you must take them with a meal.

Which medicine	When	Dose

VOCABRIA	**For 1 Month (at least 28 days)**	30 mg tablet once a day
Rilpivirine	**For 1 Month (at least 28 days)**	25 mg tablet once a day

If you will miss a VOCABRIA Injection:
If you are not able to receive your injection, your doctor may recommend you take VOCABRIA tablets instead, until you can receive an injection again. Your doctor will advise you to take one tablet a day until you next VOCABRIA injection.

Antacid medicines:

Antacids, to treat **indigestion** and **heartburn,** can stop VOCABRIA being absorbed into your body and make it less effective.

Antacids should be taken at least 2 hours before or 4 hours after you take VOCABRIA. Talk to your doctor for further advice on taking acid-lowering (antacid) medicines with VOCABRIA.

If you forget to take VOCABRIA:

If you miss a dose, take it as soon as you remember. Then continue your treatment as before.

Don't take a double dose to make up for a missed dose.

If you take too much VOCABRIA:

If you take too many tablets of VOCABRIA, **contact your doctor or pharmacist for advice**. If possible, show them the VOCABRIA pack.

Don’t stop VOCABRIA without advice

Take VOCABRIA for as long as your doctor recommends. Don’t stop unless your doctor advises you to.

4. Possible side effects:

When you’re being treated for HIV, it can be hard to tell whether a symptom is a side effect of VOCABRIA or other medicines you are taking, or an effect of the HIV disease

itself. **So, it is very important to talk to your doctor about any changes in your health**.

Some side effects may only be seen in your blood tests and may not appear immediately after you start taking VOCABRIA. If you get any of these effects, and if they are severe, your doctor may advise you to stop taking VOCABRIA.

As well as the effects listed below for VOCABRIA and rilpivirine, other conditions can develop during therapy for HIV.

➔ **It is important to read the information** in '*Conditions you need to look out for'*, later in this section.

Very common side effects:

These may affect **more than 1 in 10** people:

- Headache
- Feeling hot (*pyrexia*)

Common side effects

These may affect **up to 1 in 10** people:

- depression
- anxiety
- abnormal dreams
- difficulty in sleeping *(insomnia)*
- dizziness
- feeling sick *(nausea*)
- vomiting
- stomach pain *(abdominal pain)*
- wind *(flatulence)*
- diarrhoea
- rash
- muscle pain *(myalgia)*
- lack of energy *(fatigue)*

- feeling weak *(asthenia)*
- generally feeling unwell *(malaise).*

Uncommon side effects:

These may affect **up to 1 in 100** people:

- feeling drowsy *(somnolence)*
- liver damage (signs may include yellowing of the skin and the whites of the eyes loss of appetite, itching, tenderness of the stomach, light-coloured stools or unusually dark urine) *(hepatotoxicity)*
- weight gain
- changes in liver blood tests (increase in transaminases).

Other side effects that may show up in blood tests:

Other side effects have occurred in some people but their exact frequency is unknown:

- an increase in *bilirubin* (a substance produced by the liver) in the blood
- an increase in lipase (an enzyme produced by the pancreas)
- an increase in the level of enzymes produced in the muscles (*creatine phosphokinase, creatinine*).

➔ **Tell your doctor or pharmacist** if any of the side effects listed becomes **severe or troublesome**, or if you notice any side effects not listed in this leaflet.

Conditions you need to look out for:

Some other conditions may develop during HIV treatment.

Allergic Reactions:

Contact your doctor promptly if you develop a:

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

Symptoms of Liver Injury:

Signs include yellowing of the skin and the whites of the eyes, loss of appetite, itching, tenderness of the stomach, light coloured stools or unusually dark urine.

Your doctor will check for liver injury by doing blood tests before, during and after VOCABRIA treatment. If liver enzyme levels increase and remain high, your doctor may take you off VOCABRIA.

➔ **Tell your doctor or pharmacist** if you notice any of these symptoms.

Symptoms of Infection:

People with advanced HIV infection (AIDS) have weak immune systems and are more likely to develop serious infections (opportunistic infections).

If you get any symptoms of infection:

➔ **Tell your doctor immediately**. Don't take other medicines for the infection without your doctor's advice.

5. How to store VOCABRIA:

Store at or below 30ºC.

Keep out of the sight and reach of children.

Do not take VOCABRIA after the expiry date shown on the pack.

Don't throw away any medicines in wastewater or household waste. Ask your pharmacist how to throw away medicines no longer required. This will help to protect the environment.

6. Further information:

What VOCABRIA contains:

The active substance is cabotegravir (as cabotegravir sodium). Each tablet contains 30 mg cabotegravir.

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

The other ingredients are:

Tablet core:

Lactose Monohydrate
Microcystalline Cellulose
Hypromellose
Sodium Starch Glycolate
Magnesium Stearate

Tablet coating:

Hypromellose
Titanium Dioxide (E171)
Macrogol

What VOCABRIA looks like and contents of the pack:

The 30 mg tablets are White, oval, film-coated tablets marked with 'SV CTV' on one side.

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

Name and address of the holder of the certificate of registration:

GlaxoSmithKline South Africa (Pty) Ltd

Block A Nicol Main Office Park
2 Bruton Road, Bryanston 2191,
South Africa

Manufactured by:

Glaxo Operations UK Ltd

Priory Street, Ware, Hertfordshire SG12 0DJ, United Kingdom.

Registration details:

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