ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

400 mg

Vocabria 400 mg prolonged-release suspension for injection

600 mg

Vocabria 600 mg prolonged-release suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

400 mg

Each vial contains 400 mg cabotegravir in 2 mL.

600 mg

Each vial contains 600 mg cabotegravir in 3 mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vocabria injection is indicated, in combination with rilpivirine injection, for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents (at least 12 years of age and weighing at least 35 kg), who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the non-nucleoside reverse transcriptase inhibitor (NNRTI) and integrase inhibitor (INI) class (see sections 4.2, 4.4 and 5.1).

4.2 Posology and method of administration

Vocabria should be prescribed by physicians experienced in the management of HIV infection.

Each injection should be administered by a healthcare professional.

Vocabria injection is indicated for the treatment of HIV-1 in combination with rilpivirine injection, therefore, the prescribing information for rilpivirine injection should be consulted for recommended dosing.

<u>Prior to starting Vocabria injection</u>, 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.

<u>Following discontinuation of Vocabria and rilpivirine injection</u>, 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 (see section 4.4).

The healthcare provider and patient may decide to use cabotegravir tablets as an oral lead-in prior to the initiation of Vocabria injection to assess tolerability to cabotegravir (see Table 1) or may proceed directly to Vocabria injections (see Table 2 for monthly and Table 3 for every 2 month dosing recommendations).

<u>Posology</u>

Adults and adolescents (at least 12 years of age and weighing at least 35 kg)

<u>Oral lead-in</u>

When used for oral lead-in, oral cabotegravir together with oral rilpivirine should be taken for approximately one month (at least 28 days) to assess tolerability to cabotegravir and rilpivirine (see section 4.4). One cabotegravir 30 mg tablet should be taken with one rilpivirine 25 mg tablet, once daily. When administered with rilpivirine, cabotegravir tablets should be taken with a meal (see cabotegravir tablet prescribing information).

Table 1 Oral Lead-in Dosing Schedule

	ORAL LEAD-IN
Medicinal product	**For one month (at least 28 days), followed by the Initiation Injection[a]**
Cabotegravir	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.

<u>Monthly dosing</u>
Initiation injection (600 mg corresponding to 3 mL dose)
On the final day of current antiretroviral therapy or oral lead-in therapy, the recommended initial dose of Vocabria injection is a single 600 mg intramuscular injection. Vocabria injection and rilpivirine injection should be administered at separate gluteal injection sites at the same visit.

Continuation injection (400 mg corresponding to 2 mL dose)
After the initiation injection, the continuation injection dose of Vocabria is a single 400 mg monthly intramuscular injection. Vocabria injection and rilpivirine injection should be administered at separate gluteal injection sites at the same visit. Patients may be given injections up to 7 days before or after the date of the monthly 400 mg injection schedule.

Table 2 Recommended monthly intramuscular dosing schedule

	INITIATION INJECTION	**CONTINUATION INJECTION**
Medicinal product	**Initiate injection on the last day of either current ART therapy**	**One month after initiation injection and monthly onwards**

	or oral lead-in (if used)	
Vocabria	600 mg	400 mg
Rilpivirine	900 mg	600 mg

Every 2 Month Dosing
Initiation Injections – one month apart (600 mg)
On the final day of current antiretroviral therapy or oral lead-in therapy, the recommended initial Vocabria injection is a single 600 mg intramuscular injection.

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

Vocabria injection and rilpivirine injection should be administered at separate gluteal injection sites at the same visit.

Continuation Injections – 2 months apart (600 mg)
After the initiation injections, the recommended Vocabria continuation injection dose is a single 600 mg intramuscular injection administered every 2 months. Vocabria injection and rilpivirine injection should be administered at separate gluteal injection sites at the same visit. Patients may be given injections up to 7 days before or after the date of the every 2 month, 600 mg injection schedule.

Table 3 Recommended every 2 month intramuscular dosing schedule

	INITIATION INJECTIONS	**CONTINUATION INJECTIONS**
Medicinal product	**Initiate injection on the last day of either current ART therapy or oral lead-in (if used). One month later, a second initiation injection should be administered.**	**Two months after last initiation injection and every 2 months onwards**
Vocabria	600 mg	600 mg
Rilpivirine	900 mg	900 mg

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 schedule should receive a single 600 mg intramuscular injection of cabotegravir one month after the last 400 mg continuation injection dose and then 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 cabotegravir 2 months after the last 600 mg continuation injection dose and then 400 mg monthly thereafter.

Missed doses
Patients who miss a scheduled injection visit should be clinically reassessed to ensure resumption of therapy remains appropriate. See Tables 4 and 5 for dosing recommendations after a missed injection.

Missed monthly injection
If a patient plans to miss a scheduled injection visit by more than 7 days, oral therapy (one 30 mg cabotegravir tablet and one 25 mg rilpivirine tablet once daily) may be used to replace up to 2 consecutive monthly injection visits. Limited data is available on oral bridging with other fully suppressive antiretroviral therapy (ART) (mainly INI-based), see section 5.1. 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 doses of Vocabria and rilpivirine. Injection dosing should be resumed on the day oral dosing completes, as recommended in Table 4.

Table 4 Vocabria 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 400 mg injection schedule as soon as possible
>2 months:	Re-initiate the patient on the 600 mg dose, and then continue to follow the monthly 400 mg injection schedule.

Missed 2 month injection
If a patient plans to miss a scheduled Vocabria injection visit by more than 7 days, oral therapy (one 30 mg cabotegravir tablet and one 25 mg rilpivirine tablet, once daily) may be used to replace one, 2-monthly injection visit. Limited data is available on oral bridging with other fully suppressive ART (mainly INI-based), see section 5.1. 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 doses of cabotegravir and rilpivirine. Injection dosing should be resumed on the day oral dosing completes, as recommended in Table 5.

Table 5 Vocabria 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 600 mg injection as soon as possible and then continue with the every 2 month injection schedule.
	>2 months	Re-initiate the patient on the 600 mg dose, followed by a second 600 mg initiation injection one month later. Then follow the every 2 month injection schedule.
Injection 3 or later	**≤3 months**	Resume with 600 mg injection as soon as possible and then continue with the every 2 month injection schedule.
	>3 months	Re-initiate the patient on the 600 mg dose, followed by a second 600 mg initiation injection one month later. Then follow the every 2 month injection schedule.

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).

Renal impairment
No dosage adjustment is required in patients with mild (creatinine clearance ≥60 to <90 mL/min), moderate (creatinine clearance ≥30 to <60 mL/min) or severe renal impairment (creatinine clearance ≥15 to <30 mL/min and not on dialysis [see section 5.2]). Cabotegravir has not been studied in patients with end-stage renal disease on renal replacement therapy. As cabotegravir is greater than 99% protein bound, dialysis is not expected to alter exposures of cabotegravir. If administered in a patient on renal replacement therapy, cabotegravir should be used with caution.

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

Paediatric population
The safety and efficacy of Vocabria in children aged less than 12 years and adolescents weighing less than 35 kg have not been established. No data are available.

Method of administration

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

Vocabria injection should be administered by a healthcare professional. For instructions on administration, see "Instructions for Use" in the package leaflet. These instructions should be carefully followed when preparing the suspension for injection to avoid leakage.

Vocabria injection should always be co-administered with rilpivirine injection. The order of injections is not important. The prescribing information for rilpivirine injection should be consulted for recommended dosing.

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

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

Injections must be administered to the ventrogluteal (recommended) or the dorsogluteal sites.

4.3 Contraindications

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

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

4.4 Special warnings and precautions for use

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.

Long acting properties of Vocabria injection

Residual concentrations of cabotegravir 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 sections 4.5, 4.6, 4.7 and 4.9).

Baseline factors associated with virological failure

Before starting the regimen, it should be taken into account that multivariable analyses indicate that a combination of at least 2 of the following baseline factors may be associated with an increased risk of virological failure: archived rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI ≥30 kg/m^2. Available data suggest that virologic failure occurs more often when these patients are treated according to the every 2 month dosing regimen as compared to the monthly dosing regimen. In patients with an incomplete or uncertain treatment history without pre-treatment resistance analyses, caution is warranted in the presence of either BMI ≥30 kg/m^2 or HIV-1 A6/A1 subtype (see section 5.1).

Severe cutaneous adverse reactions (SCARs)

The severe cutaneous adverse reactions, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported very rarely in association with cabotegravir treatment.

At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, cabotegravir should be withdrawn immediately and an alternative treatment considered (as appropriate). If the patient has developed a serious reaction such as SJS or TEN with the use of cabotegravir, treatment with cabotegravir must not be restarted in this patient at any time.

Hypersensitivity reactions

Hypersensitivity reactions have been reported in association with integrase inhibitors including cabotegravir. These reactions were characterised by rash, constitutional findings and sometimes organ dysfunction, including liver injury. Vocabria and other suspected medicinal products should be discontinued immediately, should signs or symptoms of hypersensitivity develop (including, but not limited to, severe rash, or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia or angioedema). Clinical status, including liver aminotransferases should be monitored and appropriate therapy initiated. (See sections 4.2, Long acting properties of Vocabria injection, 4.8 and 5.1).

Hepatoxicity

Hepatotoxicity has been reported in a limited number of patients receiving Vocabria with or without known pre-existing hepatic disease (see section 4.8). Administration of cabotegravir oral lead-in was used in clinical studies to help identify patients who may be at risk of hepatotoxicity. Monitoring of liver chemistries is recommended and treatment with Vocabria should be discontinued if hepatotoxicity is suspected (see Long acting properties of Vocabria injection).

HBV/HCV co-infection

Patients with hepatitis B co-infection were excluded from studies with Vocabria. It is not recommended to initiate Vocabria in patients with hepatitis B co-infection. Physicians should refer to current treatment guidelines for the management of HIV infection in patients co-infected with hepatitis B virus.

Limited data is available in patients with hepatitis C co-infection. Monitoring of liver function is recommended in patients with hepatitis C co-infection.

Interactions with medicinal products

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

Concomitant use of Vocabria injection with rifabutin is not recommended (see section 4.5).

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution, however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Opportunistic infections

Patients should be advised that Vocabria or any other antiretroviral therapy do not cure HIV infection and that they 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.

4.5 Interaction with other medicinal products and other forms of interaction

Vocabria injection, in combination with rilpivirine injection, is indicated for the treatment of HIV-1, therefore, the prescribing information for rilpivirine injection should be consulted for associated interactions.

Effect of other medicinal products on the pharmacokinetics of cabotegravir

Cabotegravir is primarily metabolised by uridine diphosphate glucuronosyl transferase (UGT) 1A1 and to a lesser extent by UGT1A9. Medicinal products which are strong inducers of UGT1A1 or UGT1A9 are expected to decrease cabotegravir plasma concentrations leading to lack of efficacy (see section 4.3 and table 6 below). In poor metabolizers of UGT1A1, representing a maximum clinical UGT1A1 inhibition, the mean AUC, C_{max} and C_{tau} of oral cabotegravir increased by up to 1.5-fold. The impact of an UGT1A1 inhibitor may be slightly more pronounced, however, considering the safety margins of cabotegravir, this increase is not expected to be clinically relevant. No dosing adjustments for Vocabria are, therefore, recommended in the presence of UGT1A1 inhibitors (e.g. atazanavir, erlotinib, sorafenib).

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

Effect of cabotegravir on the pharmacokinetics of other medicinal products

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

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

Vocabria and rilpivirine injections are intended for use as a complete regimen for the treatment of HIV-1 infection and should not be administered with other antiretroviral medicinal products for the treatment of HIV. The following information regarding drug-drug interactions with other antiretroviral medicinal products is provided in the event that Vocabria and rilpivirine injections are stopped and initiation of an alternative antiviral therapy is necessary (see section 4.4). 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 or ibalizumab.

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 (increase is indicated as "↑", decrease as "↓", no change as "↔", area under the concentration versus time curve as "AUC", maximum observed concentration as "C_{max}", concentration at end of dosing interval as "Cτ").

Table 6 Drug Interactions

Medicinal products by therapeutic areas	**Interaction** Geometric mean change (%)	**Recommendations concerning co-administration**
HIV-1 Antiviral medicinal products		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine	Cabotegravir ↔ AUC ↑ 1% C_{max} ↑ 4% Cτ ↔ 0%	Etravirine did not significantly change cabotegravir plasma concentration. No dose adjustment of Vocabria is necessary when initiating injections following etravirine use.
Non-nucleoside Reverse Transcriptase Inhibitor: Rilpivirine	Cabotegravir ↔ AUC ↑ 12% C_{max} ↑ 5% Cτ ↑ 14% Rilpivirine ↔ AUC ↓ 1% C_{max} ↓ 4% Cτ ↓ 8%	Rilpivirine did not significantly change cabotegravir plasma concentration. No dose adjustment of Vocabria injection is necessary when co-administered with rilpivirine.
Anticonvulsants		
Carbamazepine Oxcarbazepine Phenytoin Phenobarbital	Cabotegravir ↓	Metabolic inducers may significantly decrease cabotegravir plasma concentration. Concomitant use is contraindicated (see section 4.3).
Antimycobacterials		
Rifampicin	Cabotegravir ↓ AUC ↓ 59% C_{max} ↓ 6%	Rifampicin significantly decreased cabotegravir plasma concentration which is likely to result in loss of therapeutic effect. Dosing recommendations for co-administration of Vocabria with rifampicin have not been established and co-administration of Vocabria with rifampicin is contraindicated (see section 4.3).
Rifapentine	Cabotegravir ↓	Rifapentine may significantly decrease cabotegravir plasma concentrations. Concomitant use is contraindicated (see section 4.3).

Rifabutin	Cabotegravir ↓ AUC ↓ 21% C_{max} ↓ 17% Cτ ↓ 26%	Rifabutin may decrease cabotegravir plasma concentration. Concomitant use should be avoided.
Oral contraceptives		
Ethinyl estradiol (EE) and Levonorgestrel (LNG)	EE ↔ AUC ↑ 2% C_{max} ↓ 8% Cτ ↔ 0% LNG ↔ AUC ↑ 12% C_{max} ↑ 5% Cτ ↑ 7%	Cabotegravir did not significantly change ethinyl estradiol and levonorgestrel plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with Vocabria.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

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

Cabotegravir has been detected in systemic circulation for up to 12 months or longer after an injection (see section 4.4).

Breast-feeding

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

It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions (ARs) from monthly dosing studies were injection site reactions (up to 84%), headache (up to 12%) and pyrexia[5] (10%).
The most frequently reported ARs from ATLAS-2M every 2 month dosing were injection site reactions (76%), headache (7%) and pyrexia[5] (7%).
The SCARs SJS and TEN have been reported in association with cabotegravir treatment (see section 4.4).

Tabulated list of adverse reactions

The ARs identified for cabotegravir or rilpivirine are listed in Table 7 by body system organ class and frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000).

Table 7 Tabulated summary of adverse reactions[1]

MedDRA System Organ Class (SOC)	**Frequency Category**	**ARs for Vocabria + rilpivirine regimen**
Immune system disorders	Uncommon	Hypersensitivity*
Psychiatric disorders	Common	Depression Anxiety Abnormal dreams Insomnia
	Uncommon	Suicide attempt; Suicidal ideation (particularly in patients with a pre-existing history of psychiatric illness)
Nervous system disorders	Very common	Headache
	Common	Dizziness
	Uncommon	Somnolence Vasovagal reactions (in response to injections)
Gastrointestinal disorders	Common	Nausea Vomiting Abdominal pain[2] Flatulence Diarrhoea
Hepatobiliary Disorders	Uncommon	Hepatotoxicity
Skin and subcutaneous tissue disorders	Common	Rash[3]
	Uncommon	Urticaria* Angioedema*
	Very rare	Stevens-Johnson syndrome*, toxic epidermal necrolysis*
Musculoskeletal and connective tissue disorders	Common	Myalgia
General disorders and administrative site conditions	Very common	Injection site reactions (pain[4] and discomfort, nodule, induration) Pyrexia[5]
	Common	Injection site reactions (swelling, erythema, pruritus, bruising, warmth, haematoma) Fatigue Asthenia Malaise
	Uncommon	Injection site reactions (cellulitis, abscess, anaesthesia, haemorrhage, discolouration)
Investigations	Common	Weight increased

	Uncommon	Transaminase increased Blood bilirubin increased

[1]The frequency of the identified ARs are based on all reported occurrences of the events and are not limited to those considered at least possibly related by the investigator.
[2]Abdominal pain includes the following grouped MedDRA preferred term: abdominal pain, upper abdominal pain.
[3]Rash includes the following grouped MedDRA preferred terms: rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic.
[4]May rarely result in temporary gait disturbance.
[5]Pyrexia includes the following grouped MedDRA preferred terms: feeling hot, body temperature increased. The majority of pyrexia events were reported within one week of injections.
*Please refer to section 4.4.

The overall safety profile at Week 96 and Week 124 in the FLAIR study was consistent with that observed at Week 48, with no new safety findings identified. In the extension phase of the FLAIR study, initiating the Vocabria and rilpivirine injection regimen with Direct to Injection did not identify any new safety concerns related to omitting the oral lead-in phase (see section 5.1).

Description of selected adverse reactions

Local injection site reactions (ISRs)
Up to 1% of subjects discontinued treatment with Vocabria plus rilpivirine because of ISRs. When dosing monthly, up to 84% of subjects reported injection site reactions; out of 30393 injections, 6815 ISRs were reported. When dosing every 2 months, 76% of patients reported injection site reactions; 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. 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 studies FLAIR and ATLAS, who received Vocabria plus rilpivirine gained a median of 1.5 kg in weight subjects continuing on their current antiretroviral therapy (CAR) gained a median of 1.0 kg (pooled analysis). In the individual studies FLAIR and ATLAS, the median weight gains in the Vocabria plus 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 Vocabria plus rilpivirine 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 Vocabria plus 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 Vocabria plus rilpivirine during clinical studies. These elevations were primarily attributed to acute viral hepatitis. A few subjects on oral therapy had transaminase elevations attributed to suspected drug-related hepatotoxicity; these changes were reversible upon discontinuation of treatment (see section 4.4).

Elevated lipases were observed during clinical trials with Vocabria plus rilpivirine; Grade 3 and 4 lipase increases occurred at a higher incidence with Vocabria plus rilpivirine compared with CAR. These elevations were generally asymptomatic and did not lead to Vocabria plus rilpivirine discontinuation. One case of fatal pancreatitis with Grade 4 lipase and confounding factors (including history of pancreatitis) has been reported in study ATLAS-2M, for which causality to the injection regimen could not be ruled out.

Paediatric population

Based on data from the week 16 (Cohort 1C, n=30) and week 24 analysis (Cohort 2, n=144) of the MOCHA study (IMPAACT 2017), no new safety concerns were identified in adolescents (aged at least 12 years and weighing 35 kg or more) when compared with the safety profile established in adults.

Reporting of suspected adverse reactions

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

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Pharmacodynamic effects

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

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

Resistance in vitro
Isolation from wild-type HIV-1 and activity against resistant strains: Viruses with >10-fold increase in cabotegravir EC_{50} were not observed during the 112-day passage of strain IIIB. The following integrase (IN) mutations emerged after passaging wild type HIV-1 (with T124A polymorphism) in the

presence of cabotegravir: Q146L (fold-change [FC] range 1.3-4.6), S153Y (FC range 2.8-8.4), and I162M (FC = 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 FC was observed with mutants containing Q148K or Q148R. E138K/Q148H resulted in a 0.92-fold decrease in susceptibility to cabotegravir but E138K/Q148R resulted in a 12-fold decrease in susceptibility and E138K/Q148K resulted in an 81-fold decrease in susceptibility to cabotegravir. G140C/Q148R and G140S/Q148R resulted in a 22- and 12-fold decrease in susceptibility to cabotegravir, respectively. While N155H did not alter susceptibility to cabotegravir, N155H/Q148R resulted in a 61-fold decrease in susceptibility to cabotegravir. Other multiple mutants, which resulted in a FC between 5 and 10, are: T66K/L74M (FC=6.3), G140S/Q148K (FC=5.6), G140S/Q148H (FC=6.1) and E92Q/N155H (FC=5.3).

Resistance in vivo
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 plus rilpivirine in FLAIR with resistance data had Subtype A1. In addition, 2 of the 3 CVFs had treatment-emergent integrase inhibitor resistance associated substitution Q148R while one of the three 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 two of the three showed reduced phenotypic susceptibility to rilpivirine. The 3 CVFs in ATLAS had subtype A, A1 and AG. One of the three CVFs carried the INI resistance-associated substitution N155H at failure with reduced cabotegravir phenotype susceptibility. All three CVFs carried one rilpivirine resistance-associated substitution at failure: E138A, E138E/K or E138K, and showed reduced phenotypic susceptibility to rilpivirine. In two of these three CVFs, the rilpivirine resistance-associated substitutions observed at failure 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 were 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 Baseline in the Q8W arm, 5 subjects had rilpivirine 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 rilpivirine resistance-associated mutation). At the suspected virologic failure (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 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 integrase strand transfer inhibitor (INSTI) resistance-associated substitutions, N155H (n=2); Q148R; Q148Q/R+N155N/H (n=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. FCs 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 rilpivirine 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 rilpivirine. Both subjects also had INSTI resistance-associated mutations, either Q148R + E138E/K or

N155N/H at SVF and 1 subject had reduced susceptibility to cabotegravir. Neither subject had the INSTI substitution, L74I. FCs 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.

Clinical efficacy and safety

Adults

The efficacy of cabotegravir plus rilpivirine has been evaluated in two Phase III randomised, multicentre, active-controlled, parallel-arm, open-label, non-inferiority studies, FLAIR (study 201584) and ATLAS (study 201585). The primary analysis was conducted after all subjects completed their Week 48 visit or discontinued the study prematurely.

Patients virologically suppressed (on prior dolutegravir based regimen for 20 weeks)
In FLAIR, 629 HIV-1-infected, antiretroviral treatment (ART)-naive subjects received a dolutegravir INSTI-containing regimen for 20 weeks (either dolutegravir/abacavir/lamivudine or dolutegravir plus 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 the 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 one 30 mg cabotegravir tablet plus one 25 mg rilpivirine 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. This study was extended to 96 weeks.

Patients virologically suppressed (stable on prior ARV therapy for at least 6 months)
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 the 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 one 30 mg cabotegravir tablet plus one 25 mg rilpivirine 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, 50%, 17%, and 33% of subjects received an NNRTI, PI, or INI (respectively) as their baseline third treatment medicine class prior to randomisation and this was similar between treatment arms.

Pooled data
At baseline, in the pooled analysis, for the cabotegravir plus rilpivirine arm, the median age of subjects was 38 years, 27% were female, 27% were non-white, 1% were ≥ 65 years and 7% had CD4+ cell count less than 350 cells per mm3; 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 plus 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 plus 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%).

The primary endpoint and other week 48 outcomes, including outcomes by key baseline factors, for FLAIR and ATLAS are shown in Tables 8 and 9.

Table 8 Virologic outcomes of randomised treatment of FLAIR and ATLAS at 48 Weeks (Snapshot analysis)

	FLAIR		ATLAS		Pooled Data	
	Cabotegravir + RPV N=283	**CAR N=283**	**Cabotegravir + RPV N=308**	**CAR N=308**	**Cabotegravir +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 9 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**	
		Cabotegravir+RPV N=591 n/N (%)	**CAR N=591 n/N (%)**
Baseline CD4+ (cells/ mm^3)	<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/m^2	6/491 (1.2)	8/488 (1.6)
	≥30 kg/m^2	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 the FLAIR and ATLAS studies, treatment differences across baseline characteristics (CD4+ count, gender, race, BMI, age, baseline third medicine treatment class) were comparable.

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 vs Oral Lead-in.

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

Patients virologically suppressed (stable on prior ARV therapy for at least 6 months)

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-cabotegravir/rilpivirine treatment received oral lead-in treatment comprising one 30 mg cabotegravir tablet plus one 25 mg rilpivirine 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) 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 cabotegravir plus rilpivirine 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, 4% were ≥ 65 years 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 and 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 and 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%).

Table 10 Virologic outcomes of randomised treatment of 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 11 Proportion of subjects with Plasma HIV-1 RNA ≥50 copies/mL at Week 48 for key baseline factors (Snapshot Outcomes).

Baseline factors		**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

Baseline factors		Number of HIV-1 RNA ≥50 c/mL/Total Assessed (%)	
		2 Month Dosing (Q8W)	**Monthly dosing (Q4W)**
	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.

The efficacy results at Week 96 are consistent with the results of the primary endpoint at Week 48. Cabotegravir plus rilpivirine injections administered every 2 months is non-inferior to cabotegravir and rilpivirine administered every month. The proportion of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 96 in cabotegravir plus rilpivirine every 2 months dosing (n=522) and cabotegravir plus rilpivirine monthly dosing (n=523) was 2.1% and 1.1% respectively (adjusted treatment difference between cabotegravir plus rilpivirine every 2 months dosing and monthly dosing [1.0; 95% CI: -0.6, 2.5]). The proportion of subjects having plasma HIV-1 RNA <50 c/mL at Week 96 in cabotegravir plus rilpivirine every 2 months dosing and cabotegravir plus rilpivirine monthly dosing was 91% and 90.2% respectively (adjusted treatment difference between cabotegravir plus rilpivirine every 2 months dosing and monthly dosing [0.8; 95% CI: -2.8, 4.3]).

The efficacy results at Week 152 are consistent with the results of the primary endpoint at Week 48 and at Week 96. Cabotegravir plus rilpivirine injections administered every 2 months is non-inferior to cabotegravir and rilpivirine administered every month. In an ITT analysis, the proportion of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 152 in cabotegravir plus rilpivirine every 2 months dosing (n=522) and cabotegravir plus rilpivirine monthly dosing (n=523) was 2.7% and 1.0% respectively (adjusted treatment difference between cabotegravir plus rilpivirine every 2 months dosing and monthly dosing [1.7; 95% CI: 0.1, 3.3]). In an ITT analysis, the proportion of subjects having plasma HIV-1 RNA <50 c/mL at Week 152 in cabotegravir plus rilpivirine every 2 months dosing and cabotegravir plus rilpivirine monthly dosing was 87% and 86% respectively (adjusted treatment difference between cabotegravir plus rilpivirine every 2 months dosing and monthly dosing [1.5; 95% CI: -2.6, 5.6]).

Post-hoc analyses
Multivariable analyses of pooled phase 3 studies (ATLAS through 96 weeks, FLAIR through 124 weeks and ATLAS-2M through 152 weeks) examined the influence of various factors on the risk of CVF. The baseline factors analysis (BFA) examined baseline viral and participant characteristics and

dosing regimen; and the multivariable analysis (MVA) included the baseline factors and incorporated post-baseline predicted plasma drug concentrations on CVF using regression modelling with a variable selection procedure. Following a total of 4291 person-years, the unadjusted CVF incidence rate was 0.54 per 100 person-years; 23 CVFs were reported (1.4% of 1651 individuals in these studies).

The BFA demonstrated rilpivirine resistance mutations (incidence rate ratio IRR=21.65, p<0.0001), HIV-1 subtype A6/A1 (IRR=12.87, p<0.0001), and body mass index (IRR=1.09 per 1 unit increase, p=0.04; IRR=3.97 of ≥30 kg/m2, p=0.01) were associated with CVF. Other variables including Q4W or Q8W dosing, female gender, or CAB/INSTI resistance mutations had no significant association with CVF. A combination of at least 2 of the following key 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 12).

Table 12 Virologic outcomes by presence of key baseline factors of rilpivirine resistance mutations, Subtype A6/A1[1] and BMI ≥30 kg/m^2

Baseline Factors (number)	Virologic Successes (%)[2]	Confirmed Virologic Failure (%)[3]
0	844/970 (87.0)	4/970 (0.4)
1	343/404 (84.9)	8/404 (2.0)[4]
≥2	44/57 (77.2)	11/57 (19.3)[5]
TOTAL (95% Confidence Interval)	1231/1431 (86.0) (84.1%, 87.8%)	23/1431 (1.6)[6] (1.0%, 2.4%)

[1] HIV-1 subtype A1 or A6 classification based on Los Alamos National Library panel from HIV Sequence database (June 2020)
[2] Based on the FDA Snapshot algorithm of RNA <50 copies/mL at Week 48 for ATLAS, at Week 124 for FLAIR, at Week 152 for ATLAS-2M.
[3] Defined as two consecutive measurements of HIV RNA ≥200 copies/mL.
[4] Positive Predictive Value (PPV) <2%; Negative Predictive Value (NPV) 98.5%; sensitivity 34.8%; specificity 71.9%
[5] PPV 19.3%; NPV 99.1%; sensitivity 47.8%; specificity 96.7%
[6] Analysis dataset with all non-missing covariates for baseline factors (out of a total of 1651 individuals)

In patients with at least two of these risk factors, the proportion of subjects who had a CVF was higher than observed in patients with none or one risk factor, with CVF identified in 6/24 patients [25.0%, 95%CI (9.8%, 46.7%)] treated with the every 2 months dosing regimen and 5/33 patients [15.2%, 95%CI (5.1%, 31.9%)] treated with the monthly dosing regimen.

Oral bridging with other ART
In a retrospective analysis of pooled data from 3 clinical studies (FLAIR, ATLAS-2M, and LATTE-2/study 200056), 29 subjects were included who received oral bridging for a median duration of 59 days (25th and 75th percentile 53-135) with ART other than cabotegravir plus rilpivirine (alternative oral bridging) during treatment with cabotegravir plus rilpivirine long-acting (LA) intramuscular (IM) injections. The median age of subjects was 32 years, 14% were female, 31% were non-white, 97% received an integrase inhibitor (INI)-based regimen for alternative oral bridging, 41% received an NNRTI as part of their alternative oral bridging regimen (including rilpivirine in 11/12 cases), and 62% received an NRTI. Three subjects withdrew during oral bridging or shortly following oral bridging for non-safety reasons. The majority (≥96%) of subjects maintained virologic suppression (plasma HIV-1 RNA <50 c/mL). During bridging with alternative oral bridging and during the period following alternative oral bridging (up to 2 cabotegravir plus rilpivirine injections following oral bridging), no cases of CVF (plasma HIV-1 RNA ≥200 c/mL) were observed.

Paediatric population
The safety, tolerability and pharmacokinetics (PK) of long-acting injectable cabotegravir in combination with long acting rilpivirine in adolescents has been evaluated in an ongoing Phase I/II multicentre, open-label, non-comparative study, MOCHA (IMPAACT 2017).

In Cohort 2 of this study, 144 virologically suppressed adolescents discontinued their pre-study cART regimen and received cabotegravir 30 mg tablet and rilpivirine 25 mg tablet once daily for at least 4 weeks followed by every 2 month cabotegravir intramuscular injections (months 1 and 2: 600 mg, and then 600 mg every 2 months) and rilpivirine intramuscular injections (months 1 and 2: 900 mg, and then 900 mg every 2 months).

At baseline the median age of participants was 15.0 years, the median weight was 48.5 kg (range: 35.2, 100.9), the median BMI was 19.5 kg/m^2 (range: 16.0, 34.3), 51.4 % were female, 98.6 % were non-white, and 4 participants had a CD4+ cell count less than 350 cells per mm^3.

Antiviral activity was assessed as a secondary objective, with 139 of the 144 participants (96.5 %) (snapshot algorithm) remaining virologically suppressed (plasma HIV-1 RNA value <50 c/mL) at Week 24.

The European Medicines Agency has deferred the obligation to submit the results of studies with cabotegravir film-coated tablets and prolonged-release suspension for injection in one or more subsets of the paediatric population in the treatment of HIV-1 infection. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Adults

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 13 Pharmacokinetic parameters following cabotegravir orally once daily, and initiation, monthly and every 2 month continuation intramuscular injections in Adult participants

Dosing Phase	Dosage Regimen	Geometric Mean (5^{th}, 95^{th} Percentile)[a]		
		$AUC_{(0\text{-}tau)}$[b] (µg•h/mL)	C_{max} (µg/mL)	C_{tau} (µg/mL)
Oral lead-in[c]	30 mg once daily	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, 3 245)	8.0 (5.3, 11.9)	1.5 (0.65, 2.9)
Monthly injection[e]	400 mg IM monthly	2415 (1 494, 3 645)	4.2 (2.5, 6.5)	2.8 (1.7, 4.6)
Every 2-month injection[e]	600 mg IM Every 2-month	3764 (2 431, 5 857)	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 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 month 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 (5^{th}, 95^{th} 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

Cabotegravir injection exhibits absorption-limited (flip-flop) kinetics resulting from slow absorption from the gluteal muscle into the systemic circulation 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 (>99%) to human plasma proteins, based on *in vitro* data. Following administration of oral tablets, the mean apparent oral volume of distribution (Vz/F) in plasma was 12.3 L. In humans, the estimate of plasma cabotegravir Vc/F was 5.27 L and Vp/F was 2.43 L. These volume estimates, along with the assumption of high bioavailability, suggest some distribution of cabotegravir to the extracellular space.

Cabotegravir is present in the female and male genital tract. 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 intramuscular injection (IM) 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 plus rilpivirine injection, the cabotegravir CSF to plasma concentration ratio [median (range)] (n=16) was 0.003(range: 0.002 to 0.004) one week following a steady-state long acting 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.

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

Biotransformation

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

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

Elimination

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

Linearity/non-linearity

Plasma 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.

Polymorphisms

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

Special 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.

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

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 (creatinine clearance ≥15 to <30 mL/min and not on dialysis) and matching healthy subjects were observed. No dosage adjustment is necessary for patients with mild, moderate or 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.

Paediatric population
Population pharmacokinetic simulations revealed no clinically relevant differences in exposure between adolescent (at least 12 years of age and weighing 35 kg or more) participants and HIV-1 infected and uninfected adult participants from the cabotegravir development programme, therefore, no dosage adjustment is needed for adolescents weighing ≥ 35 kg.

Table 14 Pharmacokinetic parameters following cabotegravir orally once daily, and initiation, monthly, and every 2 month continuation intramuscular injections in Adolescent participants Aged 12 to less than 18 years (≥35 kg)

Dosing Phase	Dosage Regimen	Geometric Mean (5th, 95th Percentile)[a]		
		$AUC_{(0\text{-}tau)}$[b] (µg•h/mL)	C_{max} (µg/mL)	C_{tau} (µg/mL)
Oral lead-in[c]	30 mg once daily	203 (136, 320)	11 (7.4, 16.6)	6.4 (4.2, 10.5)
Initial injection[d]	600 mg IM Initial Dose	2085 (1056, 4259)	11 (7.4, 16.6)	1.9 (0.80, 3.7)
Every 1-month injection[e]	400 mg IM Every 1-month	3416 (2303, 5109)	5.7 (3.8, 8.9)	4.2 (2.7, 6.5)
Every 2-month injection[e]	600 mg IM Every 2-month	5184 (3511, 7677)	5.1 (3.1, 8.2)	2.5 (1.3, 4.2)

[a] Pharmacokinetic (PK) parameter values were based on individual post-hoc estimates from population PK models in both a HIV-1 infected adolescent population (n=147) weighing 35.2-98.5 kg and a HIV-1 uninfected adolescent population (n=62) weighing 39.9–167 kg.

[b] tau is dosing interval: 24 hours for oral administration; 1 month for the initial injection and monthly IM injections 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.

[e] Pharmacokinetic parameter values represent steady state.

5.3 Preclinical safety data

Carcinogenesis and mutagenesis

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

Reproductive toxicology studies

No effect on male or female fertility was observed in rats treated with cabotegravir at oral doses up to 1,000 mg/kg/day (>20 times the exposure in humans at the maximum recommended dose).

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

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

Repeated dose toxicity

The effect of prolonged daily treatment with high doses of cabotegravir has been evaluated in repeat oral dose toxicity studies in rats (26 weeks) and in monkeys (39 weeks). There were no drug-related adverse effects in rats or monkeys given cabotegravir orally at doses up to 1,000 mg/kg/day or 500 mg/kg/day, respectively.

In a 14 day and 28 day monkey toxicity study, gastro-intestinal (GI) effects (body weight loss, emesis, loose/watery faeces, and moderate to severe dehydration) were observed and were the result of local 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

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

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial
3 years

Shelf life of suspension in syringe

Chemical and physical in-use stability has been demonstrated for 2 hours at 25°C.
Once the suspension has been drawn into the syringe, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Unopened vial

This medicinal product does not require any special storage conditions.
Do not freeze.

Suspension in syringe

For storage conditions after first opening of the product, see section 6.3.

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

400 mg (2 mL vial)

Brown 2 mL type I glass vial, with bromobutyl rubber stopper and a grey aluminium overseal with a dark grey plastic flip-cap.

Each pack contains: 1 vial (400 mg), 1 graduated syringe (sterile, single use with volumetric markings every 0.2 mL), 1 vial adaptor and 1 injection needle (0.65 mm, 38 mm [23 gauge, 1½ inch]).

600 mg (3mL vial)

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

Each pack contains: 1 vial (600 mg), 1 graduated syringe (sterile, single use with volumetric markings every 0.2 mL), 1 vial adaptor and 1 injection needle (0.65 mm, 38 mm [23 gauge, 1½ inch]).

6.6 Special precautions for disposal and other handling

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

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1481/002
EU/1/20/1481/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 December 2020

10. DATE OF REVISION OF THE TEXT

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

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

1. NAME OF THE MEDICINAL PRODUCT

Vocabria 30 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains cabotegravir sodium equivalent to 30 mg cabotegravir.

Excipient with known effect

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vocabria tablets are indicated in combination with rilpivirine tablets for the short-term treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents (at least 12 years of age and weighing at least 35 kg) who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the non-nucleoside reverse transcriptase inhibitor (NNRTI) and integrase inhibitor (INI) class (see sections 4.2, 4.4 and 5.1) for:

- Oral lead-in to assess tolerability of Vocabria and rilpivirine prior to administration of long acting cabotegravir injection plus long acting rilpivirine injection.
- Oral therapy for adults and adolescents who will miss planned dosing with cabotegravir injection plus rilpivirine injection.

4.2 Posology and method of administration

Vocabria should be prescribed by physicians experienced in the management of HIV infection.

Vocabria tablets are indicated for the short-term treatment of HIV in combination with rilpivirine tablets, therefore, the prescribing information for rilpivirine tablets should be consulted for recommended dosing.

Prior to starting Vocabria, healthcare professionals should carefully select patients who agree to the required monthly or every 2 month injection schedules 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 (see section 4.4).

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

Posology

Adults and adolescents (at least 12 years of age and weighing at least 35 kg)

Oral lead-in
When used for oral lead-in, Vocabria tablets together with rilpivirine tablets should be taken for approximately one month (at least 28 days) to assess tolerability to cabotegravir and rilpivirine (see section 4.4). One Vocabria 30 mg tablet should be taken with one rilpivirine 25 mg tablet, once daily.

Table 1 Recommended Dosing Schedule

	ORAL LEAD-IN
Medicinal Product	**During month 1**
Vocabria	30 mg once daily
Rilpivirine	25 mg once daily

Oral dosing for missed injections of cabotegravir
If a patient plans to miss a scheduled injection visit by more than 7 days, oral therapy (one Vocabria 30 mg tablet and one rilpivirine 25 mg tablet once daily) may be used to replace up to 2 consecutive monthly injection visits or one, every 2 month injection visit. Limited data is available on oral bridging with other fully suppressive antiretroviral therapy (ART) (mainly INI-based), see section 5.1. 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 doses of cabotegravir and rilpivirine for patients being given monthly injections. For patients being given every 2-month injections, the first dose of oral therapy should be taken 2 months (+/- 7 days) after the last injection doses of cabotegravir and rilpivirine. Injection dosing should be resumed on the day oral dosing completes.

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

If a patient vomits within 4 hours of taking Vocabria tablets, another Vocabria tablet should be taken. If a patient vomits more than 4 hours after taking Vocabria tablets, the patient does not need to take another dose of Vocabria until the next regular scheduled dose.

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).

Renal impairment
No dosage adjustment is required in patients with mild (creatinine clearance ≥60 to <90 mL/min), moderate (creatinine clearance ≥30 to <60 mL/min) or severe renal impairment (creatinine clearance ≥15 to <30 mL/min and not on dialysis [see section 5.2]). Cabotegravir has not been studied in patients with end-stage renal disease on renal replacement therapy. As cabotegravir is greater than 99% protein bound, dialysis is not expected to alter exposures of cabotegravir. If administered in a patient on renal replacement therapy, cabotegravir should be used with caution.

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

Paediatric population
The safety and efficacy of Vocabria in children aged less than 12 years and adolescents weighing less than 35 kg have not been established. No data are available.

Method of administration

Oral use.

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

4.3 Contraindications

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

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

4.4 Special warnings and precautions for use

Baseline factors associated with virological failure

Before starting the regimen, it should be taken into account that multivariable analyses indicate that a combination of at least 2 of the following baseline factors may be associated with an increased risk of virological failure: archived rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI ≥30 kg/m^2. Available data suggest that virologic failure occurs more often when these patients are treated according to the every 2 month dosing regimen as compared to the monthly dosing regimen. In patients with an incomplete or uncertain treatment history without pre-treatment resistance analyses, caution is warranted in the presence of either BMI ≥30 kg/m^2 or HIV-1 A6/A1 subtype (see section 5.1).

Severe cutaneous adverse reactions (SCARs)

The severe cutaneous adverse reactions, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported very rarely in association with cabotegravir treatment.

At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, cabotegravir should be withdrawn immediately and an alternative treatment considered (as appropriate). If the patient has developed a serious reaction such as SJS or TEN with the use of cabotegravir, treatment with cabotegravir must not be restarted in this patient at any time.

Hypersensitivity reactions

Hypersensitivity reactions have been reported in association with integrase inhibitors including cabotegravir. These reactions were characterised by rash, constitutional findings and sometimes organ dysfunction, including liver injury. Vocabria and other suspected medicinal products should be discontinued immediately, should signs or symptoms of hypersensitivity develop (including, but not limited to, severe rash, or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia or angioedema). Clinical

status, including liver aminotransferases should be monitored and appropriate therapy initiated. (See sections 4.2, 4.8 and 5.1).

Hepatoxicity

Hepatotoxicity has been reported in a limited number of patients receiving Vocabria with or without known pre-existing hepatic disease (see section 4.8). Administration of cabotegravir oral lead-in was used in clinical studies to help identify patients who may be at risk of hepatotoxicity.
Monitoring of liver chemistries is recommended and treatment with Vocabria should be discontinued if hepatotoxicity is suspected.

HBV/HCV co-infection

Patients with hepatitis B co-infection were excluded from studies with Vocabria. It is not recommended to initiate Vocabria in patients with hepatitis B co-infection. Physicians should refer to current treatment guidelines for the management of HIV infection in patients co-infected with hepatitis B virus.
Limited data is available in patients with hepatitis C co-infection. Monitoring of liver function is recommended in patients with hepatitis C co-infection

Interactions with medicinal products

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

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

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency at the time of institution of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated, and treatment instituted when necessary. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution, however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Opportunistic infections

Patients should be advised that Vocabria or any other antiretroviral therapy do not cure HIV infection and that they 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.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take this medicine.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Vocabria tablets, in combination with rilpivirine tablets, are indicated for the treatment of HIV-1, therefore, the prescribing information for rilpivirine tablets should be consulted for associated interactions.

Effect of other agents on the pharmacokinetics of cabotegravir

Cabotegravir is primarily metabolised by uridine diphosphate glucuronosyl transferase (UGT) 1A1 and to a lesser extent by UGT1A9. Medicinal products which are strong inducers of UGT1A1 or UGT1A9 are expected to decrease cabotegravir plasma concentrations leading to lack of efficacy (see section 4.3 and table 2 below). In poor metabolizers of UGT1A1, representing a maximum clinical UGT1A1 inhibition, the mean AUC, C_{max} and C_{tau} of oral cabotegravir increased by up to 1.5-fold. The impact of an UGT1A1 inhibitor may be slightly more pronounced, however, considering the safety margins of cabotegravir, this increase is not expected to be clinically relevant. No dosing adjustments for Vocabria are, therefore, recommended in the presence of UGT1A1 inhibitors (e.g. atazanavir, erlotinib, sorafenib).

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

Effect of cabotegravir on the pharmacokinetics of other medicinal products

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

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

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.

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

Table 2 Drug Interactions

Medicinal products by therapeutic areas	**Interaction Geometric mean change (%)**	**Recommendations concerning co-administration**
HIV-1 Antiviral medicinal products		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine	Cabotegravir ↔ AUC ↑ 1% C_{max} ↑ 4% Cτ ↔ 0%	Etravirine did not significantly change cabotegravir plasma concentration. No dose adjustment of Vocabria tablets is necessary.
Non-nucleoside Reverse Transcriptase Inhibitor: Rilpivirine	Cabotegravir ↔ AUC ↑ 12% C_{max} ↑ 5% Cτ ↑ 14% Rilpivirine ↔	Rilpivirine did not significantly change cabotegravir plasma concentration. No dose adjustment of Vocabria tablets is necessary when co-administered with rilpivirine.

	AUC ↓ 1% C_{max} ↓ 4% Cτ ↓ 8%	
Anticonvulsants		
Carbamazepine Oxcarbazepine Phenytoin Phenobarbital	Cabotegravir ↓	Metabolic inducers may significantly decrease cabotegravir plasma concentrations, concomitant use is contraindicated (see section 4.3).
Antacids		
Antacids (e.g. magnesium, aluminium, or calcium)	Cabotegravir ↓	Co-administration of antacid supplements has the potential to decrease oral cabotegravir absorption and has not been studied. Antacid products containing polyvalent cations are recommended to be administered at least 2 hours before or 4 hours after oral Vocabria (see section 4.4).
Antimycobacterials		
Rifampicin	Cabotegravir ↓ AUC ↓ 59% C_{max} ↓ 6%	Rifampicin significantly decreased cabotegravir plasma concentration which is likely to result in loss of therapeutic effect. Dosing recommendations for co-administration of Vocabria with rifampicin have not been established and co-administration of Vocabria with rifampicin is contraindicated (see section 4.3).
Rifapentine	Cabotegravir ↓	Rifapentine may significantly decrease cabotegravir plasma concentrations, concomitant use is contraindicated (see section 4.3).
Rifabutin	Cabotegravir ↓ AUC ↓ 21% C_{max} ↓ 17% Cτ ↓ 26%	Rifabutin did not significantly change cabotegravir plasma concentration. No dose adjustment is required. Prior to initiation of oral cabotegravir therapy, the prescribing information for cabotegravir injection should be consulted regarding concomitant use with rifabutin.
Oral Contraceptives		
Ethinyl estradiol (EE) and Levonorgestrel (LNG)	EE ↔ AUC ↑ 2% C_{max} ↓ 8% Cτ ↔ 0% LNG ↔ AUC ↑ 12% C_{max} ↑ 5% Cτ ↑ 7%	Cabotegravir did not significantly change ethinyl estradiol and levonorgestrel plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with Vocabria tablets.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

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

Breast-feeding

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

It is recommended that women living with HIV do not breast-feed their infants in order to avoid transmission of HIV.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reaction (ARs) from monthly dosing studies were headache (up to 12%) and pyrexia[4] (10%).
The most frequently reported ARs, considered by the investigator as causally related, from ATLAS-2M every 2 month dosing were headache (7%) and pyrexia[4] (7%).
The SCARs SJS and TEN have been reported in association with cabotegravir treatment (see section 4.4).

Tabulated list of adverse reactions

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

Table 3 Tabulated summary of adverse reactions[1]

MedDRA System Organ Class (SOC)	Frequency Category	ARs for Vocabria + rilpivirine regimen
Immune system disorders	Uncommon	Hypersensitivity*
Psychiatric disorders	Common	Depression Anxiety Abnormal dreams Insomnia
	Uncommon	Suicide attempt; Suicidal ideation (particularly in patients with a pre-existing history of psychiatric illness)
Nervous system disorders	Very common	Headache
	Common	Dizziness
	Uncommon	Somnolence
Gastrointestinal disorders	Common	Nausea Vomiting Abdominal pain[2] Flatulence Diarrhoea
Hepatobiliary Disorders	Uncommon	Hepatotoxicity
Skin and subcutaneous tissue disorders	Common	Rash[3]
	Uncommon	Urticaria* Angioedema*
	Very rare	Stevens-Johnson syndrome*, toxic epidermal necrolysis*
Musculoskeletal and connective tissue disorders	Common	Myalgia
General disorders and administrative site conditions	Very common	Pyrexia[4]
	Common	Fatigue Asthenia Malaise
Investigations	Common	Weight increased
	Uncommon	Transaminase increased Blood bilirubin increased

[1] The frequency of the identified ARs are based on all reported occurrences of the events and are not limited to those considered at least possibly related by the investigator.
[2] Abdominal pain includes the following grouped MedDRA preferred term: upper abdominal pain.
[3] Rash includes the following grouped MedDRA preferred terms: rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic.
[4] Pyrexia includes the following grouped MedDRA preferred terms: feeling hot, body temperature increased.
* Please refer to section 4.4.

The overall safety profile at Week 96 and Week 124 in the FLAIR study was consistent with that observed at Week 48, with no new safety findings identified. In the extension phase of the 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 section 5.1).

Description of selected adverse reactions

Weight increased
At the Week 48 time point, subjects in studies FLAIR and ATLAS, who received Vocabria plus rilpivirine gained a median of 1.5 kg in weight; subjects continuing on their current antiretroviral therapy (CAR) gained a median of 1.0 kg (pooled analysis). In the individual studies FLAIR and ATLAS, the median weight gains in the Vocabria plus 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 Vocabria plus rilpivirine 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 Vocabria plus 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 Vocabria plus rilpivirine during clinical studies. These elevations were primarily attributed to acute viral hepatitis. A few subjects on oral therapy had transaminase elevations attributed to suspected drug-related hepatotoxicity; these changes were reversible upon discontinuation of treatment (see section 4.4).

Elevated lipases were observed during clinical trials with Vocabria plus rilpivirine; Grade 3 and 4 lipase increases occurred at a higher incidence with Vocabria plus rilpivirine compared with CAR. These elevations were generally asymptomatic and did not lead to Vocabria plus rilpivirine discontinuation. One case of fatal pancreatitis with Grade 4 lipase and confounding factors (including history of pancreatitis) has been reported in study ATLAS-2M, for which causality to the injection regimen could not be ruled out.

Paediatric population

Based on data from the week 16 (Cohort 1C, n=30) and week 24 analysis (Cohort 2, n=144) of the MOCHA study (IMPAACT 2017), no new safety concerns were identified in adolescents (aged at least 12 years and weighing 35 kg or more) when compared with the safety profile established in adults.

Reporting of suspected adverse reactions

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

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Pharmacodynamic effects

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

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

Resistance in vitro
Isolation from wild-type HIV-1 and activity against resistant strains: Viruses with >10-fold increase in cabotegravir EC_{50} were not observed during the 112-day passage of strain IIIB. The following integrase (IN) mutations emerged after passaging wild type HIV-1 (with T124A polymorphism) in the presence of cabotegravir: Q146L (fold-change [FC] range 1.3-4.6), S153Y (FC range 2.8-8.4), and I162M (FC = 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 FC was observed with mutants containing Q148K or Q148R. E138K/Q148H resulted in a 0.92-fold decrease in susceptibility to cabotegravir but E138K/Q148R resulted in a 12-fold decrease in susceptibility and E138K/Q148K resulted in an 81-fold decrease in susceptibility to cabotegravir. G140C/Q148R and G140S/Q148R resulted in a 22- and 12-fold decrease in susceptibility to cabotegravir, respectively. While N155H did not alter susceptibility to cabotegravir, N155H/Q148R resulted in a 61-fold decrease in susceptibility to cabotegravir. Other multiple mutants, which resulted in a FC between 5 and 10, are: T66K/L74M (FC=6.3), G140S/Q148K (FC=5.6), G140S/Q148H (FC=6.1) and E92Q/N155H (FC=5.3).

Resistance in vivo
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 plus rilpivirine in FLAIR with resistance data had Subtype A1. In addition, 2 of the 3 CVFs had treatment-emergent integrase inhibitor resistance associated substitution Q148R while one of the three 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 two of the three showed reduced phenotypic susceptibility to rilpivirine. The 3 CVFs in ATLAS had subtype A, A1

and AG. One of the three CVFs carried the INI resistance-associated substitution N155H at failure with reduced cabotegravir phenotype susceptibility. All three CVFs carried one rilpivirine resistance-associated substitution at failure: E138A, E138E/K or E138K, and showed reduced phenotypic susceptibility to rilpivirine. In two of these three CVFs, the rilpivirine resistance-associated substitutions observed at failure 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 were 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 Baseline in the Q8W arm, 5 subjects had rilpivirine 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 rilpivirine resistance-associated mutation). At the suspected virologic failure (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 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 (n=2); Q148R; Q148Q/R+N155N/H (n=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. FCs 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 rilpivirine 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 rilpivirine. Both subjects also had INSTI resistance-associated mutations, either Q148R + E138E/K or N155N/H at SVF and 1 subject had reduced susceptibility to cabotegravir. Neither subject had the INSTI substitution, L74I. FCs 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.

Clinical efficacy and safety

Adults

The efficacy of cabotegravir plus rilpivirine has been evaluated in two Phase III randomised, multicentre, active-controlled, parallel-arm, open-label, non-inferiority studies, FLAIR (study 201584) and ATLAS (study 201585). The primary analysis was conducted after all subjects completed their Week 48 visit or discontinued the study prematurely.

Patients virologically suppressed (on prior dolutegravir based regimen for 20 weeks)
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 plus 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 the 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 one 30 mg cabotegravir tablet plus one 25 mg rilpivirine 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. This study was extended to 96 weeks.

Patients virologically suppressed (stable on prior ARV therapy for at least 6 months)
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 the 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 one 30 mg cabotegravir tablet plus one 25 mg rilpivirine 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, 50%, 17%, and 33% of subjects received an NNRTI, PI, or INI (respectively) as their baseline third treatment medicine class prior to randomisation and this was similar between treatment arms.

Pooled data
At baseline, in the pooled analysis, for the cabotegravir plus rilpivirine arm, the median age of subjects was 38 years, 27% were female, 27% were non-white, 1% were ≥ 65 years and 7% had CD4+ cell count less than 350 cells per mm3; 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 plus 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 plus 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%).

The primary endpoint and other week 48 outcomes, including outcomes by key baseline factors, for FLAIR and ATLAS are shown in Tables 4 and 5.

Table 4 Virologic Outcomes of randomised treatment of FLAIR and ATLAS at 48 Weeks (Snapshot analysis)

	FLAIR		ATLAS		Pooled Data	
	Cabotegravir + RPV N=283	**CAR N=283**	**Cabotegravir + RPV N=308**	**CAR N=308**	**Cabotegravir +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 5 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**	
		Cabotegravir+RPV N=591 n/N (%)	**CAR N=591 n/N (%)**
Baseline CD4+ (cells/ mm^3)	<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/m^2	6/491 (1.2)	8/488 (1.6)
	≥30 kg/m^2	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, race, BMI, age, baseline third agent treatment class) were comparable.

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 vs Oral Lead-in.
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
Patients virologically suppressed (stable on prior ARV therapy for at least 6 months)
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-cabotegravir/rilpivirine treatment received oral lead-in treatment comprising one 30 mg cabotegravir tablet plus one 25 mg rilpivirine 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) 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 cabotegravir plus rilpivirine 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, 4% were ≥ 65 years 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 and 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 and 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%).

Table 6 Virologic Outcomes of Randomised Treatment of 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 7 Proportion of Subjects with Plasma HIV-1 RNA ≥50 copies/mL at Week 48 for key baseline factors (Snapshot Outcomes).

Baseline factors		**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)

Baseline factors		Number of HIV-1 RNA ≥50 c/mL/Total Assessed (%)	
		2 Month Dosing (Q8W)	Monthly dosing (Q4W)
	≥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.

The efficacy results at Week 96 are consistent with the results of the primary endpoint at Week 48. Cabotegravir plus rilpivirine injections administered every 2 months is non-inferior to cabotegravir and rilpivirine administered every month. The proportion of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 96 in cabotegravir plus rilpivirine every 2 months dosing (n=522) and cabotegravir plus rilpivirine monthly dosing (n=523) was 2.1% and 1.1% respectively (adjusted treatment difference between cabotegravir plus rilpivirine every 2 months dosing and monthly dosing [1.0; 95% CI: -0.6, 2.5]). The proportion of subjects having plasma HIV-1 RNA <50 c/mL at Week 96 in cabotegravir plus rilpivirine every 2 months dosing and cabotegravir plus rilpivirine monthly dosing was 91% and 90.2% respectively (adjusted treatment difference between cabotegravir plus rilpivirine every 2 months dosing and monthly dosing [0.8; 95% CI: -2.8, 4.3]).

The efficacy results at Week 152 are consistent with the results of the primary endpoint at Week 48 and at Week 96. Cabotegravir plus rilpivirine injections administered every 2 months is non-inferior to cabotegravir and rilpivirine administered every month. In an ITT analysis, the proportion of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 152 in cabotegravir plus rilpivirine every 2 months dosing (n=522) and cabotegravir plus rilpivirine monthly dosing (n=523) was 2.7% and 1.0% respectively (adjusted treatment difference between cabotegravir plus rilpivirine every 2 months dosing and monthly dosing [1.7; 95% CI: 0.1, 3.3]). In an ITT analysis, the proportion of subjects having plasma HIV-1 RNA <50 c/mL at Week 152 in cabotegravir plus rilpivirine every 2 months dosing and cabotegravir plus rilpivirine monthly dosing was 87% and 86% respectively (adjusted treatment difference between cabotegravir plus rilpivirine every 2 months dosing and monthly dosing [1.5; 95% CI: -2.6, 5.6]).

Post-hoc analyses
Multivariable analyses of pooled phase 3 studies (ATLAS through 96 weeks, FLAIR through 124 weeks and ATLAS-2M through 152 weeks) examined the influence of various factors on the risk of CVF. The baseline factors analysis (BFA) examined baseline viral and participant characteristics, and dosing regimen; and the multivariable analysis (MVA) included the baseline factors and incorporated post-baseline predicted plasma drug concentrations on CVF using regression modelling with a variable selection procedure. Following a total of 4291 person-years, the unadjusted CVF incidence rate was 0.54 per 100 person-years; 23 CVFs were reported (1.4% of 1651 individuals in these studies).

The BFA demonstrated rilpivirine resistance mutations (incidence rate ratio IRR=21.65, p<0.0001), HIV-1 subtype A6/A1 (IRR=12.87, p<0.0001), and body mass index (IRR=1.09 per 1 unit increase, p=0.04; IRR=3.97 of ≥30 kg/m2, p=0.01) were associated with CVF. Other variables including Q4W or Q8W dosing, female gender, or CAB/INSTI resistance mutations had no significant association with CVF. A combination of at least 2 of the following key 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 8).

Table 8 Virologic outcomes by presence of key baseline factors of rilpivirine resistance mutations, Subtype A6/A1[1] and BMI ≥30 kg/m^2

Baseline Factors (number)	Virologic Successes (%)[2]	Confirmed Virologic Failure (%)[3]
0	844/970 (87.0)	4/970 (0.4)
1	343/404 (84.9)	8/404 (2.0)[4]
≥2	44/57 (77.2)	11/57 (19.3)[5]
TOTAL (95% Confidence Interval)	1231/1431 (86.0) (84.1%, 87.8%)	23/1431 (1.6)[6] (1.0%, 2.4%)

[1] HIV-1 subtype A1 or A6 classification based on Los Alamos National Library panel from HIV Sequence database (June 2020)
[2] Based on the FDA Snapshot algorithm of RNA <50 copies/mL at Week 48 for ATLAS, at Week 124 for FLAIR, at Week 152 for ATLAS-2M.
[3] Defined as two consecutive measurements of HIV RNA ≥200 copies/mL.
[4] Positive Predictive Value (PPV) <2%; Negative Predictive Value (NPV) 98.5%; sensitivity 34.8%; specificity 71.9%
[5] PPV 19.3%; NPV 99.1%; sensitivity 47.8%; specificity 96.7%
[6] Analysis dataset with all non-missing covariates for baseline factors (out of a total of 1651 individuals).

In patients with at least two of these risk factors, the proportion of subjects who had a CVF was higher than observed in patients with none or one risk factor, with CVF identified in 6/24 patients [25.0%, 95%CI (9.8%, 46.7%)] treated with the every 2 months dosing regimen and 5/33 patients [15.2%, 95%CI (5.1%, 31.9%)] treated with the monthly dosing regimen.

Oral bridging with other ART
In a retrospective analysis of pooled data from 3 clinical studies (FLAIR, ATLAS-2M, and LATTE-2/study 200056), 29 subjects were included who received oral bridging for a median duration of 59 days (25th and 75th percentile 53-135) with ART other than cabotegravir plus rilpivirine (alternative oral bridging) during treatment with cabotegravir plus rilpivirine long-acting (LA) intramuscular (IM) injections. The median age of subjects was 32 years, 14% were female, 31% were non-white, 97% received an integrase inhibitor (INI)-based regimen for alternative oral bridging, 41% received an NNRTI as part of their alternative oral bridging regimen (including rilpivirine in 11/12 cases), and 62% received an NRTI. Three subjects withdrew during oral bridging or shortly following oral bridging for non-safety reasons. The majority (≥96%) of subjects maintained virologic suppression (plasma HIV-1 RNA <50 c/mL). During bridging with alternative oral bridging and during the period following alternative oral bridging (up to 2 cabotegravir plus rilpivirine injections following oral bridging), no cases of CVF (plasma HIV-1 RNA ≥200 c/mL) were observed.

Paediatric population
The safety, tolerability and pharmacokinetics (PK) of long-acting injectable cabotegravir in combination with long-acting injectable rilpivirine in adolescents has been evaluated in an ongoing Phase I/II multicentre, open-label, non-comparative study, MOCHA (IMPAACT 2017).

In Cohort 2 of this study, 144 virologically suppressed adolescents discontinued their pre-study cART regimen and received cabotegravir 30 mg tablet and rilpivirine 25 mg tablet once daily for at least 4 weeks followed by every 2 month cabotegravir intramuscular injections (months 1 and 2: 600 mg, and then 600 mg every 2 months) and rilpivirine intramuscular injections (months 1 and 2: 900 mg, and then 900 mg every 2 months).

At baseline the median age of participants was 15.0 years, the median weight was 48.5 kg (range: 35.2, 100.9), the median BMI was 19.5 kg/m^2 (range: 16.0, 34.3), 51.4 % were female, 98.6 % were non-white, and 4 participants had a CD4+ cell count less than 350 cells per mm^3.

Antiviral activity was assessed as a secondary objective, with 139 of the 144 participants (96.5 %) (snapshot algorithm) with available data remaining virologically suppressed (plasma HIV-1 RNA value <50 c/mL) at Week 24.

The European Medicines Agency has deferred the obligation to submit the results of studies with cabotegravir film-coated tablets and prolonged-release suspension for injection in one or more subsets of the paediatric population in the treatment of HIV-1 infection. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Adults

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.

Table 9 Pharmacokinetic parameters following cabotegravir orally once daily in Adult participants

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

[a] Pharmacokinetic parameter values based on pooled FLAIR and ATLAS individual post-hoc estimates from cabotegravir population pharmacokinetic model (n = 581)
[b] tau is dosing interval: 24 hours for oral administration.
[c] Oral lead-in pharmacokinetic parameter values represent steady-state.

Absorption

Cabotegravir is rapidly absorbed following oral administration, with median T_{max} at 3 hours post dose for tablet formulation. With once daily dosing, pharmacokinetic steady-state is achieved by 7 days. Cabotegravir may be administered with or without food. 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.

Distribution

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

Cabotegravir is present in the female and male genital tract. 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 intramuscular injection (IM) 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 plus rilpivirine injection, the cabotegravir CSF to plasma concentration ratio [median (range)] (n=16) was 0.003(range: 0.002 to 0.004) one week following a steady-state long acting 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.

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

Biotransformation

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

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

Elimination

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

Polymorphisms

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

Special 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.

Body Mass Index (BMI)

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

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 (creatinine clearance ≥15 to <30 mL/min and not on dialysis) and matching healthy subjects were observed. No dosage adjustment is necessary for patients with mild, moderate or 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.

Paediatric population
Population pharmacokinetic simulations revealed no clinically relevant differences in exposure between adolescent (at least 12 years of age and weighing 35 kg or more) participants and HIV-1 infected and uninfected adult participants from the cabotegravir development programme, therefore, no dosage adjustment is needed for adolescents weighing ≥ 35 kg.

Table 10 Pharmacokinetic parameters following cabotegravir orally once daily in Adolescent participants aged 12 to less than 18 years (≥35 kg)

Dosing Phase	Dosage Regimen	Geometric Mean (5th, 95th Percentile)[a]		
		$AUC_{(0\text{-}tau)}$[b] (µg•h/mL)	C_{max} (µg/mL)	C_{tau} (µg/mL)
Oral lead-in[c]	30 mg once daily	203 (136, 320)	11 (7.4, 16.6)	6.4 (4.2, 10.5)

[a] Pharmacokinetic (PK) parameter values were based on individual post-hoc estimates from population PK models in both a HIV-1 infected adolescent population (n=147) weighing 35.2-98.5 kg and a HIV-1 uninfected adolescent population (n=62) weighing 39.9–167 kg.
[b] tau is dosing interval: 24 hours for oral administration.
[c] Oral lead-in pharmacokinetic parameter values represent steady-state.

5.3 Preclinical safety data

Carcinogenesis and mutagenesis

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

Reproductive toxicology studies

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

In an embryo-foetal development study there were no adverse developmental outcomes following oral administration of cabotegravir to pregnant rabbits up to a maternal toxic dose of 2,000 mg/kg/day (0.66 times the exposure in humans at the MRHD) or to pregnant rats at doses up to 1,000 mg/kg/day

(>30 times the exposure in humans at the MRHD). In rats, alterations in foetal growth (decreased body weights) 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.

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

Repeated dose toxicity

The effect of prolonged daily treatment with high doses of cabotegravir has been evaluated in repeat oral dose toxicity studies in rats (26 weeks) and in monkeys (39 weeks). There were no drug-related adverse effects in rats or monkeys given cabotegravir orally at doses up to 1,000 mg/kg/day or 500 mg/kg/day, respectively.

In a 14 day and 28 day monkey toxicity study, gastro-intestinal (GI) effects (body weight loss, emesis, loose/watery faeces, and moderate to severe dehydration) were observed and was the result of local 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

Tablet core

Lactose monohydrate
Microcrystalline cellulose (E460)
Hypromellose (E464)
Sodium starch glycolate
Magnesium stearate

Tablet coating

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1481/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 December 2020

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

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

Prolonged-release suspension for injection
GlaxoSmithKline Manufacturing SpA
Strada Provinciale Asolana, 90
San Polo di Torrile
Parma, 43056
Italy

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

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

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

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
The MAH will conduct a prospective cohort study (COMBINE-2 study) to collect data from patients in order to assess clinical effectiveness, adherence, durability and discontinuations after initiating the cabotegravir and rilpivirine long acting regimen. The study will also monitor for resistance and response to subsequent antiretroviral regimens among patients who switched from cabotegravir and rilpivirine long acting regimen to another regimen The MAH will submit interim study results annually and the final results of the study by September 2026.	September 2026
The MAH will conduct a real-world five-year Drug Utilisation Study (DUS). This observational cohort study will aim to better understand the patient population receiving cabotegravir long acting injection and/or rilpivirine long acting injection containing regimens in routine clinical practice. The study will assess usage patterns, adherence, and post marketing clinical effectiveness of these regimens and monitor for resistance among virologic failures for whom data on resistance testing are available. The MAH will submit interim study results annually and the final results of the DUS by September 2026.	September 2026

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – 400 MG INJECTION

1. NAME OF THE MEDICINAL PRODUCT

Vocabria 400 mg prolonged-release suspension for injection
cabotegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 400 mg cabotegravir.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release suspension for injection
Contents: 1 vial
1 vial adaptor
1 syringe
1 injection needle

2 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not freeze

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1481/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON INTERMEDIATE PACKAGING

BACKING CARD - 400 MG INJECTION

1. NAME OF THE MEDICINAL PRODUCT

Vocabria 400 mg prolonged-release suspension for injection
cabotegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

2 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the instructions for use before preparing Vocabria
For intramuscular use.

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

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL – 400 MG INJECTION

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

Vocabria 400 mg prolonged-release suspension for injection
cabotegravir
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – 600 MG INJECTION

1. NAME OF THE MEDICINAL PRODUCT

Vocabria 600 mg prolonged-release suspension for injection
cabotegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 600 mg cabotegravir.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release suspension for injection
Contents: 1 vial
1 vial adaptor
1 syringe
1 injection needle

3 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not freeze

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1481/003

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON INTERMEDIATE PACKAGING

BACKING CARD - 600 MG INJECTION

1. NAME OF THE MEDICINAL PRODUCT

Vocabria 600 mg prolonged-release suspension for injection
cabotegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

3 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the instructions for use before preparing Vocabria
For intramuscular use.

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

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL – 600 MG INJECTION

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

Vocabria 600 mg prolonged-release suspension for injection
cabotegravir
IM

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON - TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Vocabria 30 mg film-coated tablets
cabotegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose monohydrate (see package leaflet)

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1481/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

vocabria

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL - TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Vocabria 30 mg film-coated tablets
cabotegravir

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ViiV Healthcare BV

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1481/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Vocabria 400 mg prolonged-release suspension for injection
cabotegravir

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

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

What is in this leaflet

1. What Vocabria is and what it is used for

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

Vocabria injection is used to treat HIV (human immunodeficiency virus) infection in adults and adolescents (at least 12 years of age and weighing at least 35 kg), who are also receiving another antiretroviral medicine called rilpivirine and whose HIV-1 infection is under control.

Vocabria injections do not cure HIV infection; they keep 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 injection is always given in combination with another injection of an anti-retroviral medicine called *rilpivirine injection*. Refer to the rilpivirine package leaflet for information on that medicine.

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

Do not receive a Vocabria injection:
- if you have ever developed a severe skin rash, skin peeling, blistering and/or mouth sores.
- if you are **allergic** *(hypersensitive)* to cabotegravir or any of the other ingredients of this medicine (listed in section 6).
- if you are taking any of these medicines as they may affect the way Vocabria works:
  - **carbamazepine, oxcarbazepine, phenytoin, phenobarbital** (medicines to treat epilepsy and prevent fits).
  - **rifampicin** or **rifapentine** (medicines to treat some bacterial infections such as tuberculosis).

➔ If you think this applies to you, **tell your doctor**.

Warnings and precautions

Severe skin reaction:
The serious skin reactions, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with Vocabria. Stop using Vocabria and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions.

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

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

➔ **Read the information** in section 4 of this leaflet.

Liver problems including hepatitis B and/or C
Tell your doctor if you have or have had problems with your liver, including hepatitis B and/or C. Your doctor may evaluate how severe your liver disease is before deciding if you can take Vocabria.

Look out for important symptoms
Some people taking medicines for HIV infection develop other conditions, which can be serious. You need to know about important signs and symptoms to look out for while you're taking Vocabria. These include:

- symptoms of infections
- symptoms of liver damage.

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

If you get any symptoms of infection or liver damage:

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

Regular appointments are important
It is important that you **attend your planned appointments** to receive your Vocabria injection, to control your HIV infection, and to stop your illness from getting worse. Talk to your doctor if you are thinking about stopping treatment. If you are late receiving your Vocabria injection, or if you stop receiving Vocabria, you will need to take other medicines to treat HIV infection and to reduce the risk of developing viral resistance.

Vocabria injection is a long acting medication. If you stop treatment, low levels of cabotegravir (the active ingredient of Vocabria) can remain in your system for up to 12 months or more after your last injection. These low levels of cabotegravir will not protect you against the virus and the virus may become resistant. You must start a different HIV treatment within one month of your last Vocabria injection if you are having monthly injections, and within two months of your last Vocabria injection if you are having injections every two months.

Children and adolescents
This medicine is not for use in children less than 12 years of age or adolescents weighing less than 35 kg because it has not been studied in these patients.

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

Vocabria must not be given with some other medicines. (see 'Do not receive a Vocabria injection' earlier in section 2).

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.

Tell your doctor if you are taking:

- **rifabutin** (to treat some bacterial infections such as tuberculosis).

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

Pregnancy and breastfeeding

If you are pregnant or breastfeeding, think you may be pregnant**,** or are planning to have a baby:

➔ **Talk to your doctor** before receiving a Vocabria injection

Pregnancy
- **Vocabria is not recommended during pregnancy.** If needed, your doctor will consider the benefit to you and the risk to your baby of receiving Vocabria injections while you're pregnant. If you are planning to have a baby, **talk to your doctor in advance**
- If you have become pregnant, do not stop attending your appointments to receive a Vocabria injection without consulting your doctor.

Breast-feeding
Breast-feeding is **not recommended** in women living with HIV because HIV infection can be passed on to the baby in breast milk.

It is not known whether the ingredients of Vocabria injection can pass into breast milk. However, it is possible that cabotegravir may still pass into breast milk for 12 months after the last injection of Vocabria.

If you're breast-feeding, or thinking about breast-feeding, you should **discuss it with your doctor as soon as possible**.

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.

3. How Vocabria injections are given

You will be given Vocabria **as an injection,** either once every month or once every 2 months, together with another injection of medicine called rilpivirine. Your doctor will advise you of your dosing schedule.

A nurse or doctor will give you Vocabria through an injection in the muscle of your buttock (*intramuscular, or IM, injection*).

- **When you first start treatment** with Vocabria you and your doctor may decide to either start treatment with cabotegravir tablets or start treatment directly with a Vocabria injection: If you decide to start treatment with tablets, your doctor will tell you:

- to take one 30 mg Vocabria tablet and one 25 mg rilpivirine tablet, once a day, for approximately **one month**
- after that receive **monthly or every 2 month injections.**

This first month of Vocabria and rilpivirine tablets is called the oral **lead-in period**. It allows your doctor to assess whether it's appropriate to proceed with injections.

Injection schedule for monthly dosing

	When	
Which medicine	**First injection**	**Second injection onwards, every month**
Vocabria	600 mg injection	400 mg injection every month
Rilpivirine	900 mg injection	600 mg injection every month

Injection Schedule for every 2 month dosing

Which medicine	**When**	
	First and second injections, one month apart	**Third injection onwards, every two months**
Vocabria	600 mg injection	600 mg injection every 2 months
Rilpivirine	900 mg injection	900 mg injection every 2 months

If you miss a Vocabria injection

➔ **Contact your doctor immediately** to make a new appointment

It is important that you keep your regular planned appointments to receive your injection to control your HIV and to stop your illness from getting worse. Talk to your doctor if you are thinking about stopping treatment.

Talk to your doctor if you think you will not be able to receive your Vocabria injection at the usual time. Your doctor may recommend you take Vocabria tablets or another HIV treatment instead, until you are able to receive Vocabria injection again.

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

Don't stop receiving Vocabria injections without advice from your doctor.
Keep receiving Vocabria injections for as long as your doctor recommends. Don't stop unless your doctor advises you to. If you stop, your doctor must start you on another HIV treatment within a month of your last Vocabria injection if you are having monthly injections, and within two months of your last Vocabria injection if you are having injections every two months, to reduce the risk of developing viral resistance.

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

4. Possible side effects

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

Stop using Vocabria and seek medical attention immediately if you notice any of the following symptoms:
- reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of the mouth, throat, nose, genitals, and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome, toxic epidermal necrolysis). These serious skin reactions are very rare (may affect **up to 1 in 10,000** people).

Allergic reactions

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

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

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

Very common side effects
These may affect **more than 1 in 10** people:
- headache
- injection site reactions. In clinical studies, these were generally mild to moderate and became less frequent over time. Symptoms may include:
    - very common: pain (which can rarely include temporary difficulty in walking) and discomfort, a hardened mass or lump
    - common: redness, itching, swelling, warmth, bruising, (which may include discolouration or a collection of blood under the skin)
    - uncommon: numbness, minor bleeding, an abscess (collection of pus) or cellulitis (heat, swelling or redness).
- feeling hot (*pyrexia*), which may occur within one week after injections.

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)*
- weight gain.

Uncommon side effects
These may affect **up to 1 in 100** people:
- suicide attempt and suicidal thoughts (particularly in patients who have had depression or mental health problems before)
- allergic reaction (*hypersensitivity*)
- hives (*urticaria*)
- swelling, sometimes of the face or mouth (*angioedema*), causing difficulty in breathing
- feeling drowsy *(somnolence)*
- feeling lightheaded, during or following an injection. This may lead to fainting
- 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)
- changes in liver blood tests (increase in *transaminases* or increase in *bilirubin*).

Other side effects that may show up in blood tests
- an increase in lipases (a substance produced by the pancreas)

Other possible side effects

People receiving Vocabria and rilpivirine therapy for HIV may get other side effects.

Pancreatitis

If you get severe pain in the abdomen (tummy), this may be caused by inflammation of your pancreas (pancreatitis).

➔ **Tell your doctor,** especially if the pain spreads and gets worse.

Symptoms of infection and inflammation

People with advanced HIV infection (AIDS) have weak immune systems and are more likely to develop serious infections *(opportunistic infections)*. When they start treatment, the immune system becomes stronger, so the body starts to fight infections.

Symptoms of infection and inflammation may develop, caused by either:
- old, hidden infections flaring up again as the body fights them
- the immune system attacking healthy body tissue (*autoimmune disorders*).

The symptoms of autoimmune disorders may develop many months after you start taking medicine to treat your HIV infection.

Symptoms may include:
- **muscle weakness** and/or **muscle pain**
- **joint pain** or **swelling**
- **weakness** beginning in the hands and feet and moving up towards the trunk of the body
- **palpitations** or **tremor**
- **hyperactivity** (excessive restlessness and movement).

If you get any symptoms of infection:

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

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Vocabria

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

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

This medicine does not require any special temperature storage conditions.

Do not freeze.

6. Contents of the pack and other information

What Vocabria contains
- The active substance is cabotegravir.

Each 2 ml vial contains 400 mg cabotegravir.

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

What Vocabria looks like and contents of the pack
Cabotegravir prolonged release suspension for injection is presented in a brown glass vial with a rubber stopper. The pack also contains 1 syringe, 1 vial adaptor, and 1 injection needle.

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Other sources of information

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

The following information is intended for healthcare professionals only:

Vocabria 2 mL injection Instructions for use:

Overview

A complete dose requires two injections: **VOCABRIA and rilpivirine**

2 mL of cabotegravir and 2 mL of rilpivirine.

Cabotegravir and rilpivirine are suspensions that do not need further dilution or reconstitution. The preparation steps for both medicines are the same. Carefully follow these instructions when preparing the suspension for injection to avoid leakage.

Cabotegravir and rilpivirine are for intramuscular use only. Both injections must be administered to the gluteal sites.

Note: The ventrogluteal site is recommended. **The administration order is not important.**

Storage information

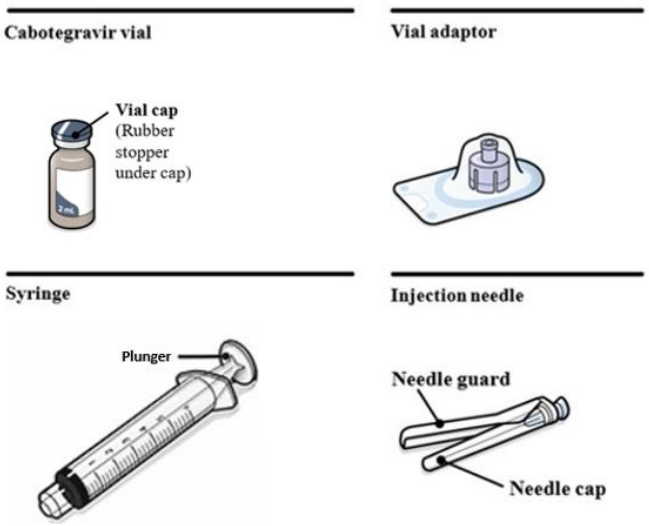
• This medicine does not require any special storage conditions.

Do not freeze.

Your pack contains

- 1 vial of cabotegravir
- 1 vial adaptor
- 1 syringe
- 1 injection needle (0.65 mm, 38 mm [23 gauge, 1.5 inches])

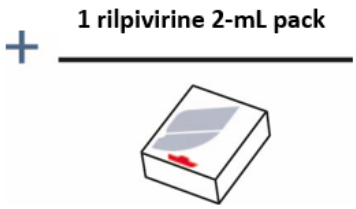
Consider the patient's build and use medical judgment to select an appropriate injection needle length.



You will also need

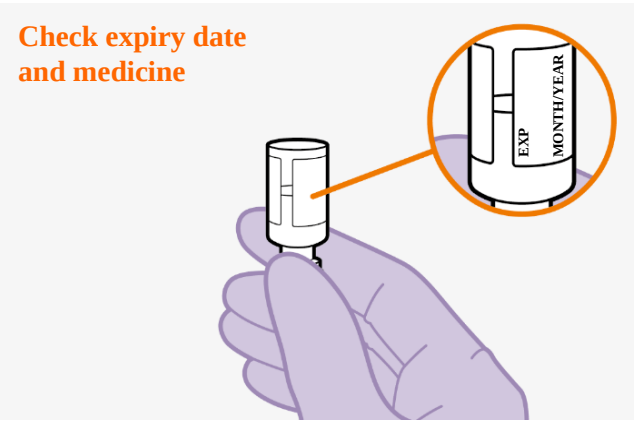
- Non-sterile gloves
- 2 alcohol swabs
- 2 gauze pads
- A suitable sharps container

Make sure to have the rilpivirine pack close by before starting.



Preparation

1. Inspect vial



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

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

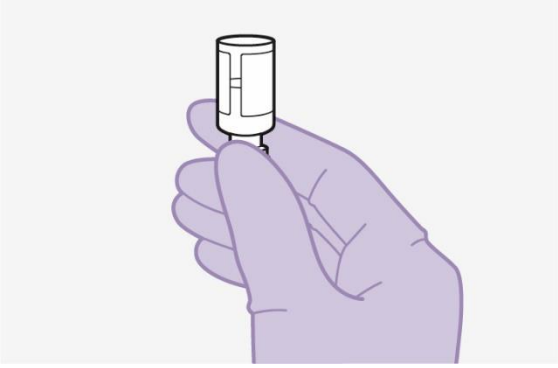
2. Wait 15 minutes

- If the pack has been stored in a fridge, remove and wait at least 15 minutes before you are ready to give the injection to allow the medicine to come to room temperature.

3. Shake vigorously

- Hold the vial firmly and vigorously shake for a full 10 seconds as shown.

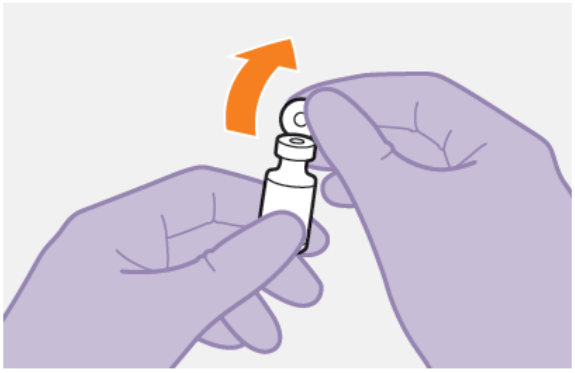
4. Inspect suspension



- Invert the vial and check the resuspension. It should look uniform. If the suspension is not uniform, shake the vial again.
- It is also normal to see small air bubbles.

Note: Vial preparation order is not important.

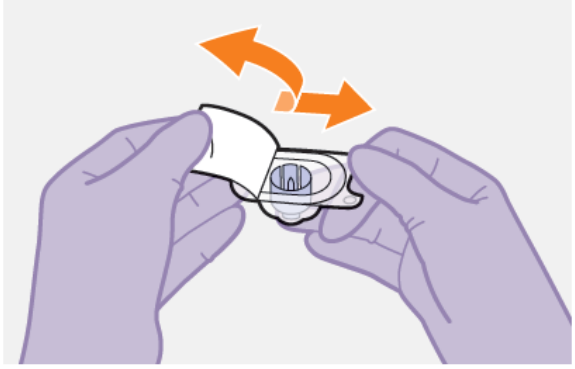
5. Remove vial cap



- Remove the cap from the vial.
- Wipe the rubber stopper with an alcohol swab.

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

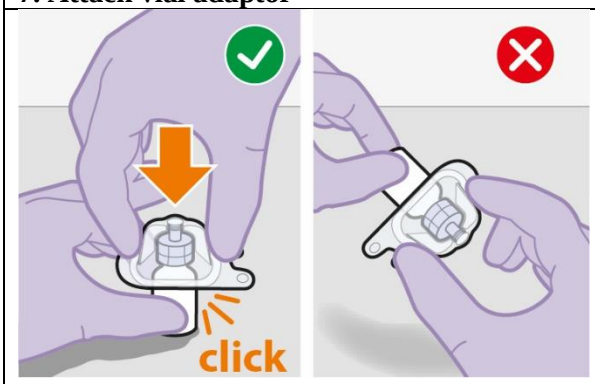
6. Peel open vial adaptor



- Peel off the paper backing from the vial adaptor packaging.

Note: Do not remove the adaptor from its packaging for the next step. The adaptor **will not** fall out when its packaging is turned upside down.

7. Attach vial adaptor

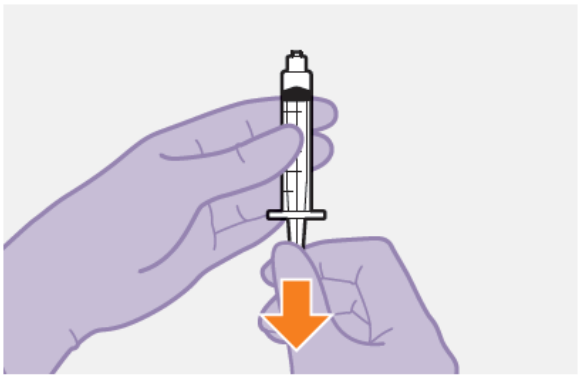


- Place the vial on a flat surface.
- Press the vial adaptor straight down onto the vial, as shown.
- The vial adaptor should click securely into place.

8. Lift off the packaging

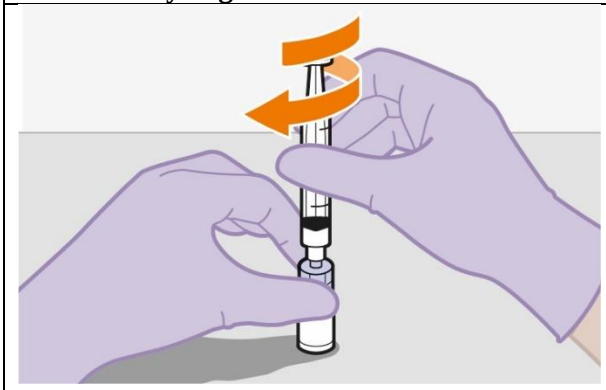
- Lift off the vial adaptor packaging, as shown.

9. Prepare syringe



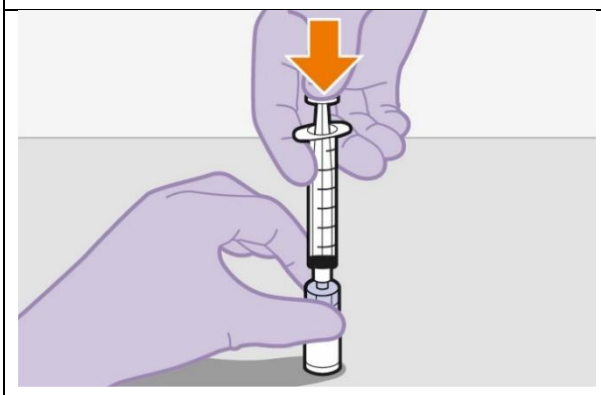
- Remove the syringe from its packaging.
- Draw 1 mL of air into the syringe. This will make it easier to draw up the liquid later.

10. Attach syringe



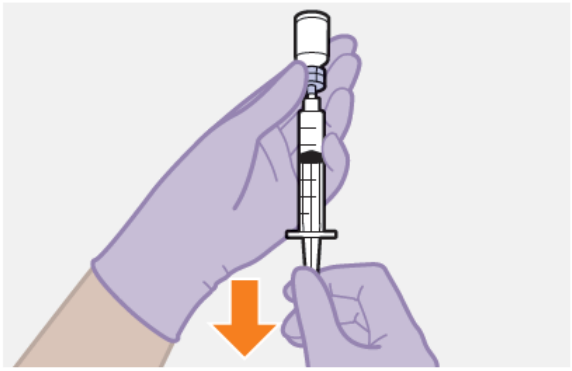
- Hold the vial adaptor and vial firmly, as shown.
- Screw the syringe firmly onto the vial adaptor.

11. Press the plunger



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

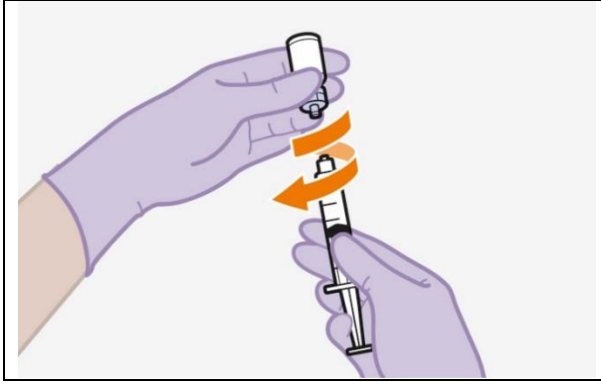
12. Slowly draw up dose



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

Note: Keep the syringe upright to avoid leakage.

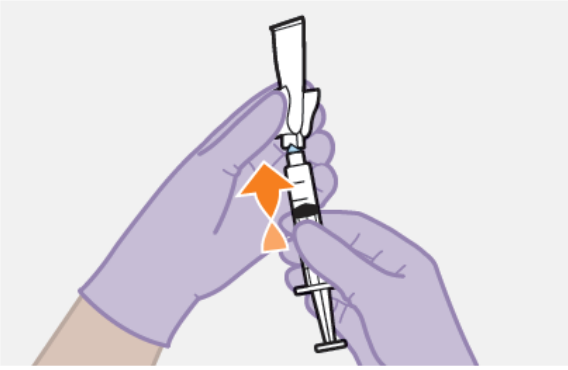
13. Unscrew syringe



- Hold the syringe plunger firmly in place as shown to prevent leakage. It is normal to feel some back pressure.
- Screw the syringe off the vial adaptor, holding the vial adaptor as shown.

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

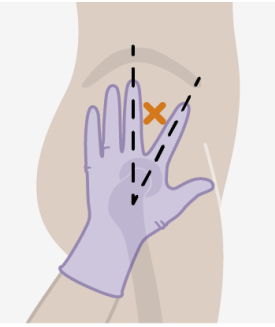
14. Attach needle



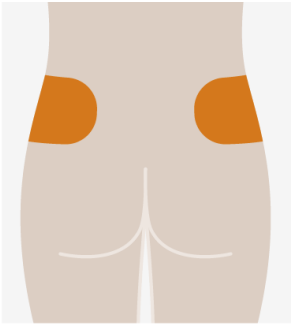
- Peel open the needle packaging part way to expose the needle base.
- Keeping the syringe upright, firmly twist the syringe onto the needle.
- Remove the needle packaging from the needle.

Injection

15. Prepare injection site



Ventrogluteal



Dorsogluteal

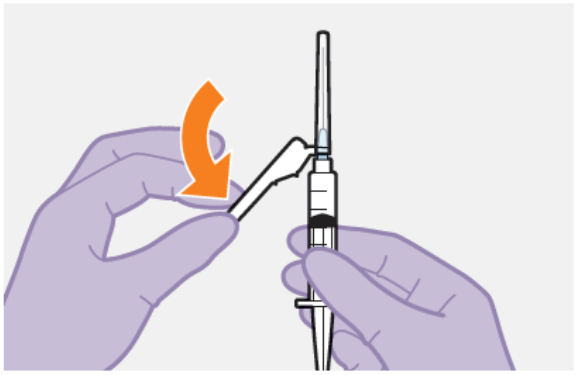
Injections must be administered to the gluteal sites. Select from the following areas for the injection:

• Ventrogluteal (recommended)

• Dorsogluteal (upper outer quadrant)

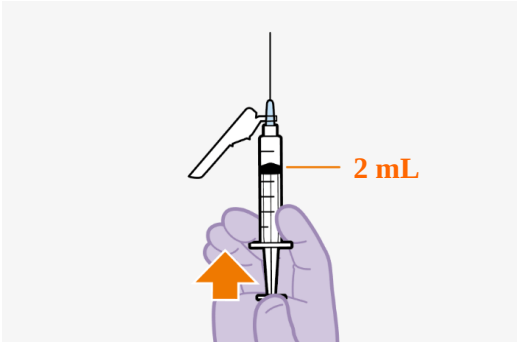
Note: For gluteal intramuscular use only. **Do not** inject intravenously.

16. Remove cap



- Fold the needle guard away from the needle.
- Pull off the injection needle cap.

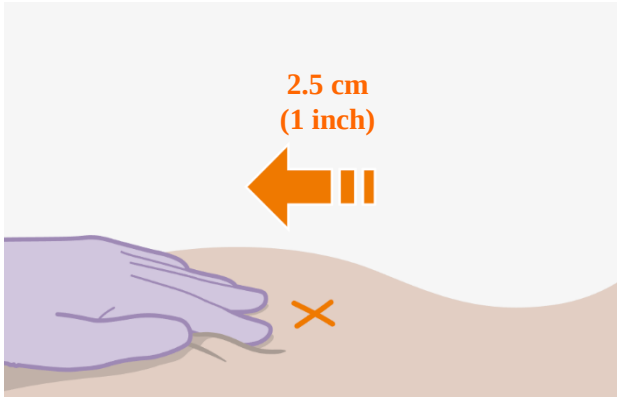
17. Remove extra liquid



- Hold the syringe with the needle pointing up. Press the plunger to the 2 mL dose to remove extra liquid and any air bubbles.

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

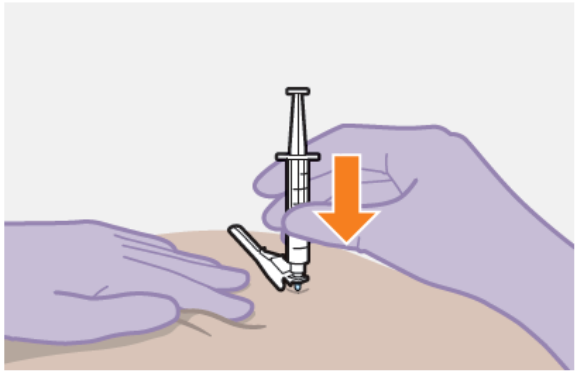
18. Stretch skin



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

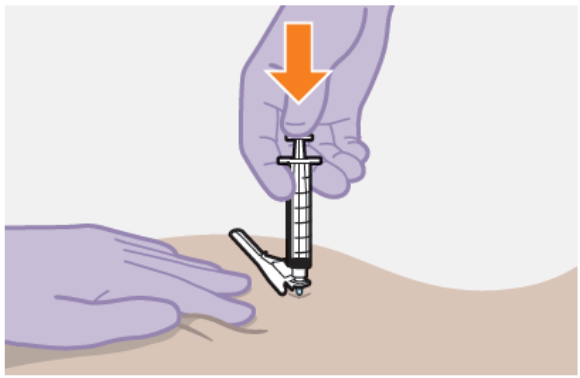
- Firmly drag the skin covering the injection site, displacing it by about 2.5 cm (1 inch).
- Keep it held in this position for the injection.

19. Insert needle



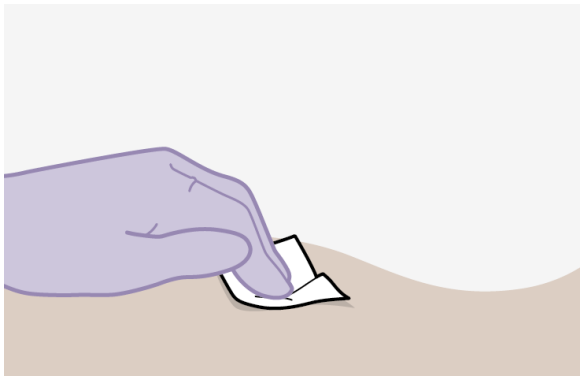
- Insert the needle to its full depth, or deep enough to reach the muscle.

20. Inject dose



- Still holding the skin stretched – slowly press the plunger all the way down.
- Ensure the syringe is empty.
- Withdraw the needle and release the stretched skin immediately.

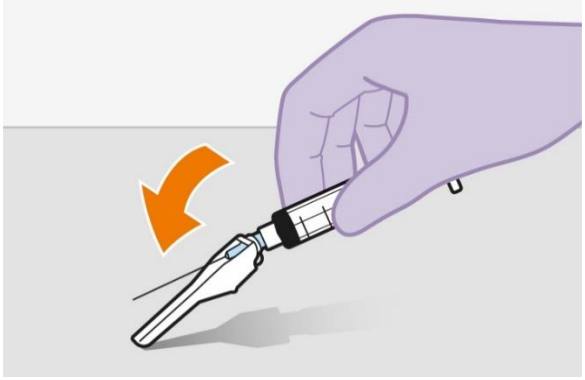
21. Assess the injection site

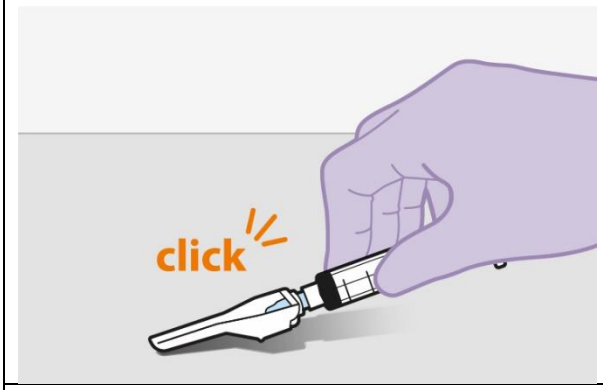


- Apply pressure to the injection site using a gauze.
- A small bandage may be used if a bleed occurs.

Do not massage the area.

22. Make needle safe

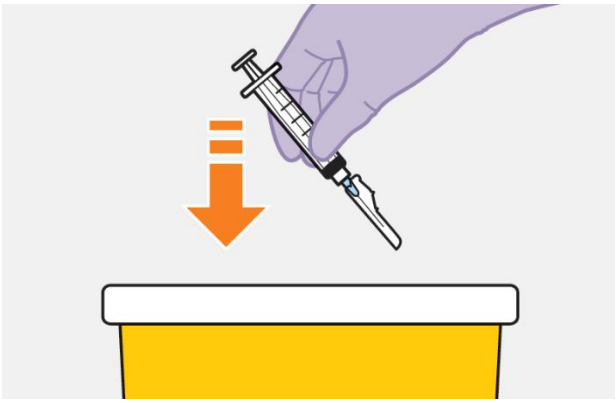




- Fold the needle guard over the needle.
- Gently apply pressure using a hard surface to lock the needle guard in place.
- The needle guard will make a click when it locks.

After injection

23. Dispose safely



- Dispose of used needles, syringes, vials and vial adaptors according to local health and safety laws.

Repeat for 2nd medicine

If you have not yet injected both medicines, use the steps for preparation and injection for rilpivirine which has its own specific Instructions for Use.

Questions and Answers

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

Once the suspension has been drawn into the syringe, the injection should be used immediately, from a microbiological point of view.

Chemical and physical in-use stability has been demonstrated for 2 hours at 25°C.

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

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

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

3. Does the order in which I give the medicines matter?

No, the order is unimportant.

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

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

Do not use any other heating methods.

5. Why is the ventrogluteal administration approach recommended?

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

Package leaflet: Information for the patient

Vocabria 600 mg prolonged-release suspension for injection
cabotegravir

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

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

What is in this leaflet

1. What Vocabria is and what it is used for

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

Vocabria injection is used to treat HIV (human immunodeficiency virus) infection in adults and adolescents (at least 12 years of age and weighing at least 35 kg) who are also receiving another antiretroviral medicine called rilpivirine and whose HIV-1 infection is under control.

Vocabria injections do not cure HIV infection; they keep 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 injection is always given in combination with another injection of an anti-retroviral medicine called *rilpivirine injection*. Refer to the rilpivirine package leaflet for information on that medicine.

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

Do not receive a Vocabria injection:
- if you have ever developed a severe skin rash, skin peeling, blistering and/or mouth sores.
- if you are **allergic** *(hypersensitive)* to cabotegravir or any of the other ingredients of this medicine (listed in section 6).
- if you are taking any of these medicines as they may affect the way Vocabria works:
  - **carbamazepine, oxcarbazepine, phenytoin, phenobarbital** (medicines to treat epilepsy and prevent fits).
  - **rifampicin** or **rifapentine** (medicines to treat some bacterial infections such as tuberculosis).

➔ If you think this applies to you, **tell your doctor**.

Warnings and precautions

Severe skin reaction:
The serious skin reactions, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with Vocabria. Stop using Vocabria and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions.

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

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

➔ **Read the information** in section 4 of this leaflet.

Liver problems including hepatitis B and/or C
Tell your doctor if you have or have had problems with your liver, including hepatitis B and/or C. Your doctor may evaluate how severe your liver disease is before deciding if you can take Vocabria.

Look out for important symptoms
Some people taking medicines for HIV infection develop other conditions, which can be serious. You need to know about important signs and symptoms to look out for while you're taking Vocabria. These include:
- symptoms of infections
- symptoms of liver damage.

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

If you get any symptoms of infection or liver damage:

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

Regular appointments are important

It is important that you **attend your planned appointments** to receive your Vocabria injection, to control your HIV infection, and to stop your illness from getting worse. Talk to your doctor if you are thinking about stopping treatment. If you are late receiving your Vocabria injection, or if you stop receiving Vocabria, you will need to take other medicines to treat HIV infection and to reduce the risk of developing viral resistance.

Vocabria injection is a long acting medication. If you stop treatment, low levels of cabotegravir (the active ingredient of Vocabria) can remain in your system for up to 12 months or more after your last injection. These low levels of cabotegravir will not protect you against the virus and the virus may become resistant. You must start a different HIV treatment within one month of your last Vocabria injection if you are having monthly injections, and within two months of your last Vocabria injection if you are having injections every two months.

Children and adolescents
This medicine is not for use in children less than 12 years of age or adolescents weighing less than 35 kg because it has not been studied in these patients.

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

Vocabria must not be given with some other medicines. (see 'Do not receive a Vocabria injection' earlier in section 2).

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.

Tell your doctor if you are taking:

- **rifabutin** (to treat some bacterial infections such as tuberculosis).

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

Pregnancy and breastfeeding

If you are pregnant or breastfeeding, think you may be pregnant**,** or are planning to have a baby:

➔ **Talk to your doctor** before receiving a Vocabria injection

Pregnancy
- **Vocabria is not recommended during pregnancy.** If needed, your doctor will consider the benefit to you and the risk to your baby of receiving Vocabria injections while you're pregnant. If you are planning to have a baby, **talk to your doctor in advance**
- If you have become pregnant, do not stop attending your appointments to receive a Vocabria injection without consulting your doctor.

Breast-feeding
Breast-feeding is **not recommended** in women living with HIV because HIV infection can be passed on to the baby in breast milk.

It is not known whether the ingredients of Vocabria injection can pass into breast milk. However, it is possible that cabotegravir may still pass into breast milk for 12 months after the last injection of Vocabria.

If you're breast-feeding, or thinking about breast-feeding, you should **discuss it with your doctor as soon as possible**.

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.

3. How Vocabria injections are given

You will be given Vocabria **as an injection,** either once every month or once every 2 months, together with another injection of medicine called rilpivirine. Your doctor will advise you of your dosing schedule.

A nurse or doctor will give you Vocabria through an injection in the muscle of your buttock (*intramuscular, or IM, injection*).

When you first start treatment with Vocabria you and your doctor may decide to either start treatment with Vocabria tablets or start treatment directly with a Vocabria injection:
- If you decide to start treatment with tablets, your doctor will tell you:

- to take one 30 mg Vocabria tablet and one 25 mg rilpivirine tablet, once a day, for approximately **one month**
- after that receive **monthly or every 2 month injections**.

This first month of Vocabria and rilpivirine tablets is called the oral **lead-in period**. It allows your doctor to assess whether it's appropriate to proceed with injections.

Injection schedule for monthly dosing

	When	
Which medicine	**First injection**	**Second injection onwards, every month**
Vocabria	600 mg injection	400 mg injection every month
Rilpivirine	900 mg injection	600 mg injection every month

Injection Schedule for every 2 month dosing

Which medicine	**When**	
	First and second injections, one month apart	**Third injection onwards, every two months**
Vocabria	600 mg injection	600 mg injection every 2 months
Rilpivirine	900 mg injection	900 mg injection every 2 months

If you miss a Vocabria injection

➔ **Contact your doctor immediately** to make a new appointment

It is important that you keep your regular planned appointments to receive your injection to control your HIV and to stop your illness from getting worse. Talk to your doctor if you are thinking about stopping treatment.

Talk to your doctor if you think you will not be able to receive your Vocabria injection at the usual time. Your doctor may recommend you take Vocabria tablets or another HIV treatment instead, until you are able to receive Vocabria injection again.

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

Don't stop receiving Vocabria injections without advice from your doctor.
Keep receiving Vocabria injections for as long as your doctor recommends. Don't stop unless your doctor advises you to. If you stop, your doctor must start you on another HIV treatment within a month of your last Vocabria injection if you are having monthly injections, and within two months of your last Vocabria injection if you are having injections every two months, to reduce the risk of developing viral resistance.

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

4. Possible side effects

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

Stop using Vocabria and seek medical attention immediately if you notice any of the following symptoms:
- reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of the mouth, throat, nose, genitals, and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome, toxic epidermal necrolysis). These serious skin reactions are very rare (may affect **up to 1 in 10,000** people).

Allergic reactions

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

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

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

Very common side effects
These may affect **more than 1 in 10** people:
- headache
- injection site reactions. In clinical studies, these were generally mild to moderate and became less frequent over time. Symptoms may include:
    - very common: pain (which can rarely include temporary difficulty in walking) and discomfort, a hardened mass or lump
    - common: redness, itching, swelling, warmth, bruising, (which may include discolouration or a collection of blood under the skin)
    - uncommon: numbness, minor bleeding, an abscess (collection of pus) or cellulitis (heat, swelling or redness).
- feeling hot (*pyrexia*), which may occur within one week after injections.

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)*

- weight gain.

Uncommon side effects
These may affect **up to 1 in 100** people:
- suicide attempt and suicidal thoughts (particularly in patients who have had depression or mental health problems before)
- allergic reaction (*hypersensitivity*)
- hives (*urticaria*)
- swelling, sometimes of the face or mouth (*angioedema*), causing difficulty in breathing
- feeling drowsy *(somnolence)*
- feeling lightheaded, during or following an injection. This may lead to fainting
- 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)
- changes in liver blood tests (increase in *transaminases* or increase in *bilirubin*).

Other side effects that may show up in blood tests
- an increase in lipases (a substance produced by the pancreas)

Other possible side effects

People receiving Vocabria and rilpivirine therapy for HIV may get other side effects.

Pancreatitis

If you get severe pain in the abdomen (tummy), this may be caused by inflammation of your pancreas (pancreatitis).

➔ **Tell your doctor,** especially if the pain spreads and gets worse.

Symptoms of infection and inflammation

People with advanced HIV infection (AIDS) have weak immune systems and are more likely to develop serious infections *(opportunistic infections)*. When they start treatment, the immune system becomes stronger, so the body starts to fight infections.

Symptoms of infection and inflammation may develop, caused by either:
- old, hidden infections flaring up again as the body fights them
- the immune system attacking healthy body tissue (*autoimmune disorders*).

The symptoms of autoimmune disorders may develop many months after you start taking medicine to treat your HIV infection.

Symptoms may include:
- **muscle weakness** and/or **muscle pain**
- **joint pain** or **swelling**
- **weakness** beginning in the hands and feet and moving up towards the trunk of the body
- **palpitations** or **tremor**
- **hyperactivity** (excessive restlessness and movement).

If you get any symptoms of infection:

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

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Vocabria

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

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

This medicine does not require any special temperature storage conditions.

Do not freeze.

6. Contents of the pack and other information

What Vocabria contains
- The active substance is cabotegravir.

Each 3 ml vial contains 600 mg cabotegravir.

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

What Vocabria looks like and contents of the pack
Cabotegravir prolonged release suspension for injection is presented in a brown glass vial with a rubber stopper. The pack also contains 1 syringe, 1 vial adaptor, and 1 injection needle.

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

Other sources of information

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

The following information is intended for healthcare professionals only:

Vocabria 3 mL injection Instructions for use:

Overview

A complete dose requires two injections: **VOCABRIA and rilpivirine**

3 mL of cabotegravir and 3 mL of rilpivirine.

Cabotegravir and rilpivirine are suspensions that do not need further dilution or reconstitution. The preparation steps for both medicines are the same. Carefully follow these instructions when preparing the suspension for injection to avoid leakage.

Cabotegravir and rilpivirine are for intramuscular use only. Both injections must be administered to the gluteal sites.

Note: The ventrogluteal site is recommended. **The administration order is not important.**

Storage information

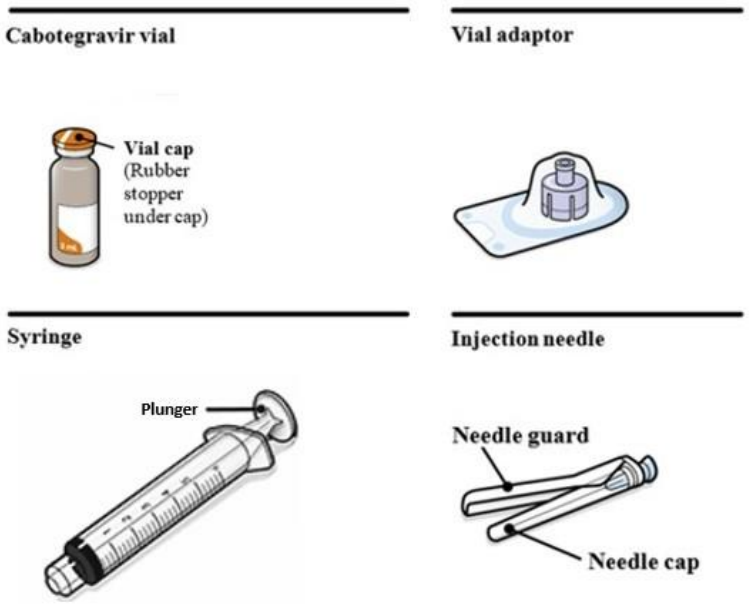
• This medicine does not require any special storage conditions.

Do not freeze.

Your pack contains

- 1 vial of cabotegravir
- 1 vial adaptor
- 1 syringe
- 1 injection needle (0.65 mm, 38 mm [23 gauge, 1.5 inches])

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



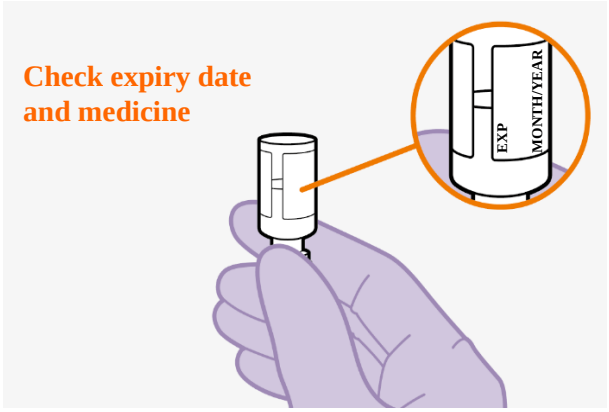
You will also need

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

Make sure to have the rilpivirine pack close by before starting.

Preparation

1. Inspect vial



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

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

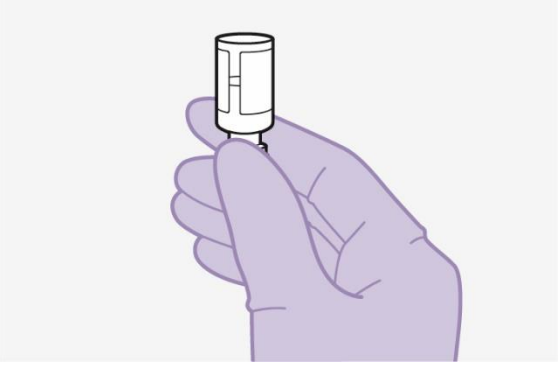
2. Wait 15 minutes

- If the pack has been stored in a fridge, remove and wait at least 15 minutes before you are ready to give the injection to allow the medicine to come to room temperature.

3. Shake vigorously

- Hold the vial firmly and vigorously shake for a full 10 seconds as shown.

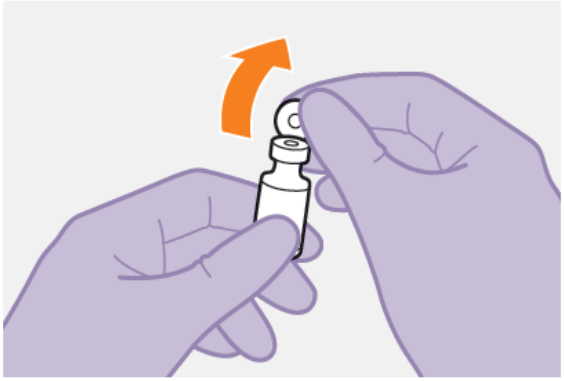
4. Inspect suspension



- Invert the vial and check the resuspension. It should look uniform. If the suspension is not uniform, shake the vial again.
- It is also normal to see small air bubbles.

Note: Vial preparation order is not important

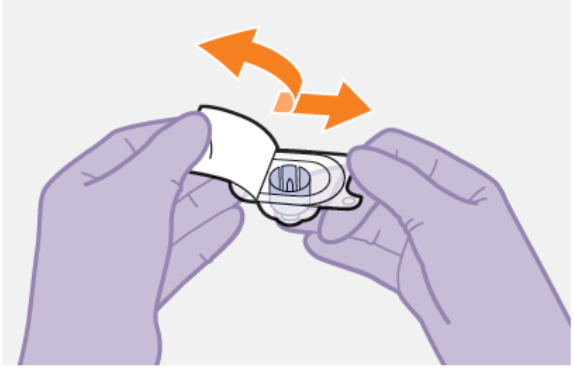
5. Remove vial cap



- Remove the cap from the vial.
- Wipe the rubber stopper with an alcohol swab.

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

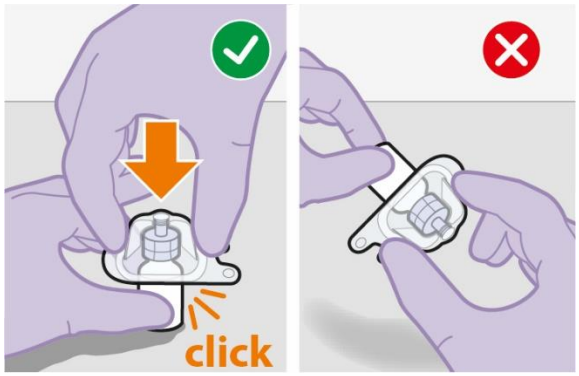
6. Peel open vial adaptor



- Peel off the paper backing from the vial adaptor packaging.

Note: Do not remove the adaptor from its packaging for the next step. The adapter **will not** fall out when its packaging is turned upside down.

7. Attach vial adaptor

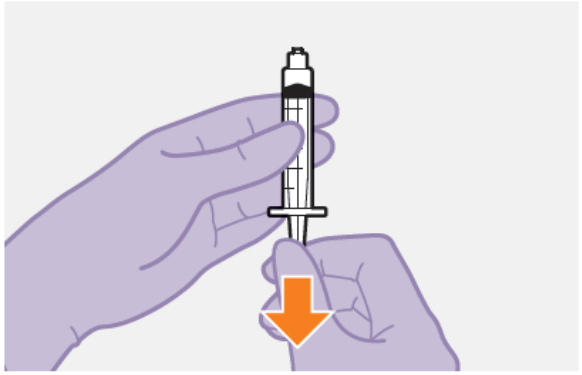


- Place the vial on a flat surface.
- Press the vial adaptor straight down onto the vial, as shown.
- The vial adaptor should click securely into place.

8. Lift off the packaging

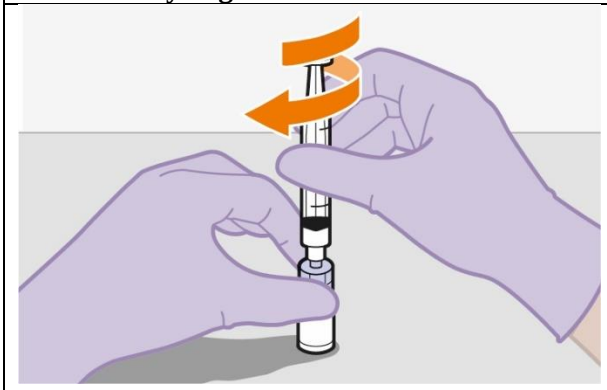
- Lift off the vial adaptor packaging, as shown.

9. Prepare syringe



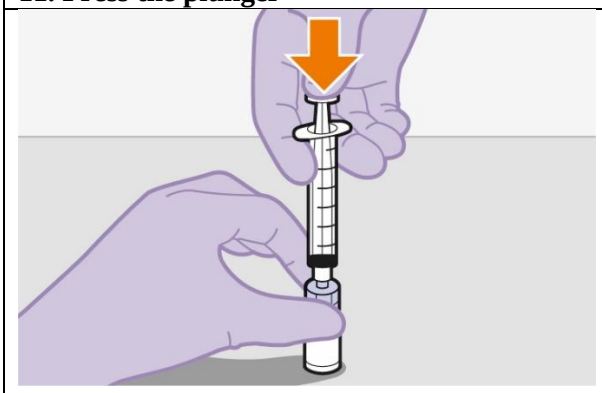
- Remove the syringe from its packaging.
- Draw 1 mL of air into the syringe. This will make it easier to draw up the liquid later.

10. Attach syringe



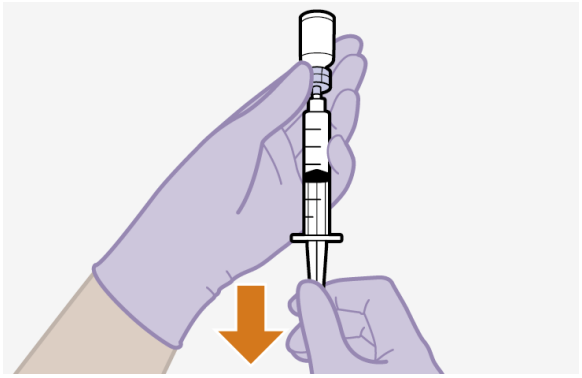
- Hold the vial adaptor and vial firmly, as shown.
- Screw the syringe firmly onto the vial adaptor.

11. Press the plunger



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

12. Slowly draw up dose



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

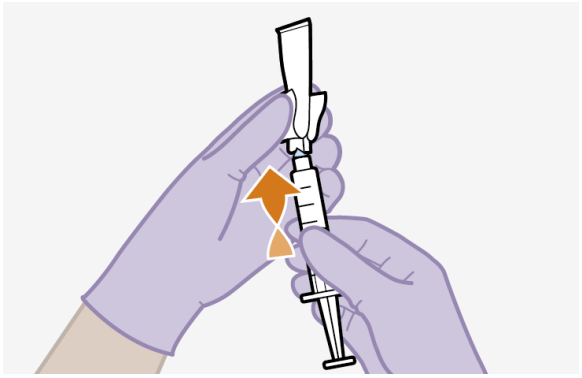
Note: Keep the syringe upright to avoid leakage.

13. Unscrew syringe

- Hold the syringe plunger firmly in place as shown to prevent leakage. It is normal to feel some back pressure.
- Screw the syringe off the vial adaptor, holding the vial adaptor as shown.

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

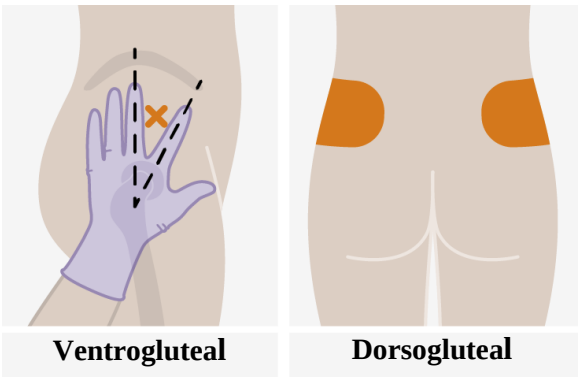
14. Attach needle



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

Injection

15. Prepare injection site



Ventrogluteal **Dorsogluteal**

Injections must be administered to the gluteal sites.

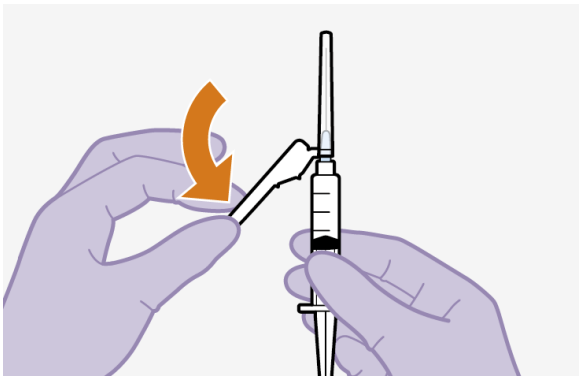
Select from the following areas for the injection:

• Ventrogluteal (recommended)

• Dorsogluteal (upper outer quadrant)

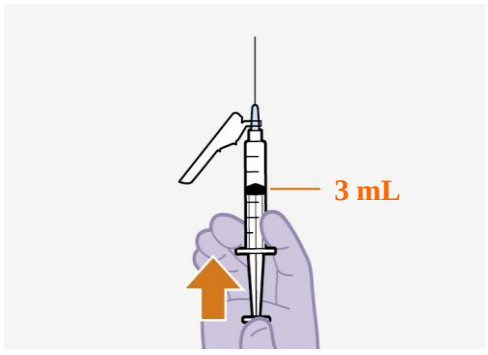
Note: For gluteal intramuscular use only. **Do not** inject intravenously.

16. Remove cap



- Fold the needle guard away from the needle.
- Pull off the injection needle cap.

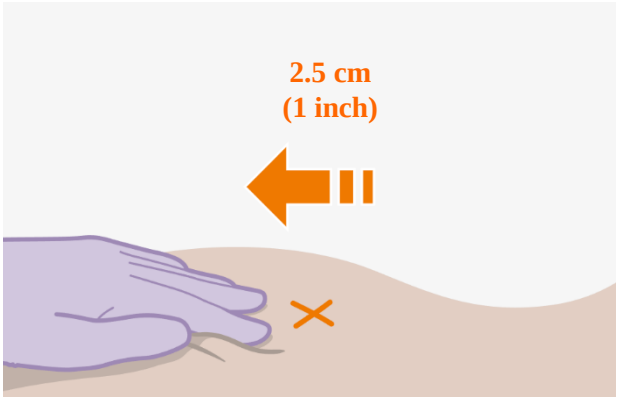
17. Remove extra liquid



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

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

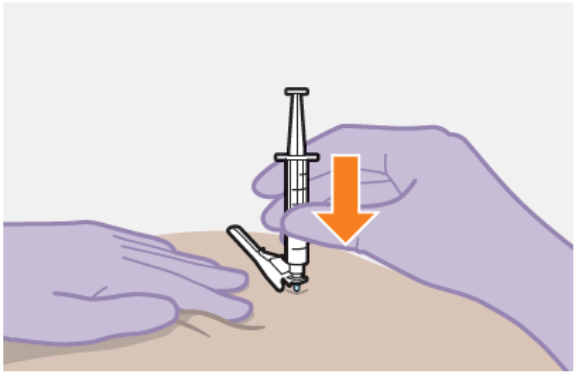
18. Stretch skin



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

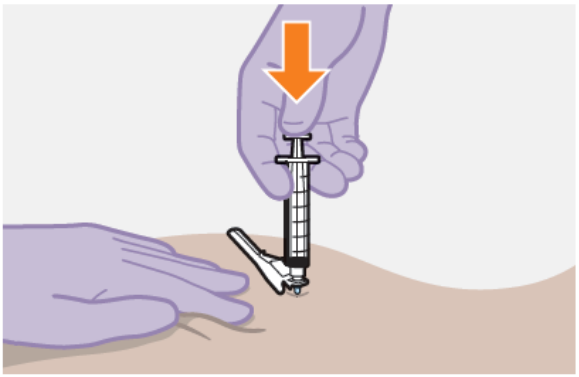
- Firmly drag the skin covering the injection site, displacing it by about 2.5 cm (1 inch).
- Keep it held in this position for the injection.

19. Insert needle



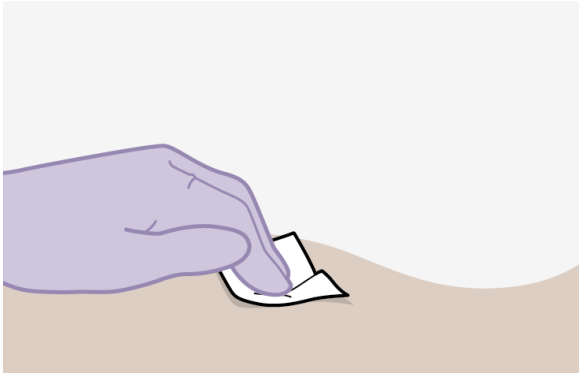
- Insert the needle to its full depth, or deep enough to reach the muscle.

20. Inject dose



- Still holding the skin stretched – slowly press the plunger all the way down.
- Ensure the syringe is empty.
- Withdraw the needle and release the stretched skin immediately.

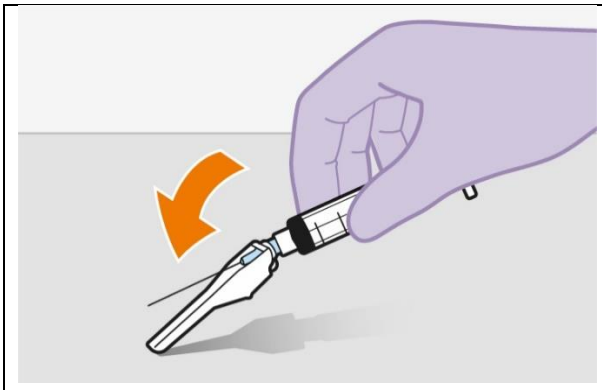
21. Assess the injection site

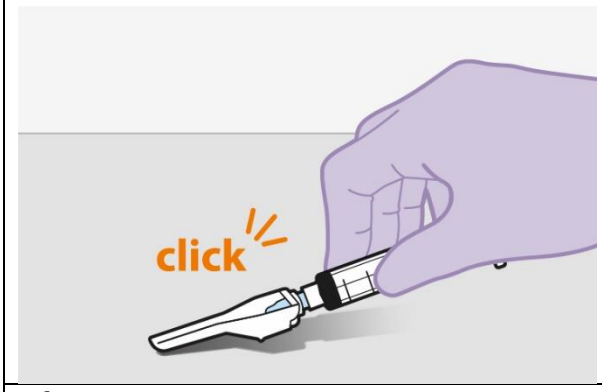


- Apply pressure to the injection site using a gauze.
- A small bandage may be used if a bleed occurs.

Do not massage the area.

22. Make needle safe

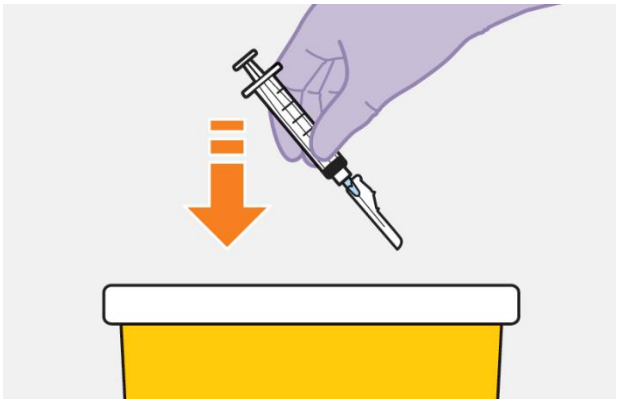




- Fold the needle guard over the needle.
- Gently apply pressure using a hard surface to lock the needle guard in place.
- The needle guard will make a click when it locks.

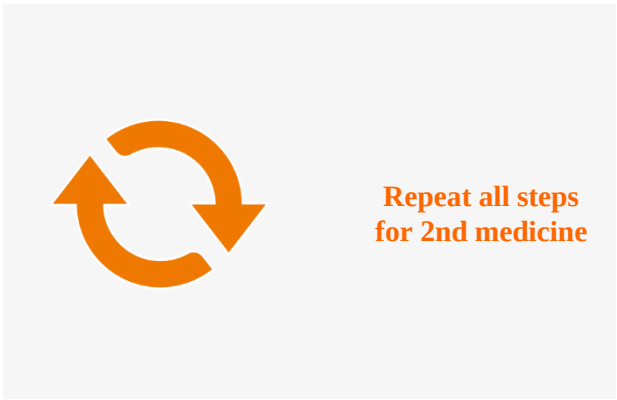
After injection

23. Dispose safely



- Dispose of used needles, syringes, vials and vial adaptors according to local health and safety laws.

Repeat for 2nd medicine



If you have not yet injected both medicines, use the steps for preparation and injection for rilpivirine which has its own specific Instructions for Use.

Questions and Answers

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

Once the suspension has been drawn into the syringe, the injection should be used immediately, from a microbiological point of view.

Chemical and physical in-use stability has been demonstrated for 2 hours at 25°C.

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

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

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

3. Does the order in which I give the medicines matter?

No, the order is unimportant.

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

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

Do not use any other heating methods.

5. Why is the ventrogluteal administration approach recommended?

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

Package leaflet: Information for the patient

Vocabria 30 mg film-coated tablets
cabotegravir

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

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

What is in this leaflet

1. What Vocabria is and what it is used for

Vocabria tablets contain the active ingredient cabotegravir. Cabotegravir belongs to a group of anti-retroviral medicines called *integrase inhibitors (INIs)*.

Vocabria tablets are used to treat HIV (human immunodeficiency virus) infection in adults and adolescents (at least 12 years of age and weighing at least 35 kg) who are also taking another antiretroviral medicine called rilpivirine and whose HIV-1 infection is under control.

Vocabria tablets do not cure HIV infection; they keep 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.

Your doctor will advise you to take Vocabria tablets before you are given a Vocabria injection for the first time.

If you are being given Vocabria injection, but you are not able to receive your injection, your doctor may also recommend that you take Vocabria tablets instead, until you can receive the injection again.

Vocabria tablets are always given in combination with another anti-retroviral medicine called *rilpivirine tablets* to treat HIV infection. Vocabria and rilpivirine tablets will replace your current antiretroviral medicines. Refer to the rilpivirine package leaflet for information on that medicine.

2. What you need to know before you take Vocabria

Do not take Vocabria tablets:

- if you have ever developed a severe skin rash, skin peeling, blistering and/or mouth sores.
- if you are **allergic** (*hypersensitive*) to cabotegravir or any of the other ingredients of this medicine (listed in section 6).
- if you are taking any of these medicines, as they may affect the way Vocabria works:

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

➔ If you think this applies to you, **tell your doctor**.

Warnings and precautions

Severe skin reaction:
The serious skin reactions, Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported very rarely in association with Vocabria. Stop taking Vocabria and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions.

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

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

➔ **Read the information** in section 4 of this leaflet.

Liver problems including hepatitis B and/or C
Tell your doctor if you have or have had problems with your liver, including hepatitis B and/or C. Your doctor may evaluate how severe your liver disease is before deciding if you can take Vocabria.

Look out for important symptoms
Some people taking medicines for HIV infection develop other conditions, which can be serious. You need to know about important signs and symptoms to look out for while you're taking Vocabria. These include:
- symptoms of infections
- symptoms of liver damage.

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

If you get any symptoms of infection or liver damage:

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

Children and adolescents
This medicine is not for use in children less than 12 years of age or adolescents weighing less than 35 kg because it has not been studied in these patients.

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

Vocabria must not be taken with some other medicines (see 'Do not take Vocabria tablets' earlier in section 2)**:**

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.

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

- **Medicines called antacids, to treat indigestion and heartburn.** Antacids can stop the medicine in Vocabria tablets from being absorbed into your body**.**
  Do not take these medicines in the 2 hours before you take Vocabria or for at least 4 hours after you take it.
- **rifabutin** (to treat some bacterial injections 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 breastfeeding

If you are pregnant or breastfeeding, think you may be pregnant**,** or are planning to have a baby:

➔ **Talk to your doctor** before taking Vocabria .

Pregnancy
- **Vocabria is not recommended during pregnancy.** If needed, your doctor will consider the benefit to you and the risk to your baby of taking Vocabria while you're pregnant. If you are planning to have a baby, **talk to your doctor in advance**
- If you have become pregnant do not stop taking Vocabria without consulting your doctor.

Breast-feeding
Breast-feeding is **not recommended** in women living with HIV because HIV infection can be passed on to the baby in breast milk.

It is not known whether the ingredients of Vocabria tablets can pass into breast milk.

If you're breast-feeding, or thinking about breast-feeding, you should **discuss it with your doctor as soon as possible**.

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.

Important information about some of the ingredients of Vocabria
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Vocabria

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

Vocabria tablets must always be taken with another HIV medicine (rilpivirine tablets). You should also follow the instructions for rilpivirine carefully. The leaflet is supplied in the rilpivirine carton.

Dosing schedule for Vocabria tablets followed by monthly injections

Which medicine	When		
	During month 1 (at least 28 days)	**At month 2 following one month of tablets**	**Month 3 onwards**
Vocabria	30 mg tablet once daily	600 mg injection	400 mg injection monthly
Rilpivirine	25 mg tablet once daily	900 mg injection	600 mg injection monthly

Dosing schedule for Vocabria tablets followed by every 2 month injections

Which medicine	**When**		
	Month 1 (at least 28 days)	**At Month 2 and Month 3 following one month of tablets**	**Month 5 onwards**
Vocabria	30 mg tablet once a day	600 mg injection	600 mg injection every 2 months
Rilpivirine	25 mg tablet once a day	900 mg injection	900 mg injection every 2 months

When you first start treatment with Vocabria, you and your doctor may decide to either start treatment with Vocabria tablets or start treatment directly with a Vocabria injection:
If you decide to start treatment with tablets, your doctor will tell you:

- to take one 30 mg Vocabria tablet and one 25 mg rilpivirine tablet, once a day, for approximately **one month.**
- after that, receive **monthly or every 2 month injections**.

The first month of Vocabria and rilpivirine tablets is called the oral **lead-in-period**. It allows your doctor to assess whether it's appropriate to proceed with injections.

How to take the tablets
Vocabria tablets should be swallowed with a small amount of water.

Vocabria can be taken with or without food. However, when Vocabria is taken at the same time as rilpivirine, both tablets should be taken with a meal.

If you cannot receive your Vocabria injection
If you are not able to receive your Vocabria injection, your doctor may recommend you take Vocabria tablets or another HIV treatment instead, until you can receive an injection again.

Antacid medicines
Antacids, to treat **indigestion** and **heartburn,** can stop Vocabria tablets being absorbed into your body and make it less effective.
Do not take an antacid during the 2 hours before you take a Vocabria tablet or for at least 4 hours after you take it. Talk to your doctor for further advice on taking acid-lowering (antacid) medicines with Vocabria tablets.

If you take more Vocabria than you should
If you take too many tablets of Vocabria, **contact your doctor or pharmacist for advice**. If possible, show them the Vocabria tablet bottle.

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

If you vomit less than 4 hours after taking Vocabria, take another tablet. If you vomit more than 4 hours after taking Vocabria you do not need to take another tablet until your next scheduled dose.

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

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

4. Possible side effects

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

Stop taking Vocabria and seek medical attention immediately if you notice any of the following symptoms:
- reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of the mouth, throat, nose, genitals, and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome, toxic epidermal necrolysis). These serious skin reactions are very rare (may affect **up to 1 in 10,000** people).

Allergic reactions
Vocabria contains cabotegravir, which is an integrase inhibitor. Integrase inhibitors including cabotegravir can cause a serious allergic reaction known as a hypersensitivity reaction.
If you get any of the following symptoms:
- skin reaction (*rash, hives*)
- a high temperature (*fever*)
- lack of energy (*fatigue*)
- swelling, sometimes of the face or mouth (*angioedema*), causing difficulty in breathing
- muscle or joint aches.

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

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)*
- weight gain.

Uncommon side effects
These may affect **up to 1 in 100** people:
- suicide attempt and suicidal thoughts (particularly in patients who have had depression or mental health problems before)
- allergic reaction (*hypersensitivity*)
- hives (*urticaria*)
- swelling, sometimes of the face or mouth (*angioedema*), causing difficulty in breathing
- 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)
- changes in liver blood tests (increase in *transaminases* or increase in *bilirubin*).

Other side effects that may show up in blood tests
- an increase in lipases (a substance produced by the pancreas)

Other possible side effects

People taking Vocabria and rilpivirine therapy for HIV may get other side effects.

Pancreatitis

If you get severe pain in the abdomen (tummy), this may be caused by inflammation of your pancreas (pancreatitis).

➔ **Tell your doctor,** especially if the pain spreads and gets worse.

Symptoms of infection and inflammation

People with advanced HIV infection (AIDS) have weak immune systems and are more likely to develop serious infections *(opportunistic infections)*. When they start treatment, the immune system becomes stronger, so the body starts to fight infections.

Symptoms of infection and inflammation may develop, caused by either:
- old, hidden infections flaring up again as the body fights them
- the immune system attacking healthy body tissue (*autoimmune disorders*).

The symptoms of autoimmune disorders may develop many months after you start taking medicine to treat your HIV infection.

Symptoms may include:
- **muscle weakness** and/or **muscle pain**
- **joint pain** or **swelling**
- **weakness** beginning in the hands and feet and moving up towards the trunk of the body
- **palpitations** or **tremor**
- **hyperactivity** (excessive restlessness and movement).

If you get any symptoms of infection and inflammation or if you notice any of the symptoms above:

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

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Vocabria

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

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

This medicine does not require any special temperature storage conditions.

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

6. Contents of the pack and other information

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

The other ingredients are:

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

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

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

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

Each bottle contains 30 film-coated tablets.

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Other sources of information

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