Summary Report of Benefit-Risk Assessment

VOCABRIA FILM-COATED TABLETS 30MG
VOCABRIA PROLONGED-RELEASE SUSPENSION FOR INJECTION 600 MG/3 ML AND 400 MG/2 ML

NEW DRUG APPLICATION

Active Ingredient(s)	Cabotegravir
Product Registrant	GlaxoSmithKline Pte Ltd
Product Registration Number	SIN16541P, SIN16542P, SIN16543P
Application Route	Abridged evaluation
Date of Approval	05 July 2022

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A INTRODUCTION

Vocabria Tablets are indicated in combination with rilpivirine tablets for short term treatment of human immunodeficiency virus (HIV)-1 infection in adults 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:

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

Vocabria Injection is indicated in combination with rilpivirine injection for treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class.

The active substance, cabotegravir, is an integrase strand transfer inhibitor. It 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.

Vocabria is available as film-coated tablets and a prolonged-release suspension for injection. The film-coated tablets contain 30 mg of cabotegravir as cabotegravir sodium. Other ingredients in the tablet core are lactose monohydrate, microcrystalline cellulose, hypromellose, sodium starch glycolate, and magnesium stearate. Ingredients in the film coating include hypromellose, titanium dioxide, and macrogol. The prolonged-release suspension for injection contains 600 mg/3 mL and 400 mg/2 mL of cabotegravir. Other ingredients in the solution are mannitol, polysorbate 20, macrogol and water for injections.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, cabotegravir sodium, is manufactured at Glaxo Wellcome Manufacturing Pte Ltd, Singapore. The drug product, Vocabria, is manufactured at Glaxo Operations UK Ltd, Hertfordshire, United Kingdom.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities were in accordance with ICH Q3A and Q3C. Potential and actual impurities are adequately controlled.

The drug substance specifications were established in accordance with ICH Q6A and the impurity limits have been appropriately qualified. The analytical methods used are adequately described and non-compendial methods are validated in accordance with ICH Q2, with information on the reference standards used for identity, assay and impurities testing presented.

The drug substance stability data presented was adequate to support the storage of drug substance at 30ºC with a re-test period of 60 months. The packaging consists of antistatic LDPE (low-density polyethylene) bags sealed with plastic ties. The bags were stored within a rigid plastic container.

Drug product:

The film coated tablet was manufactured using a wet granulation approach, followed by film-coating. The manufacturing process of the prolonged-release suspension for injection utilises terminal sterilisation. Both of these manufacturing processes are considered to be standard processes.

The manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6A and impurity limits were adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2, with information on the reference standards used for identity, assay and impurities testing presented.

For film-coated tablets, the stability data submitted was adequate to support the approved shelf-life of 48 months when stored at or below 30ºC. The container closure system is a high-density polyethylene (HDPE) bottle with child-resistant closures containing 30 film-coated tablets.

For prolonged-release suspension for injection, the stability data submitted was adequate to support the approved shelf-life of 36 months when stored at or below 30 ºC. The in-use period after first opening is less than 2 hours at 25ºC. The container closure system is type 1 glass vial with bromobutyl rubber stopper.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of cabotegravir in combination with rilpivirine as dual maintenance regimen administered every 4 weeks (Q4W) was based primarily on two pivotal Phase III switch studies (FLAIR [N=566] and ATLAS [N=616]) in HIV-1 infected patients. In addition, a Phase III study (ATLAS-2M [N=1045]) comparing the monthly regimen (Q4W) versus an alternative two-monthly regimen (Q8W) was provided to support the requested every two-month dosing as an alternative to the monthly dosing regimen.

The two pivotal trials, FLAIR and ATLAS, were broadly similar in design and objective, both assessing the rate of virological failure at Week 48 after switch from standard antiretroviral treatment (ART) regimen in virologically suppressed HIV-1 infected patients. Hence, the data from these two studies were pooled to provide additional evidence of efficacy in a larger pool comprising a total of 1182 patients. The longer-term 96 weeks data from the FLAIR and ATLAS studies were also provided as supportive evidence.

Overview of pivotal clinical studies

Study	Design	Treatment	Primary Endpoint
201584 (FLAIR)	Phase III, multicentre, open-label, randomised study to demonstrate non-inferior antiviral activity of switching to CAB + RPV compared with remaining on ABC/DTG/3TC in HIV-1 infected ART-naive adult subjects (N=566).	**Induction Phase (20 weeks):** Oral ABC/DTG/3TC fixed drug combination (NRTI substitution allowed) **Maintenance Phase (100 weeks):** CAB + RPV arm: Oral CAB 30 mg + RPV 25 mg once daily for 4-5 weeks, followed by IM CAB LA 600 mg + RPV LA 900 mg for the first IM dose and then CAB LA 400 mg + RPV LA 600 mg Q4W CAR arm: Oral ABC/DTG/3TC once daily (or alternative DTG + 2 NRTIs)	Virologic failure, i.e. plasma HIV-1 RNA ≥50 copies/mL at Week 48
201585 (ATLAS)	Phase III, multicentre, open-label, randomised study to demonstrate non-inferior antiviral activity of switching to CAB + RPV compared with remaining on current ART regimen in HIV-1 infected ART-experienced adult subjects who are virologically suppressed on a stable ART regimen for at least 6 months (N=616).	**Maintenance Phase (52 weeks):** CAB + RPV arm: Oral CAB 30 mg + RPV 25 mg once daily for 4-5 weeks, followed by IM CAB LA 600 mg + RPV LA 900 mg for the first IM dose and then CAB LA 400 mg + RPV LA 600 mg Q4W CAR arm: 2 NRTIs + INI or 2 NRTIs + PI or 2 NRTIs + NNRTI	Virologic failure, i.e. plasma HIV-1 RNA ≥50 copies/mL at Week 48
207966 (ATLAS-2M)	Phase IIIb, multicentre, open-label, randomised study to demonstrate non-inferiority of LA CAB + LA RPV Q8W compared with LA CAB + LA RPV Q4W in HIV-1 infected ART-experienced adult subjects who are virologically suppressed on a stable ART regimen (N=1045).	**Maintenance Phase (100 weeks):** Q4W arm: CAB LA 600 mg + RPV LA 900 mg initiation dose*, CAB LA 400 mg + RPV LA 600 mg Q4W Q8W arm: CAB LA 600 mg + RPV LA 900 mg initiation dose*, CAB LA 600 mg + RPV LA 900 mg second initiation dose, CAB LA 600 mg + RPV LA 900 mg Q8W * Note: Subjects were either transitioned from Study 201585 (ATLAS) (CAB + RPV Q4W or SOC) or from their current SOC. Those transitioning from SOC received oral CAB 30 mg + RPV 25 mg once daily for 4-5 weeks followed by appropriate initiation doses. Those transitioning from CAB + RPV Q4W received oral lead-in and initiation doses during their participation in Study ATLAS and started maintenance doses on Day 1 of Study ATLAS-2M according to their randomisation assignment.	Virologic failure, i.e. plasma HIV-1 RNA ≥50 copies/mL at Week 48

Study 201584 (FLAIR study)

FLAIR was a Phase III, multi-phase, randomised, open-label, active-controlled, multicentre, parallel-group, non-inferiority study in HIV-1 infected, ART-naïve adult subjects. Eligible subjects were enrolled into the Induction Phase of the study and initiated treatment with a dolutegravir containing regimen (either dolutegravir/abacavir/lamivudine [ABC/DTG/3TC] or

dolutegravir + 2 other non-abacavir nucleoside reverse transcriptase inhibitors [NRTIs] if subjects were HLA-B*5701 positive) for 20 weeks (Week -20 to Day 1).

Subjects with HIV 1 RNA <50 c/mL at the Week -4 Visit entered the Maintenance Phase where they were randomised 1:1 to receive either:

- oral current antiretroviral regimen (CAR) for at least 100 weeks, or
- oral cabotegravir (CAB) 30 mg + rilpivirine (RPV) 25 mg once daily for at least 4 weeks followed by intramuscular (IM) CAB + RPV (IM CAB 600 mg + RPV 900 mg at Week 4, IM CAB 400 mg + RPV 600 mg at Week 8, and every 4 weeks thereafter) for at least 96 weeks.

The oral formulations of CAB + RPV were administered daily for approximately one month as part of the oral lead-in phase, to ensure tolerance of the dual therapy before starting the monthly long-acting formulations. In addition, to address pre-planned missed IM CAB + RPV dosing visits, subjects could be administered daily oral CAB 30 mg + RPV 25 mg as a short-term bridging strategy.

Randomisation was stratified by subject's Induction Baseline (Week -20) HIV-1 RNA (<100,000, ≥100,000 c/mL) and sex at birth. The ART regimens used in the comparator arm are appropriate treatment options for HIV-1 infection and are currently approved locally for this use. The open-label design of the study is considered acceptable in view of the different dosage forms used in the study and the objective endpoints evaluated.

The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 c/mL (i.e., virologic failure) at Week 48 per FDA's Snapshot Algorithm. The primary objective was to demonstrate non-inferiority of CAB + RPV compared to CAR in terms of the primary endpoint at Week 48. Non-inferiority was concluded if the upper bound of the two-sided 95% confidence interval (CI) for the difference in the proportion of subjects with plasma HIV-1 RNA ≥50 c/mL between the two treatment arms was <6%. The primary efficacy analysis was performed in the Intent-to-Treat Exposed (ITT-E) population, which included all randomised subjects who received at least one dose of study drug. Sensitivity analysis was conducted on the Per-Protocol (PP) population, which included all subjects in the ITT-E population who did not have major protocol violations.

The secondary endpoints included the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48, the proportion of subjects with plasma HIV-1 RNA <200 c/mL at Week 48, and the proportion of subjects with confirmed virological failure (CVF) at Week 48. CVF was defined as two consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL.

Of the 629 subjects who were treated in the Induction Phase, 566 subjects completed the Induction Phase and were randomised 1:1 in the Maintenance Phase: 283 subjects in the CAB + RPV arm and 283 in the CAR arm. All 566 randomised subjects received study treatment and were included in the ITT-E population.

The median age was 34 years (range 18 to 68 years) and most of the subjects were male (78%). The majority were White (74%) and a small proportion were Asian (5%). Baseline characteristics (CD4 level, HIV subtype, CDC stage, HIV risk factor and medical conditions) were well balanced between both arms, except for hepatitis C positive status at Induction Baseline (6% in the CAB + RPV arm vs 3% in the CAR arm). Subjects with evidence of primary resistance to NNRTIs (except for K103N) or any known resistance to INIs were excluded from the study.

The primary efficacy analysis demonstrated that once monthly IM CAB + RPV was non-inferior to CAR in maintaining virologic suppression in HIV-1 infected subjects at Week 48. The upper bound of 95% CI for the adjusted treatment difference between CAB + RPV and CAR in terms of proportion of subjects with plasma HIV-1 RNA ≥50 c/mL was less than the pre-specified non-inferiority margin of 6%, in both the ITT-E and PP populations.

The results of the secondary endpoints generally supported the findings of the primary endpoint analysis. The proportion of subjects with CVF through Week 48 was low (1.4% in the CAB + RPV arm vs 1.1% in the CAR arm). The clinical efficacy was shown to be maintained through Week 96. Taken together, the efficacy results indicated that the once monthly IM CAB + RPV regimen is effective in maintaining virological suppression following switch from a standard ART regimen in HIV-1 infected adults.

Summary of Key Efficacy Results (FLAIR)

	Week 48		Week 96	
	CAB + RPV	**CAR**	**CAB + RPV**	**CAR**
Primary efficacy endpoint				
ITT-E population				
HIV-1 RNA ≥50 c/mL	6/283 (2.1%)	7/283 (2.5%)	9/283 (3.2%)	9/283 (3.2%)
Treatment difference (95% CI)[a]	-0.4 (-2.8, 2.1)		0.0 (-2.9, 2.9)	
PP population				
HIV-1 RNA ≥50 c/mL	6/278 (2.2%)	7/282 (2.5%)	9/278 (3.2%)	9/281 (3.2%)
Treatment difference (95% CI)[a]	-0.3 (-2.8, 2.2)		0.0 (-2.9, 2.9)	
Secondary efficacy endpoints (ITT-E population)				
HIV-1 RNA <50 c/mL	265/283 (93.6%)	264/283 (93.3%)	245/283 (86.6%)	253/283 (89.4%)
Treatment difference (95% CI)[a]	0.4 (-3.7, 4.5)		-2.8 (-8.2, 2.5)	
HIV-1 RNA <200 c/mL	266/283 (94.0%)	266/283 (94.0%)	248/283 (87.6%)	255/283 (90.1%)
CVF	4 (1.4%)	3 (1.1%)	4 (1.4%)	4 (1.4%)

[a] Based on CMH stratified analysis adjusting for the following baseline stratification factors: sex at birth (male, female) and Induction Baseline (Week -20) HIV-1 RNA (<100,000, ≥100,000 c/mL).

Study 201585 (ATLAS study)

ATLAS was a Phase III, multi-phase, randomised, open label, active-controlled, multicentre, parallel-group, non-inferiority study in HIV-1 infected, virologically suppressed, adult subjects on a stable ART regimen containing 2 NRTIs plus an INI, NNRTI or a protease inhibitor (PI) for at least 6 months. Subjects were randomised 1:1 to either continue oral CAR or switch to oral CAB 30 mg + RPV 25 mg once daily for at least 4 weeks followed by IM CAB + RPV every 4 weeks thereafter, through 52 weeks. Randomisation was stratified by baseline third agent class (PI, INI, or NNRTI) and sex at birth. Subjects who successfully completed the Week 52 visit could either continue to the Extension Phase or transit to Study 207966 (ATLAS-2M). In the Extension Phase, subjects in the CAR group switched to CAB + RPV treatment, while those in the CAB + RPV group continued their treatment for up to 96 weeks.

The study endpoints and statistical methods employed in the ATLAS study were similar to that of the FLAIR study.

A total of 618 subjects were randomised to receive either CAB + RPV or CAR. Two subjects randomised to the CAB + RPV group did not receive study treatment. Hence, the ITT-E population comprised 616 subjects: 308 in the CAB + RPV group and 308 in the CAR group.

The demographic and baseline characteristics were generally similar between the treatment groups, except for the proportion of subjects aged ≥50 years (21% in the CAB + RPV group vs 31% in the CAR group). The median age was 42 years (range 18 to 82 years) and most of the subjects were male (67%). The majority of subjects were White (68%) and a small proportion were Asian (6%). Subjects with evidence of primary resistance to NNRTIs (except for K103N) or any known resistance to INIs were excluded from the study.

The primary efficacy analysis demonstrated that once monthly CAB + RPV was non-inferior to CAR in maintaining virologic suppression in HIV-1 infected subjects at Week 48. The upper bound of 95% CI for the adjusted treatment difference between CAB + RPV and CAR in terms of proportion of subjects with plasma HIV-1 RNA ≥50 c/mL was less than the pre-specified non-inferiority margin of 6%, in both the ITT-E and PP populations.

The secondary endpoint results provided further supportive evidence of efficacy. CVF rates at Week 48 were comparable between the two treatment arms (1.0% in the CAB + RPV arm vs 1.3% in the CAR arm). The clinical efficacy was shown to be maintained through Week 96. At Week 96, all subjects (23/23, 100%) in the CAB + RPV group had viral load <50 c/mL and 28/29 (97%) subjects in the Extension Switch to CAB + RPV group had viral load <50 c/mL. No additional subjects had CVF during the Extension Phase between Week 48 and Week 96 endpoints in either treatment group.

Taken together, the efficacy results demonstrated that the once monthly IM CAB + RPV regimen is effective in maintaining virological suppression following switch from a standard ART regimen in HIV-1 infected adults.

Summary of Key Efficacy Results (ATLAS)

	CAB + RPV	CAR
Primary efficacy endpoint		
ITT-E population		
HIV-1 RNA ≥50 c/mL at Week 48	5/308 (1.6%)	3/308 (1.0%)
Treatment difference (95% CI)[a]	0.6 (-1.2, 2.5)	
PP population		
HIV-1 RNA ≥50 c/mL at Week 48	4/294 (1.4%)	3/292 (1.0%)
Treatment difference (95% CI)[a]	0.3 (-1.4, 2.1)	
Secondary efficacy endpoints (ITT-E population)		
HIV-1 RNA <50 c/mL at Week 48	285/308 (92.5%)	294/308 (95.5%)
Treatment difference (95% CI)[a]	-3.0 (-6.7, 0.7)	
HIV-1 RNA <200 c/mL at Week 48	286/308 (92.9%)	295/308 (95.8%)
CVF at Week 48	3/308 (1.0%)	4/308 (1.3%)

[a] Based on CMH stratified analysis adjusting for the following baseline stratification factors: sex at birth (male, female) and Baseline third agent class (PI, NNRTI, INI).

Pooled analysis

In addition to the results from the two pivotal studies, FLAIR and ATLAS, the applicant has submitted data from a pooled analysis of these two studies. The pooling of the studies is considered acceptable, considering the similarity in the patient population and design of these studies.

As FLAIR and ATLAS were not sufficiently powered individually to rule out a 4% excess in virologic failure, a 6% non-inferiority margin was chosen in each study while a more stringent

4% margin was applied for the pooled analysis. A non-inferiority margin of 4% for virologic failure is appropriate and is the recommended margin for switch trials in regulatory guidelines.

The pooled efficacy analysis demonstrated that monthly dosing of CAB + RPV was non-inferior to CAR in terms of the proportion of subjects with plasma HIV-1 RNA ≥50 c/mL at Week 48 in both the ITT-E and PP populations. The adjusted treatment difference between CAB + RPV and CAR met the non-inferiority criterion, i.e. the upper bound of the 95% CI was below 4%.

Overall, the pooled analysis confirmed the non-inferiority of once-monthly CAB + RPV vs the continuation of an effective ART regimen, considering a 4% non-inferiority margin.

Summary of Key Efficacy Results (Pooled Studies)

	CAB + RPV	CAR
ITT-E population		
HIV-1 RNA ≥50 c/mL at Week 48	11/591 (1.9%)	10/591 (1.7%)
Treatment difference (95% CI)[a]	0.2 (-1.4, 1.7)	
PP population		
HIV-1 RNA ≥50 c/mL at Week 48	10/572 (1.7%)	10/574 (1.7%)
Treatment difference (95% CI)[a]	0.0 (-1.5, 1.5)	

[a] Based on CMH stratified analysis adjusting to 10 strata formed by the combination of randomisation stratification factors within each study.

Study 207966 (ATLAS-2M)

ATLAS-2M was a Phase IIIb, multicentre, randomised, open-label, parallel-group, non-inferiority study comparing the antiviral activity of IM CAB 600 mg and RPV 900 mg administered every 8 weeks (Q8W) compared with IM CAB 400 mg and RPV 600 mg administered every 4 weeks (Q4W) for 48 weeks in HIV-1 infected, virologically-suppressed adult subjects. The majority of subjects were enrolled from the ongoing ATLAS study, with additional subjects on standard of care (SOC). Subjects were randomised 1:1 in the Maintenance Phase to receive IM CAB + RPV administered either Q8W or Q4W for at least 100 weeks. Randomisation was stratified by prior CAB + RPV exposure (0 weeks, 1-24 weeks, >24 weeks).

Two groups of subjects were randomised:

- Group 1: Subjects randomised from current ART SOC therapy, including those enrolled to the CAR arm of Study ATLAS (following completion of the Week 52 visit at minimum), received oral therapy with CAB 30 mg + RPV 25 mg once daily at Baseline for 28 days followed by IM CAB + RPV Q8W or IM CAB + RPV Q4W thereafter.
- Group 2: Subjects entering Study ATLAS-2M from Study ATLAS and currently receiving IM CAB + RPV Q4W were randomised to either continue IM CAB + RPV Q4W or transition to IM CAB + RPV Q8W.

The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 c/mL at Week 48. Non-inferiority was concluded if the upper bound of the two-sided 95% CI for the difference between the two treatment arms is less than 4%. Key secondary endpoints included the proportion of subjects with CVF at Week 48 and proportion of subjects with HIV-1 RNA ≥50 c/mL at Week 48.

A total of 1049 subjects were randomised into the Maintenance Phase (Q8W: 524 subjects; Q4W: 525 subjects). There were 4 subjects (2 in each arm) randomised who did not receive

any study treatment. Hence, the ITT-E population comprised a total of 1045 subjects: 522 subjects in the Q8W arm and 523 in the Q4W arm. The demographics and baseline characteristics were comparable between both arms. The median age was 42.0 years (range 19 to 83 years). The majority of subjects were White (73%) with a small proportion of Asians (5%). Most subjects (≥98%) had viral load <50 c/mL at baseline.

The primary efficacy endpoint was met as the upper bound of the 95% CI for the adjusted treatment difference between Q8W and Q4W was 2.2%, which was less than the pre-defined non-inferiority margin of 4%. While numerically higher virological failure was observed with Q8W compared to Q4W (1.7% vs 1.0%, respectively), the incidence was low and not significantly different between arms. Results for the PP population were similar to those for the ITT-E population.

CVF up to Week 48 was low with 10 subjects meeting CVF criteria: 8 subjects (1.5%) in the Q8W arm and 2 subjects (0.4%) in the Q4W arm. The NNRTI and INI resistance-associated mutations were present at baseline for respectively 6 and 5 subjects in the Q8W group and 1 and 0 subject in the Q4W group, which could be a contributing factor of the higher number of CVF subjects observed in the Q8W group.

Summary of key efficacy results (ATLAS-2M)

	Q8W (N=522)	**Q4W (N=523)**
Primary efficacy endpoint		
ITT-E population		
HIV-1 RNA ≥ 50c/ml at Week 48	9/522 (1.7%)	5/523 (1.0%)
Treatment difference (95% CI)[a]	0.8 (-0.6, 2.2)	
PP population		
HIV-1 RNA ≥ 50c/ml at Week 48	7/516 (1.4%)	5/514 (1.0%)
Treatment difference (95% CI)[a]	0.4 (-0.9, 1.7)	
Secondary efficacy endpoints (ITT-E population)		
HIV-1 RNA <50 c/mL at Week 48	492 (94.3%)	489 (93.5%)
Treatment difference (95% CI)[a]	0.8 (-2.1, 3.7)	
CVF at Week 48	8 (1.5%)	2 (0.4%)

[a] Based on CMH stratified analysis adjusting for the following baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1-24 weeks, >24 weeks).

A post-hoc multivariate analysis of pooled Phase III studies (FLAIR, ATLAS and ATLAS-2M) was conducted, including data from 1039 HIV-1 infected adults with no prior exposure to CAB + RPV, to assess the influence of baseline subject characteristics, dosing regimen and post-baseline plasma drug concentrations on CVF using regression modelling with a variable selection procedure. Through Week 48 in these studies, 13/1039 (1.25%) subjects had CVF while receiving CAB + RPV. Based on the multivariate analysis, a combination of at least two of the following baseline factors were found to be associated with an increased risk of CVF: rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI ≥30 kg/m^2. This information has been reflected in the package insert.

Overall, the pivotal studies FLAIR and ATLAS have adequately demonstrated that the Q4W dosing of CAB + RPV (i.e., oral doses for approximately 1 month followed by monthly IM administrations) is non-inferior to standard ART (2 NRTI + 1 PI/NNRTI or INI) in virologically-suppressed HIV-1 infected subjects. Few cases of virological failure were observed in both treatment arms in these studies. The ATLAS-2M study further showed that the Q8W dosing of CAB + RPV was non-inferior to the Q4W regimen, supporting the use of the Q8W dosing as an alternative regimen.

As subjects with evidence of primary resistance to NNRTIs (except for K103N) or any known resistance to INIs were excluded from the pivotal studies, the indication was restricted to patients on a stable ART regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class.

Overall summary of efficacy across studies (snapshot outcomes at Week 48; ITT-E population)

Outcome	FLAIR		ATLAS		FLAIR and ATLAS Pooled		ATLAS-2M	
	CAB + RPV Q4W (N=283)	CAR (N=283)	CAB + RPV Q4W (N=308)	CAR (N=308)	CAB + RPV Q4W (N=591)	CAR (N=591)	CAB + RPV Q8W (N=522)	CAB + RPV Q4W (N=523)
HIV-1 RNA <50 c/mL	265 (93.6%)	264 (93.3%)	285 (92.5%)	294 (95.5%)	550 (93.1%)	558 (94.4%)	492 (94.3%)	489 (93.5%)
HIV-1 RNA ≥50 c/mL	6 (2.1%)	7 (2.5%)	5 (1.6%)	3 (1.0%)	11 (1.9%)	10 (1.7%)	9 (1.7%)	5 (1.0%)
No virologic data	12 (4.2%)	12 (4.2%)	18 (5.8%)	11 (3.6%)	30 (5.1%)	23 (3.9%)	21 (4.0%)	29 (5.5%)
Discontinued study due to AE or death	8 (2.8%)	2 (0.7%)	11 (3.6%)	5 (1.6%)	19 (3.2%)	7 (1.2%)	9 (1.7%)	13 (2.5%)
Discontinued study for other reasons	4 (1.4%)	10 (3.5%)	7 (2.3%)	6 (1.9%)	11 (1.9%)	16 (2.7%)	12 (2.3%)	16 (3.1%)
On study but missing data in window	0	0	0	0	0	0	0	0

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of cabotegravir in combination with rilpivirine was based primarily on Week 48 data from the pooled Phase III studies, FLAIR and ATLAS, comprising a total of 1182 patients. Longer-term safety data up to Week 96 was also provided for the individual FLAIR and ATLAS studies. In addition, safety analysis from the Phase III ATLAS-2M study provided a comparison of the safety profile of the Q8W regimen with that of the Q4W regimen of cabotegravir in combination with rilpivirine in 1045 treated patients.

In the pooled analysis of FLAIR and ATLAS, the median duration of treatment exposure was 382 days in the CAB + RPV arm and 366 days in the CAR arm. In ATLAS-2M, the median duration of treatment exposure was 447 days in the CAB + RPV Q8W group and 445 days in the CAB + RPV Q4W group.

Overview of adverse event (AE) profile

AE	FLAIR		ATLAS		Pooled*		ATLAS-2M	
	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV Q4W (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV Q4W (N=591) n (%)	CAR (N=591) n (%)	CAB + RPV Q8W (N=522) n (%)	CAB + RPV Q4W (N=523) n (%)
Any AE	267 (94)	225 (80)	294 (95)	220 (71)	561 (95)	445 (75)	473 (91)	482 (92)
Treatment-related AE	236 (83)	28 (10)	255 (83)	8 (3)	491 (83)	36 (6)	400 (77)	399 (76)
Grade ≥3 AE	31 (11)	11 (4)	35 (11)	24 (8)	66 (11)	35 (6)	41 (8)	49 (9)
Treatment-related Grade ≥3 AE	14 (5)	0	14 (5)	1 (<1)	28 (5)	1 (<1)	16 (3)	26 (5)
Serious AE (SAE)	18 (6)	12 (4)	13 (4)	14 (5)	31 (5)	26 (4)	27 (5)	19 (4)
Treatment-related SAE	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)	3 (<1)	1 (<1)
Discontinuations due to AE	9 (3)	4 (1)	13 (4)	5 (2)	22 (4)	9 (2)	12 (2)	13 (2)

Deaths due to AE	0	0	0	1 (<1)	0	1 (<1)	1 (<1)	-
Treatment-related deaths due to AE	0	0	0	0	0	0	0	0

* Pooled studies of ATLAS and FLAIR

In the pooled data of studies FLAIR and ATLAS, more subjects reported AEs in the CAB + RPV arm compared to the CAR arm (95% vs 75%). The most commonly reported AEs were injection site pain (77% vs 0%), nasopharyngitis (18% vs 15%), injection site nodule (14% vs 0%), injection site induration (12% vs 0%), upper respiratory tract infection (12% vs 9%), headache (12% vs 6%), diarrhoea (9% vs 7%), injection site swelling (8% vs 0%), influenza (7% vs 6%), back pain (7% vs 4%), and pyrexia (7% vs 2%). It is not unexpected that injection site reactions were reported only in the CAB + RPV arm and not in the oral CAR arm.

Treatment-related AEs were reported in 83% of subjects in the CAB + RPV arm vs 6% in the CAR arm, the majority of which were injection site reactions (ISRs) in the CAB + RPV arm. The most common non-ISR treatment-related AEs were headache (4% vs <1%), pyrexia (4% vs 0%), nausea (3% vs 1%), fatigue (3% vs <1%), asthenia (2% vs 0%), and body temperature increased (2% vs 0%).

The majority of subjects in FLAIR and ATLAS had an AE with a maximum intensity of Grade 1 or 2 in both treatment groups. The proportion of subjects who reported Grade ≥3 AEs was slightly higher for CAB + RPV compared with CAR (11% vs 6%). The difference between treatment groups may be partially attributable to the higher incidence of Grade ≥3 injection site reactions in the CAB + RPV group compared to the CAR group (3.7% vs 0%). The incidence of SAEs was low and similar between the CAB + RPV and CAR groups (5% vs 4%). The most frequently reported SAEs were hepatitis A (4 subjects in the CAB + RPV arm vs 2 subjects in the CAR arm), colitis (1 vs 2 subjects), anal abscess (0 vs 2 subjects), and anogenital warts (1 vs 2 subjects). The incidence of AEs leading to treatment discontinuation were low in both treatment groups (4% vs 2%). AEs leading to treatment discontinuation reported in more than 1 subject were hepatitis A (4 vs 0 subjects), acute hepatitis B (3 vs 0 subjects), headache (2 vs 0 subjects), and diarrhoea (2 vs 0 subjects). One subject in the CAR group died due to a methamphetamine overdose that was not considered related to study drug.

In ATLAS-2M, AEs were reported at a similar incidence between the CAB + RPV Q8W and Q4W groups (91% vs 92%). The incidences of individual AEs were also comparable between the Q8W and Q4W groups, with the exception of injection site nodule reported at a lower incidence in the Q8W vs Q4W group (10% vs 17%). However, this may be attributed to the lower frequency of IM injections in the Q8W arm. The incidences of treatment-related AEs (77% vs 76%), Grade ≥3 AEs (8% vs 9%), treatment-related Grade ≥3 AEs (3% vs 5%), SAEs (5% vs 4%), treatment-related SAEs (<1% vs <1%), and AEs leading to treatment discontinuation (2% vs 2%) were also generally comparable between the Q8W and Q4W groups. One subject in the Q8W group died due to sepsis, a complication of acute pancreatitis, which was considered related to study drug by the investigator.

The AEs of special interest were mainly ISRs, hepatotoxicity, and neuropsychiatric AEs. These AEs have been adequately described in the package insert.

ISRs are expected AEs with CAB and RPV administered by IM injection. In the pooled FLAIR and ATLAS studies, ISR events in the CAB + RPV group comprised mainly injection site pain (77%), nodule (14%), induration (12%), swelling (8%), erythema (4%), and pruritus (4%). Most ISRs were mild to moderate (Grade 1 or 2) in intensity, with 4% of subjects reporting Grade 3 events and none Grade 4 or 5. The proportion of subjects who withdrew due to ISRs were low

(1%). Most ISRs (94%) resolved within 14 days with a median duration of 3 days, and 5% lasted more than 14 days. In ATLAS-2M, the overall incidence of ISRs was generally comparable between the Q8W and Q4W groups (76% vs 75%).

Hepatotoxicity has been observed with the INI class of drugs, including cabotegravir. Elevated transaminases have been reported with CAB + RPV in the clinical studies. These elevations were primarily attributed to occurrence of acute viral hepatitis. Six cases of possible/probable drug-induced liver injury (DILI) had been identified in subjects receiving oral cabotegravir with or without rilpivirine across the Vocabria clinical studies (5 in the Phase I/II studies and 1 in ATLAS-2M). Aminotransaminase elevations in these subjects were transient and reversible on discontinuation. Hepatotoxicity is an important identified risk for cabotegravir and will continue to be monitored and evaluated post-marketing. The package insert has included adequate warnings on hepatotoxicity, including recommendations for monitoring of liver chemistries and treatment discontinuation if hepatotoxicity is suspected.

Suicidal behaviour notably in patients with pre-existing history of mental illness together with depression are known AEs of INIs. In the pooled FLAIR and ATLAS studies, neuropsychiatric AEs reported included sleep disorders (6% in the CAB + RPV arm vs 4% in the CAR arm), anxiety (5% vs 3%), depression (3% vs 2%), and suicidal ideation and behaviour (<1% vs <1%). Most of the sleep disorder AEs were insomnia, reported in 4% of subjects in the CAB + RPV group and 1% in the CAR group. There were no serious neuropsychiatric events with CAB + RPV Q4W with 2 withdrawals (1 subject for depression suicidal and 1 subject for anxiety). In ATLAS-2M, neuropsychiatric AEs of depression, anxiety, and sleep disorders were reported in 2% to 7% of subjects in either treatment group, with few events leading to withdrawal. These AEs have been adequately reflected in the package insert.

The safety data across the clinical studies support a favourable safety profile of CAB + RPV, for both the monthly dosing and the every 2 months regimen. The overall safety profile for CAB + RPV administered every 2 months was similar to the safety profile for CAB + RPV administered every month for both ISRs and systemic AEs. Overall, the safety profile for CAB + RPV in the target HIV-1 population was considered acceptable and manageable.

E ASSESSMENT OF BENEFIT-RISK PROFILE

The current standard of care for the treatment of HIV-1 infection uses a combination of ARTs to delay disease progression and prolong survival by achieving maximal and durable suppression of HIV-1 replication. Combined ART, mostly consisting of triple therapy with one main agent (boosted PI, INI or NNRTI) and a backbone regimen (with two NRTIs), are able to achieve high level of viral suppression in HIV infected patients. Simplification of regimen in virologically suppressed patients who have undergone standard multitherapy is a valuable approach to reduce the treatment burden in the long-term management of this chronic disease to sustain viral suppression. There are currently no approved two-drug long-acting injectable regimens for the treatment of HIV-1 infection. The IM administration of a two-drug combination therapy with cabotegravir and rilpivirine, incorporating less frequent dosing (with options for monthly or two-monthly injections), could present a convenient treatment option for patients.

In the pivotal studies FLAIR and ATLAS, the simplified dual regimen consisting of cabotegravir and rilpivirine administered Q4W was shown to be non-inferior to standard of care ART regimen in HIV-1 infected virologically suppressed patients. The upper bound of the two-sided 95% CI for the difference in the proportion of subjects with virologic failure (i.e., HIV-1 RNA

≥50 c/mL) at Week 48 between the two treatment arms was <6% in both studies, with consistency between the ITT-E and PP populations. This was further supported by the pooled analysis of the FLAIR and ATLAS studies, which met the tighter non-inferiority margin of 4% with comparable rates of virologic failure (1.9% vs 1.7%; treatment difference 0.2%; 95% CI: -1.4, 1.7). Maintenance of efficacy was also demonstrated through 96 weeks in the studies.

The ATLAS-2M study showed that the Q8W regimen of CAB + RPV was non-inferior to the Q4W regimen in terms of the proportion of subjects with plasma HIV-1 RNA ≥50 c/mL at Week 48 (1.7% vs 1.0%; treatment difference 0.8%; 95% CI: -0.6, 2.2). The rate of virologic failure was observed to be numerically higher with the Q8W regimen compared to Q4W regimen, although the difference was not statistically significant. For patients who could have a higher risk of virologic failure, consideration could be given to starting with the Q4W regimen to minimise the risk. Based on multivariate analyses, risk factors for virologic failure have been identified, i.e., at least two of the following baseline factors: rilpivirine resistance mutations identified by proviral resistance testing, HIV-1 subtype A6/A1, or BMI ≥30 mg/m^2. This information has been included in the package insert to highlight to clinicians.

The safety of cabotegravir is characterised mainly by injection site reactions. ISRs were mostly mild to moderate and self-limiting with few discontinuations (1% of subjects). Other safety risks noted with cabotegravir include hepatotoxicity and psychiatric events (including suicidal ideation), in common with other drugs of the INI class. These risks have been appropriately addressed in the package insert through the provision of relevant warnings and precautions.

On balance, the dual maintenance regimen with cabotegravir and rilpivirine have been shown to be able to keep HIV-1 viral load suppressed in the majority of patients with low rates of virologic failure, with an acceptable safety profile that is consistent with drugs of the same class. Hence, the overall benefit-risk profile of cabotegravir in combination with rilpivirine for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen with no evidence of viral resistance and no prior virological failure with agents of the NNRTI and INI class was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefits have been demonstrated to outweigh the risks for Vocabria in combination with rilpivirine for the treatment of HIV-1 infection in adults who are virologically suppressed on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class, and approval of the product registration was granted on 05 July 2022.

APPROVED PACKAGE INSERT AT REGISTRATION

VOCABRIA

Cabotegravir

QUALITATIVE AND QUANTITATIVE COMPOSITION

Film-coated Tablet
White, film-coated, oval tablet; SV CTV on one face.
Each film-coated tablet contains 30 mg of cabotegravir (as cabotegravir sodium).

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

CLINICAL INFORMATION

Indications

Film-coated Tablets:

VOCABRIA tablets are indicated in combination with rilpivirine tablets for short term (*see Dosage and Administration)* treatment of human immunodeficiency virus (HIV)-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class:

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

Suspension for Injection:

VOCABRIA injection is indicated in combination with rilpivirine injection for treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class (*see Clinical studies*).

Dosage and Administration

Pharmaceutical Form

Film-coated tablet and suspension for injection

Posology

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

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

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

Method of Administration

Film-coated Tablet

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

Suspension for Injection

Refer to the Instructions for Use for detailed step by step injection procedure (*see Instructions for Use & Handling*).

VOCABRIA injection should be administered by a healthcare professional.

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

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

Adults

Oral lead-in (Film-coated Tablets)

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

Monthly Dosing (Suspension for Injection)

Initiation Injection

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

Continuation Injection

After the initiation injection, the recommended *VOCABRIA* continuation injection dose in adults is a single 2 mL (400 mg) intramuscular injection, administered monthly. Patients

may be given injections up to 7 days before or after the date of the monthly 2 mL dosing schedule.

Table 1 Recommended Oral Lead-in and Monthly Intramuscular Dosing Schedule in Adults

	ORAL LEAD-IN		INITIATION INJECTION		CONTINUATION INJECTION
Drug	**For 1 Month (at least 28 days)**		**At Month 2**		**Month 3 onwards**
VOCABRIA	30 mg once daily		3 mL (600 mg)		2 mL (400 mg) monthly
Rilpivirine	25 mg once daily		3 mL (900 mg)		2 mL (600 mg) monthly

Every 2 Month Dosing (Suspension for Injection)

Initiation Injections

On the final day of oral lead-in, the recommended initial *VOCABRIA* injection dose in adults is a single 3 mL (600 mg) intramuscular injection. One month later, a second 3 mL (600 mg) intramuscular injection should be administered. Patients may be given the second 3 mL (600 mg) initiation injection up to 7 days before or after the scheduled dosing date.

Continuation Injections

After the second initiation injection, the recommended *VOCABRIA* continuation injection dose in adults is a single 3 mL (600 mg) intramuscular injection administered every 2 months. Patients may be given injections up to 7 days before or after the date of the every 2 month, 3 mL dosing schedule.

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

	ORAL LEAD-IN		INITIATION INJECTIONS (one month apart)		CONTINUATION INJECTIONS (two months apart)
Drug	**For 1 Month (at least 28 days)**		**At Month 2 and Month 3**		**Month 5 onwards**
VOCABRIA	30 mg once daily		3 mL (600 mg)		3 mL (600 mg)
Rilpivirine	25 mg once daily		3 mL (900 mg)		3 mL (900 mg)

Change in Dosing Frequency

Dosing Recommendations when Switching from Monthly to Every 2 Month Injections

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

Dosing Recommendations when Switching from Every 2 Month to Monthly Injections

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

Missed dose

Film-coated Tablet

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

Suspension for Injection

Adherence to the injection dosing schedule is strongly recommended. Patients who miss a scheduled injection visit should be clinically reassessed to ensure resumption of therapy remains appropriate (see Tables 3 and 4).

Missed monthly injection

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

The first dose of oral therapy should be taken one month (+/–7 days) after the last injection dose of *VOCABRIA* or rilpivirine. Injection dosing should be resumed on the day oral dosing completes, as recommended in Table 3.

Table 3 Injection dosing recommendations after missed injections or oral therapy for patients on monthly injection dosing

Time since last injection	**Recommendation**
≤*2* months:	Continue with the monthly 2 mL (400 mg) injections dosing schedule as soon as possible

>*2* months:	Re-initiate the patient on the 3 mL (600 mg) dose, and then continue to follow the monthly 2 mL (400 mg) injection dosing schedule.

Missed 2 month injection

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

The first dose of oral therapy should be taken two months (+/–7 days) after the last injection dose of *VOCABRIA* or rilpivirine.
Injection dosing should be resumed on the day oral dosing completes, as recommended in Table 4.

Table 4 Injection dosing recommendations after missed injections or oral therapy for patients on every 2 month injection dosing

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

Adolescents and Children

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

Elderly

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

Renal impairment

No dosage adjustment is required in patients with mild to severe renal impairment and not on dialysis (*see Pharmacokinetics - Special Patient Populations*). Cabotegravir has not been studied in patients with end-stage renal disease on renal replacement therapy.

Hepatic impairment

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

Contraindications

VOCABRIA is contraindicated in patients:

- with known hypersensitivity to cabotegravir or to any of the excipients in the tablets or the injection formulation.
- receiving rifampicin, rifapentine, phenytoin, phenobarbital, carbamazepine and oxcarbazepine.

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

Warnings and Precautions

Hypersensitivity reactions

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

Hepatotoxicity

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

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

Long acting properties of VOCABRIA injection

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

Risk of resistance following treatment discontinuation

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

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

Interactions with medicinal products

Caution should be given to prescribing *VOCABRIA* with medicinal products that may reduce its exposure (*see Interactions*).

Opportunistic infections

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

Transmission of infection

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

Concomitant treatment with rilpivirine

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

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/m2. 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/m2 or HIV-1 A6/A1 subtype (see pharmacodynamics).

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, generalized 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.

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

Interactions

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

Effect of cabotegravir on the pharmacokinetics of other agents

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

Cabotegravir inhibited the organic anion transporters (OAT) 1 (IC50=0.81 µM) and OAT3 (IC50=0.41 µM) *in vitro*, however, based on physiologically based pharmacokinetic (PBPK) modelling no interaction with OAT substrates is expected at clinically relevant concentrations.

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

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

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

Effect of other agents on the pharmacokinetics of cabotegravir

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

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

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

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

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

Table 5 Drug interactions

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

Rifampicin	Cabotegravir ↓ AUC ↓ 59% C_{max} ↓ 6%	Rifampicin significantly decreased cabotegravir plasma concentration, which is likely to result in loss of therapeutic effect. Co-administration of *VOCABRIA* with rifampicin is contraindicated. Dosing recommendations for co-administration of *VOCABRIA* (oral and injection) with rifampicin have not been established.
Rifapentine	Cabotegravir ↓	Rifapentine may significantly decrease cabotegravir plasma concentrations, concomitant use is contraindicated.
Rifabutin	Cabotegravir↓ AUC ↓ 21% C_{max} ↓ 17% Cτ ↓ 8%	*VOCABRIA tablets:* Rifabutin did not significantly change cabotegravir plasma concentration. No dose adjustment is required. Prior to initiation of oral *VOCABRIA* therapy, the prescribing information for *VOCABRIA* injection should be consulted regarding concomitant use with rifabutin. *VOCABRIA injection:* Rifabutin may decrease cabotegravir plasma concentrations, concomitant use should be avoided.
Anticonvulsants: Carbamazepine Oxcarbazepine Phenytoin Phenobarbital	Cabotegravir ↓	Metabolic inducers may significantly decrease cabotegravir plasma concentrations. Concomitant use is contraindicated.

Antacids (e.g., magnesium, calcium or aluminium)	Cabotegravir ↓	*VOCABRIA tablets:* Co-administration of antacid supplements has the potential to decrease oral cabotegravir absorption and has not been studied. Antacid products containing polyvalent cations are recommended to be administered at least 2 hours before or 4 hours after oral *VOCABRIA.* *VOCABRIA injection:* Interaction is not relevant following parenteral administration.
Oral contraceptives (Ethinyl estradiol (EE) and levonorgestrel	EE ↔ AUC ↑ 2% C_{max} ↓ 8% Cτ ↔ 0% LNG ↔	Cabotegravir did not significantly change ethinyl estradiol and levonorgestrel plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with *VOCABRIA*.

Pregnancy and Lactation

Fertility

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

Pregnancy

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

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

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

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

Lactation

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

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

Effects on Ability to Drive and Use Machines

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

Adverse Reactions

Clinical trial data

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

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

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

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

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

Table 6 Adverse reactions

MedDRA System Organ Class (SOC)	Frequency Category	ADRs for cabotegravir + rilpivirine regimen
Psychiatric disorders	Common	Depression Anxiety Abnormal dreams Insomnia
	Uncommon	Suicide related AEs (eg. suicide attempt and suicidal ideation) particularly in patients with pre-existing history of psychiatric illness
Nervous system disorders	Very common	Headache
	Common	Dizziness
	Uncommon	Somnolence Vasovagal reactions[4] (in response to injections)
Gastrointestinal disorders	Common	Nausea Vomiting Abdominal pain[1] Flatulence Diarrhoea
Hepatobiliary Disorders	Uncommon	Hepatotoxicity
Skin and subcutaneous tissue disorders	Common	Rash[2]
Musculoskeletal and connective tissue disorders	Common	Myalgia
General disorders and administrative site conditions	Very common	Injection site reactions[4] (pain and discomfort, site nodule, induration) Pyrexia[3]
	Common	Injection site reactions[4] (swelling, erythema, pruritus, bruising, warmth, haematoma) Fatigue Asthenia Malaise
	Uncommon	Injection site reactions[4] (cellulitis, abscess, anaesthesia, haemorrhage, discolouration)
Investigations	Common	Weight increased
	Uncommon	Transaminase increased

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

[3] Pyrexia includes the following grouped MedDRA preferred terms: pyrexia, body temperature increased, feeling hot. The majority of pyrexia events were reported within one week of injections.

[4] Associated with injection formulation only. Injection site reactions listed in the table have been reported in 2 subjects or more.

The overall safety profile at Week 96 in FLAIR study were consistent with that observed at Week 48, with no new safety findings identified.

Local Injection Site Reactions

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

When dosing monthly, out of 30393 injections, 6815 ISRs were reported. When dosing every 2 months, out of 8470 injections, 2507 ISRs were reported.

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

Weight increased

At the Week 48 time point, subjects in FLAIR and ATLAS, who received cabotegravir + rilpivirine gained a median of 1.5 kg in weight; those in the CAR group gained a median of 1.0 kg (pooled analysis). In the individual studies FLAIR and ATLAS, the median weight gains in the cabotegravir + rilpivirine arms were 1.3 kg and 1.8 kg respectively, compared to 1.5 kg and 0.3 kg in the CAR arms. At the 48 week timepoint, in ATLAS-2M, the median weight gain in both the monthly and 2-monthly CAB+RPV dosing arms was 1.0 kg.

Changes in laboratory chemistries

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

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

Elevated lipases were observed during clinical trials with *VOCABRIA* + rilpivirine; Grade 3 and 4 lipase increases occurred at a higher incidence with *VOCABRIA* + rilpivirine compared with the CAR group. These elevations were generally asymptomatic and did not lead to discontinuation.

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

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

Back pain
During the clinical development programme, based on pooled analysis from the 201584 (FLAIR) and 201585 (ATLAS) study at week 48, a numerically higher incidence of back pain was observed in the CAB+RPV group (7%) versus CAR group (4%). These events were non serious, not considered causally related by the investigator, grade 1 or 2, and did not lead to withdrawal.

Haemarrhoids
During the clinical development programme, based on the pooled analysis from the 201584 (FLAIR) and 201585 (ATLAS) study at week 48, a numerically higher incidence of haemorrhoids was observed in the CAB+RPV group (3%) versus CAR group(<1%). These events were non serious, not considered causally related by the investigator, grade 1 or 2, and did not lead to withdrawal.

Post-marketing data

No data

Overdose

Symptoms and signs

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

Treatment

There is no specific treatment for overdose with *VOCABRIA.* If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC code

Pharmacotherapeutic group: Antivirals for systemic use, Integrase inhibitors.

ATC code: J05AJ04

Mechanism of action

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

Pharmacodynamic effects

Antiviral Activity in cell culture
Cabotegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean concentration of cabotegravir necessary to reduce viral replication by 50 percent (EC50) values of 0.22 nM in peripheral blood mononuclear cells (PBMCs), 0.74nM in 293T cells and 0.57 nM in MT-4 cells. Cabotegravir demonstrated antiviral activity in cell culture against a panel of 24 HIV-1 clinical isolates (three in each group of M clades A, B, C, D, E, F, and G, and 3 in group O) with EC50 values ranging from 0.02 nM to 1.06 nM for HIV-1. Cabotegravir EC50 values against three HIV-2 clinical isolates ranged from 0.10 nM to 0.14 nM. No clinical data is available in patients with HIV-2.

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

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

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

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

Resistance in vivo
The number of subjects who met Confirmed Virologic Failure (CVF) criteria was low across the pooled FLAIR and ATLAS trials. In the pooled analysis, there were 7 CVFs on cabotegravir plus rilpivirine (7/591, 1.2%) and 7 CVFs on current antiretroviral regimen (7/591, 1.2%). The three CVFs on cabotegravir + rilpivirine in 201584 (FLAIR) with resistance data had Subtype A1 with IN substitution L74I (which by itself does not cause resistance to any INI) detected at Baseline and suspected virologic failure (SVF). In addition, 2/3 CVFs had treatment-emergent INI resistance associated substitution Q148R while 1/3 had G140R with reduced phenotypic susceptibility to cabotegravir. All 3 CVFs

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

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

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

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

In the Q4W arm, neither subject had any RPV or INSTI resistance-associated substitutions at Baseline. One subject had the NNRTI substitution, G190Q, in combination with the NNRTI polymorphism, V189I. At SVF timepoint, one subject had on-treatment rilpivirine resistance-associated mutations, K101E + M230L and the other retained the G190Q + V189I NNRTI substitutions with the addition of V179V/I. Both subjects showed reduced phenotypic susceptibility to RPV. Both subjects also had INSTI resistance-associated mutations, either Q148R + E138E/K or N155N/H at SVF and 1 subject had reduced susceptibility to CAB. Neither subject had the INSTI substitution, L74I. Fold-changes for the Q4W subjects were 1.8 and 4.6 for cabotegravir, 1.0 and 1.4 for dolutegravir and 1.1 and 1.5 for bictegravir.

Effects on Electrocardiogram

In a randomised, placebo-controlled, three-period cross-over trial, 42 healthy subjects were randomized into 6 random sequences and received three doses of oral administration of placebo, cabotegravir 150 mg every 12 hours (mean steady-state C_{max} was approximately 2.8-fold, 5.4-fold and 5.6-fold above the 30 mg oral once-daily dose, the 400 mg cabotegravir injection monthly dose and the 600 mg cabotegravir injection

every 2 month dose, respectively), or single dose of moxifloxacin 400 mg (active control). After baseline and placebo adjustment, the maximum time-matched mean QTc change based on Fridericia's correction method (QTcF) for cabotegravir was 2.62 msec (1-side 90% upper CI:5.26 msec). Cabotegravir did not prolong the QTc interval over 24 hours postdose.

Pharmacokinetics

Oral

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

Suspension for Injection

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

Table 7. Pharmacokinetic parameters following cabotegravir orally once daily, and initiation, monthly and every 2 month continuation intramuscular injections

		Geometric Mean (5th, 95th Percentile)[a]		
Dosing Phase	Dosage Regimen	$AUC_{(0\text{-}tau)}$[b] (µ•h/mL)	C_{max} (µ/mL)	C_{tau} (µ/mL)
Oral lead-in[c]	30 mg once daily	145 (93.5, 224)	8.0 (5.3, 11.9)	4.6 (2.8, 7.5)
Initial injection[d]	600 mg IM Initial Dose	1591 (714, 3245)	8.0 (5.3, 11.9)	1.5 (0.65, 2.9)
Monthly injection[e]	400 mg IM monthly	2415 (1494, 3645)	4.2 (2.5, 6.5)	2.8 (1.7, 4.6)
Every 2-month injection[e]	600 mg IM Every 2-month	3764 (2431, 5857)	4.0 (2.3, 6.8)	1.6 (0.8, 3.0)

[a] Pharmacokinetic (PK) parameter values were based on individual post-hoc estimates from population PK models for patients in FLAIR and ATLAS for the oral, initial and monthly regimen; and in ATLAS-2M for the every 2 month regimen.

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

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

[d] Initial injection C_{max} values primarily reflect oral dosing because the initial injection was administered on the same day as the last oral dose; however, the $AUC_{(0\text{-}tau)}$ and C_{tau} values reflect the initial injection. When administered without OLI (DTI n=110), observed geometric mean (5th, 95th percentile) CAB C_{max} (1 week post initial injection) was 1.89 µg/mL (0.438, 5.69) and CAB C_{tau} was 1.43 µg/mL (0.403, 3.90).

[e] Monthly and every 2 month injection pharmacokinetic parameter values represent Week 48 data.

Absorption

Oral

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

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

The absolute bioavailability of cabotegravir has not been established.

Suspension for Injection

VOCABRIA injection exhibits absorption-limited pharmacokinetics because cabotegravir is slowly absorbed into the systemic circulation from the gluteal muscle resulting in sustained plasma concentrations. Following a single intramuscular dose, plasma cabotegravir concentrations are detectable on the first day and gradually rise to reach maximum plasma concentration with a median T_{max} of 7 days. Cabotegravir has been detected in plasma up to 52 weeks or longer after administration of a single injection. Pharmacokinetic steady-state is achieved by 44 weeks.

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

Distribution

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

Cabotegravir is present in the female and male genital tract. Median cervical and vaginal tissue:plasma ratios ranged from 0.16 to 0.28 and median rectal tissue:plasma ratios were ≤0.08 following a single 400 mg IM injection at 4, 8, and 12 weeks after dosing.

Cabotegravir is present in cerebrospinal fluid (CSF). In HIV-infected subjects receiving a regimen of cabotegravir injection + rilpivirine injection, the cabotegravir CSF to plasma concentration ratio [median (range)] (n=16) was 0.003 (0.002 to 0.004), one week following a steady-state cabotegravir (Q4W or Q8W) injection. Consistent with therapeutic cabotegravir concentrations in the CSF, CSF HIV-1 RNA (n=16) was <50 c/mL in 100% and <2 c/mL in 15/16 (94%) of subjects. At the same time point, plasma HIV-1 RNA (n=18) was <50 c/mL in 100% and <2 c/mL in 12/18 (66.7%) of subjects.

Metabolism

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

Elimination

Oral

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

Suspension for Injection

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

Special patient populations

Gender

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

Race

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

BMI

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

Elderly

Population pharmacokinetic analysis of cabotegravir revealed no clinically relevant effect of age on cabotegravir exposure.

Pharmacokinetic data for cabotegravir in subjects of >65 years old are limited.

Renal impairment

No clinically important pharmacokinetic differences between subjects with severe renal impairment (CrCL <30 mL/min and not on dialysis) and matching healthy subjects were observed. No dosage adjustment is necessary for patients with mild to severe renal impairment (not on dialysis). Cabotegravir has not been studied in patients on dialysis.

Hepatic impairment

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

HBV and HCV Co-infected Patients

There are limited data for the use of cabotegravir in subjects with HCV co-infection. Monitoring of liver function is recommended in patients with hepatitis C co-infection. There are no data for the use of cabotegravir in subjects with HBV co-infection as 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.

Polymorphisms in Drug Metabolising Enzymes

In a meta-analysis of healthy and HIV-infected subjects, HIV-infected subjects with UGT1A1 genotypes conferring poor cabotegravir metabolism had a 1.2-fold increase in mean steady-state cabotegravir AUC, C_{max}, and C_{tau} following cabotegravir injection vs. 1.38-fold mean increase following oral cabotegravir administration. This was similar to 1.3- to 1.5-fold mean increase in steady-state cabotegravir, cabotegravir AUC, C_{max}, and C_{tau} observed following oral cabotegravir in healthy and HIV infected subjects combined. These differences are not considered clinically relevant. Polymorphisms in UGT1A9

were not associated with differences in the pharmacokinetics of cabotegravir, therefore, no dose adjustment is required in subjects with either UGT1A1 or UGT1A9 polymorphisms.

Clinical Studies

Monthly Dosing

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

In FLAIR, 629 HIV-1-infected, antiretroviral treatment (ART)-naive subjects received a

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

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

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

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

In a pooled analysis of the two pivotal studies, cabotegravir + rilpivirine was non-inferior to CAR on the proportion of subjects having plasma HIV-1 RNA ≥50 c/mL (1.9% and 1.7% respectively) at Week 48. The adjusted treatment difference between cabotegravir + rilpivirine and CAR (0.2; 95% CI: -1.4, 1.7) for the pooled analysis met the non-inferiority criterion (upper bound of the 95% CI below 4%). Furthermore, in the pooled analysis, cabotegravir + rilpivirine was non-inferior to CAR on the proportion of subjects having plasma HIV-1 RNA <50 c/mL (93.1% and 94.4%, respectively) at Week 48. The adjusted treatment difference between cabotegravir + rilpivirine and CAR (-1.4; 95% CI: -4.1, 1.4) for the pooled analysis met the non-inferiority criteria (lower bound of the 95% CI greater than -10%. [See Table 8]).

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

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

Table 8 Virologic outcomes of randomized treatment of FLAIR and

ATLAS at 48 weeks (snapshot analysis)

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

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

Table 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	
		CAB+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, age, race, BMI, age, baseline third agent treatment class) were comparable.

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

Week 96 FLAIR

In the FLAIR study at 96 Weeks, the results remained consistent with the results at 48 Weeks. The proportion of subjects having plasma HIV-1 RNA ≥50 c/mL in cabotegravir plus rilpivirine (n=283) and CAR (n=283) was 3.2% and 3.2% respectively (adjusted treatment difference between cabotegravir plus rilpivirine and CAR [0.0; 95% CI: -2.9, 2.9]). The proportion of subjects having plasma HIV-1 RNA <50 c/mL in cabotegravir plus rilpivirine and CAR was 87% and 89%, respectively (adjusted treatment difference between cabotegravir plus rilpivirine and CAR [-2.8; 95% CI: -8.2, 2.5]).

Every 2 month Dosing

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

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

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

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

In ATLAS-2M, cabotegravir + rilpivirine administered every 2 months was non-inferior to cabotegravir and rilpivirine administered every month on the proportion of subjects having plasma HIV-1 RNA ≥50 c/mL (1.7% and 1.0% respectively) at Week 48. The adjusted treatment difference between cabotegravir + rilpivirine administered every 2 months and every month (0.8; 95% CI: -0.6, 2.2) met the non-inferiority criterion (upper bound of the 95% CI below 4%). Furthermore, cabotegravir + rilpivirine dosed every 2 months was non-inferior to CAB+RPV dosed every month on the proportion of subjects having plasma HIV-1 RNA <50 c/mL (94% and 93%, respectively) at Week 48. The adjusted treatment difference between cabotegravir + rilpivirine dosed every 2 months and monthly (0.8; 95% CI: -2.1, 3.7) met the non-inferiority criteria (lower bound of the 95% CI greater than -10%. [See Table 10]).

Table 10 Virologic outcomes of randomized treatment for ATLAS-2M at 48 weeks (snapshot analysis)

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

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

Table 11 Proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at week 48 for key baseline factors (snapshot outcomes)

		Number of HIV-1 RNA ≥50 c/mL / Total Assessed (%)	
		2 Month Dosing (Q8W)	Monthly dosing (Q4W)
Baseline CD4+ cell count (cells/mm3)	<350	1/ 35 (2.9)	1/ 27 (3.7)
	350 to <500	1/ 96 (1.0)	0/ 89
	≥500	7/391 (1.8)	4/407 (1.0)
Gender	Male	4/385 (1.0)	5/380 (1.3)

	Female	5/137 (3.5)	0/143
Race	White	5/370 (1.4)	5/393 (1.3)
	Non-White	4/152 (2.6)	0/130
	Black/African American	4/101 (4.0)	0/ 90
	Non-Black/African American	5/421 (1.2)	5/421 (1.2)
BMI	<30 kg/m^2	3/409 (0.7)	3/425 (0.7)
	≥30 kg/m^2	6/113 (5.3)	2/98 (2.0)
Age (years)	<35	4/137 (2.9)	1/145 (0.7)
	35 to <50	3/242 (1.2)	2/239 (0.8)
	>50	2/143 (1.4)	2/139 (1.4)
Prior exposure CAB/RPV	None	5/327 (1.5)	5/327 (1.5)
	1-24 weeks	3/69 (4.3)	0/68
	>24 weeks	1/126 (0.8)	0/128

BMI= body mass index

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

Post-Hoc Analysis: Baseline Factors Associated with Virologic Failure

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

Four covariates were significantly associated ($P<0.05$ for each adjusted odds ratio) with increased risk of CVF: rilpivirine resistance mutations at baseline identified by proviral DNA genotypic assay, HIV-1 subtype A6/A1 (associated with integrase L74I polymorphism), rilpivirine trough concentration 4 weeks following initial injection dose, body mass index of at least 30 kg/m^2 (associated with cabotegravir pharmacokinetics). Other variables including Q4W or Q8W dosing, female gender, or other viral subtypes (non A6/A1) had no significant association with CVF. No baseline factor, when present in isolation, was predictive of virologic failure. However, a combination of at least 2 of the following baseline factors was associated with an increased risk of CVF: rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI $\geq$30 kg/m^2 (see Table 12).

Table 12 Week 48 Outcomes by Presence of Key Baseline Factors of Rilpivirine-Resistance Associated Mutations, Subtype A6/A1[a] and BMI ≥30 kg/m^2

Baseline Factors (number)	Virologic Successes (%)[b]	Confirmed Virologic Failure (%)[c]
0	694/732 (94.8)	3/732 (0.41)
1	261/272 (96.0)	1/272 (0.37)[d]
≥2	25/35 (71.4)	9/35 (25.7)[e]
TOTAL (95% Confidence Interval)	980/1039 (94.3) (92.74%, 95.65%)	13/1039 (1.25) (0.67%, 2.13%)

[a] HIV-1 subtype A1 or A6 classification based on Los Alamos National Library panel from HIV Sequence database (June 2020)

[b] Based on the FDA Snapshot algorithm of RNA <50 copies/mL.

[c] Defined as two consecutive measurements of HIV RNA ≥200 copies/mL.

[d] Positive Predictive Value (PPV) <1%; Negative Predictive Value (NPV) 98%; sensitivity 8%; specificity 74%

[e] PPV 26%; NPV 99.6%; sensitivity 69%; specificity 97.5%

Non-Clinical Information

Carcinogenesis/mutagenesis

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

Reproductive Toxicology

Fertility

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

Pregnancy

In an embryo-foetal development study there were no adverse developmental outcomes following oral administration of cabotegravir to pregnant rabbits at doses up to 2000mg/kg/day (0.66 times the exposure in humans at the MRHD of 30 mg oral or approximately 1 times 400 mg IM dose) or to pregnant rats at doses up to 1000 mg/kg/day (>30 times the exposure in humans at the MRHD of 30 mg oral or 400 mg IM dose). In rats, alterations in foetal growth (decreased body weights) in the absence of maternal toxicity were observed at 1,000 mg/kg/day. Studies in pregnant rats showed that cabotegravir crosses the placenta and can be detected in foetal tissue.

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

Animal toxicology and/or pharmacology

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

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

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

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

PHARMACEUTICAL INFORMATION

List of Excipients

Film-coated tablets

Tablet core

Lactose Monohydrate
Microcrystalline Cellulose
Hypromellose
Sodium Starch Glycolate
Magnesium Stearate

Tablet coating

Hypromellose
Titanium Dioxide (E171)
Macrogol

Suspension for Injection

Mannitol (E421)
Polysorbate 20
Macrogol 3350
Water for injections

Shelf Life

The expiry date is indicated on the packaging.

Storage

Unopened packs

The storage conditions are detailed on the packaging.

Open packs

Suspension for Injection

Once the suspension has been drawn into the syringe, the injection should be administered as soon as possible, but may be stored for up to 2 hours at below or at 25°C. If 2 hours are exceeded, the medication, syringe and needle must be discarded.

Nature and Contents of Container

Film-coated tablets

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

Each bottle contains 30 film-coated tablets.

Suspension for Injection

Individual vial only pack (single entity vial SEV):

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

Cabotegravir is presented in a Type I glass vial with bromobutyl rubber

stopper.

Not all presentations are available in every country.

Incompatibilities

Film-coated tablets

None

Suspension for Injection

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

Use and Handling

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

Product Registrant: GlaxoSmithKline Pte Ltd, 23 Rochester Park, Singapore 139234

Version number: VGDS04/IPI02(SI)

Date of issue: 15 March 2021

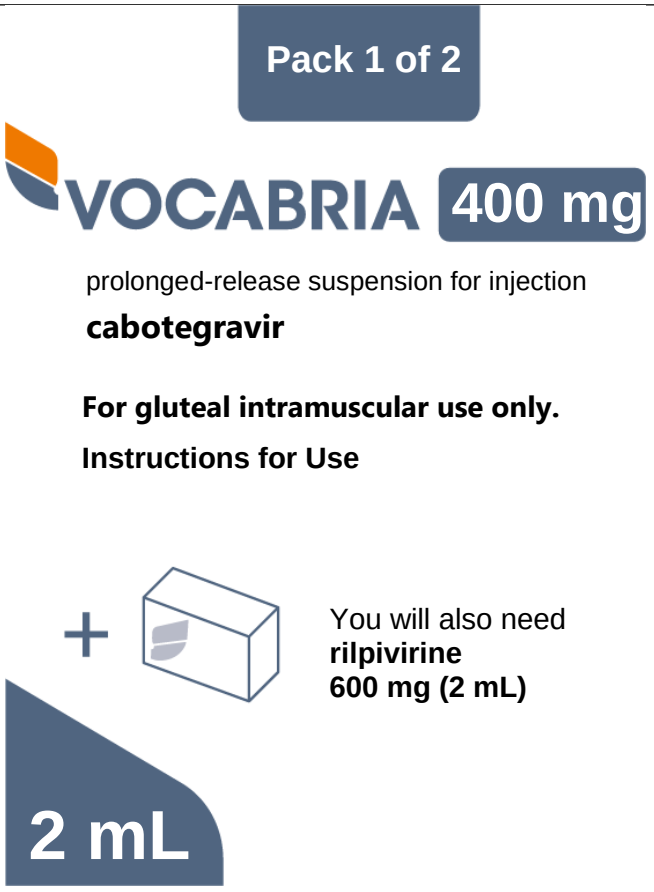
[ViiV Healthcare logo]

INSTRUCTIONS FOR USE

The following information is intended for healthcare professionals only:

For Single Entity Vial (SEV) packs:

VOCABRIA 400 mg prolonged release suspension for injection (2 mL vial)



Overview

At each visit, 2 injections are required to complete treatment: **VOCABRIA** 2 mL and rilpivirine 2 mL.

Cabotegravir and rilpivirine are suspensions that do not need further dilution or reconstitution. The preparation steps for both medicines are the same.

Cabotegravir and rilpivirine are for intramuscular use only. Both injections must be administered to the gluteal sites. The administration order is not important.

Note: The ventrogluteal site is recommended.

Storage information

• The storage conditions are detailed on the packaging

Do not freeze.

Your pack contains

- 1 vial of cabotegravir

To prepare the injection

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

To administer the injection

- 1 additional Luer-Lock needle (use safety needle if available) of 23 gauge, 1.5 inches

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

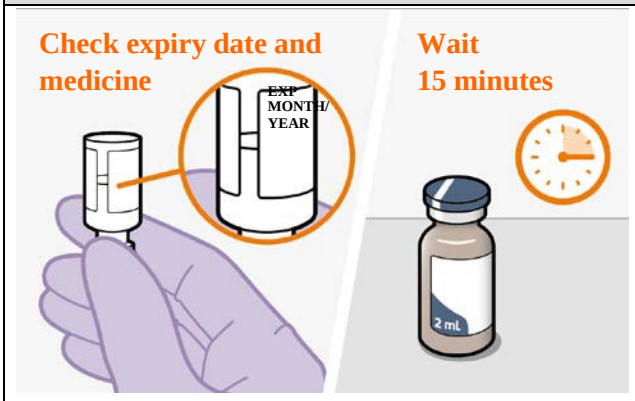
You will also need

- Non-sterile gloves
- 2 alcohol swabs
- 2 gauze pads
- A suitable sharps container
- 1 rilpivirine 2 mL pack

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

Preparation

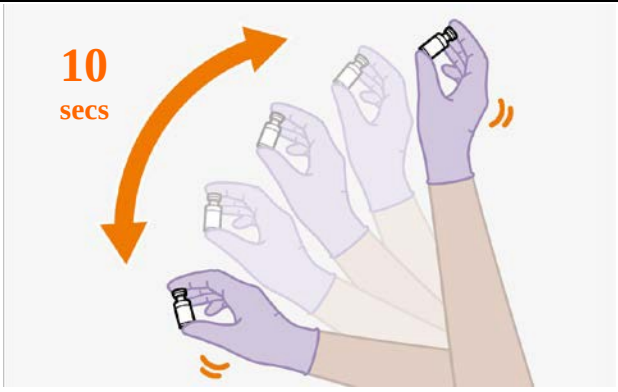
1. Inspect vial



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

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

2. Shake vigorously

<table>
<tr>
<td> 
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<td>

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

Do not allow anything to touch the rubber stopper after wiping it.
</td>
</tr>
<tr>
<td colspan="2">3. Prepare syringe and needle</td>
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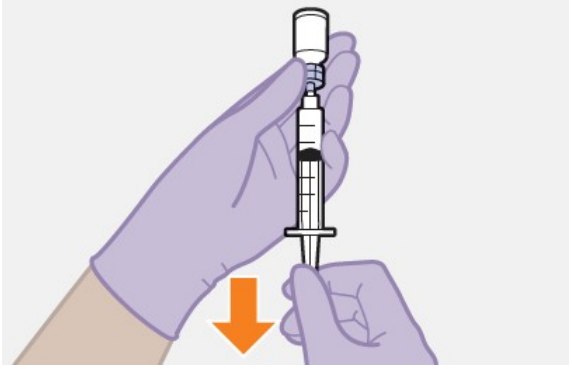
<td>  </td>
<td>

Attach the aspiration needle to the syringe. Continue to prepare the injection in line with local guidelines.
Use the aspiration needle to perforate the rubber stopper of the vial.
It is recommended that you inject 1 mL of air into the vial to allow the required volume to be drawn off.
If using an aspiration device, follow device instructions to prepare the injection.

</td>
</tr>
</table>

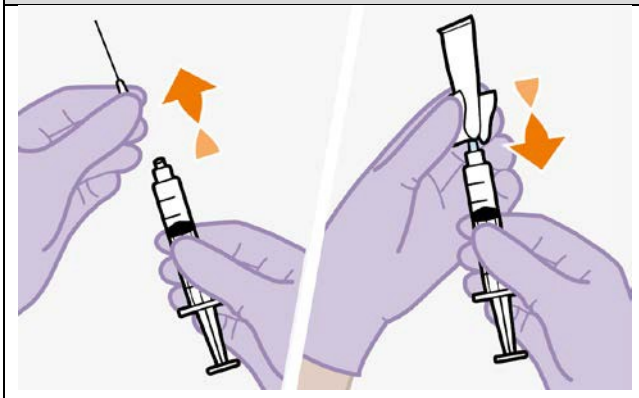
4. Slowly draw up dose



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

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

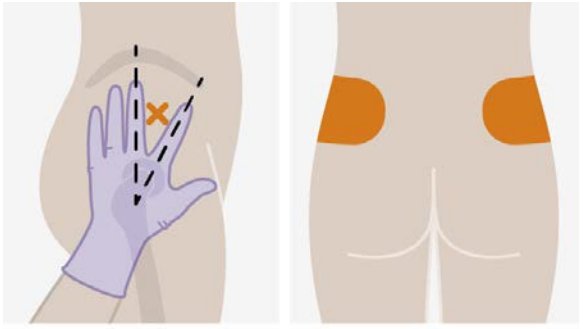
5. Attach injection needle



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

Injection

6. Prepare injection site

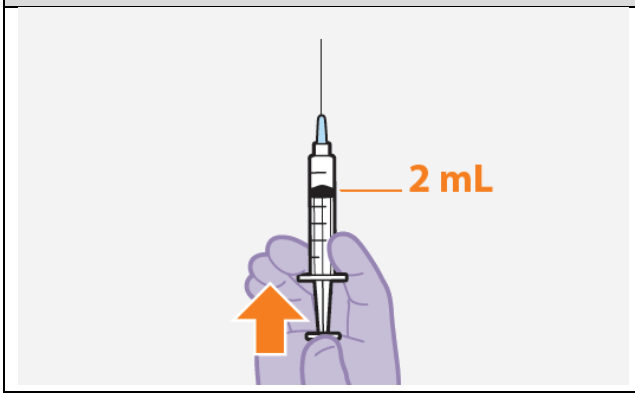
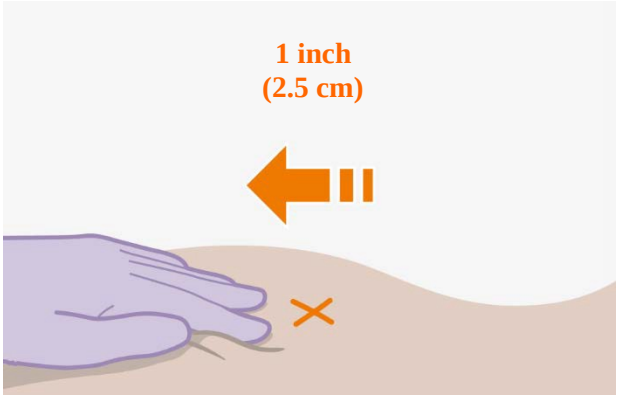
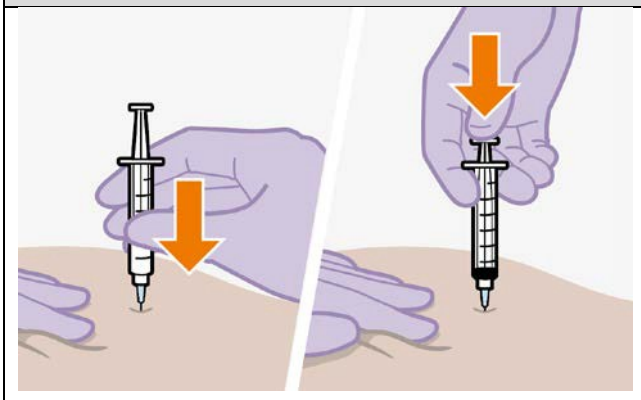


Ventrogluteal **Dorsogluteal**

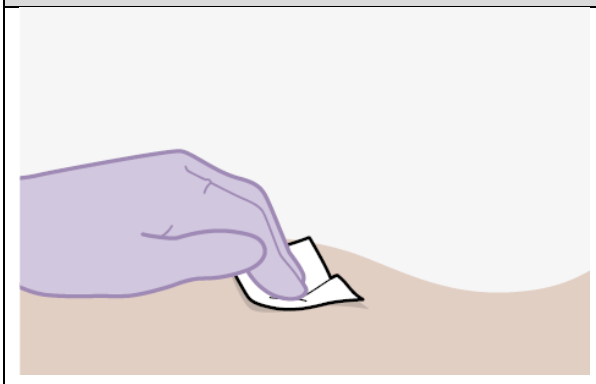
Injections must be administered to the gluteal sites. Select from the following areas for the injection:

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

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

7. Remove extra liquid	
	• Pull off the injection needle cap. • Hold the syringe with the needle pointing up. Press the plunger to the 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.
8. Stretch skin	
	Use the z-track injection technique to minimise medicine leakage from the injection site. • Firmly drag the skin covering the injection site, displacing it by about an inch (2.5 cm). • Keep it held in this position for the injection.
9. Inject dose	
	• Insert the needle to its full depth, or deep enough to reach the muscle. • Still holding the skin stretched – slowly press the plunger all the way down. • Ensure the syringe is empty. • Withdraw the needle and release the stretched skin immediately.

10. Assess the injection site



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

Do not massage the area.

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?

It is best to inject the (room temperature) medicine as soon as possible after drawing it up. However, the medicine can remain in the syringe for up to 2 hours before injecting.

If 2 hours are exceeded, the medicine, syringe and needle must be discarded.

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.

VOCABRIA 600 mg Prolonged release suspension for injection (3 mL vial)

Overview

At each visit, 2 injections are required to complete treatment: **VOCABRIA** 3 mL and rilpivirine 3 mL.

Cabotegravir and rilpivirine are suspensions that do not need further dilution or reconstitution. The preparation steps for both medicines are the same.

Cabotegravir and rilpivirine are for intramuscular use only. Both injections must be administered to the gluteal sites. The administration order is not important.

Note: The ventrogluteal site is recommended.

Storage information

• The storage conditions are detailed on packaging.

Do not freeze.

Your pack contains

- 1 vial of cabotegravir

To prepare the injection

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

To administer the injection

- 1 additional Luer-Lock needle (use safety needle if available) of 23 gauge, 1.5 inches

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

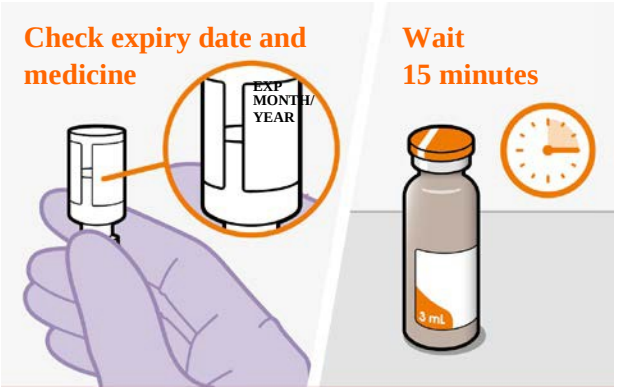
You will also need

- Non-sterile gloves
- 2 alcohol swabs
- 2 gauze pads
- A suitable sharps container
- 1 rilpivirine 3 mL pack

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

Preparation

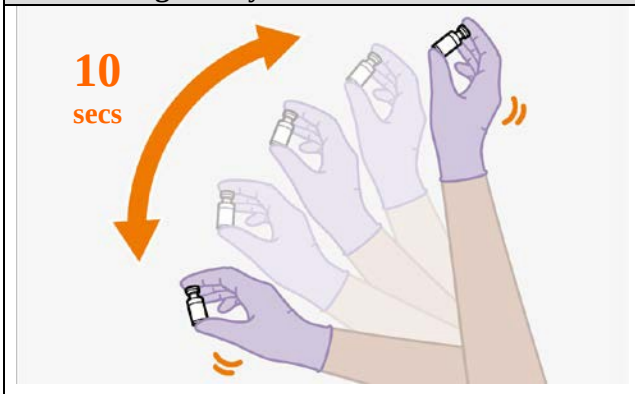
1. Inspect vial



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

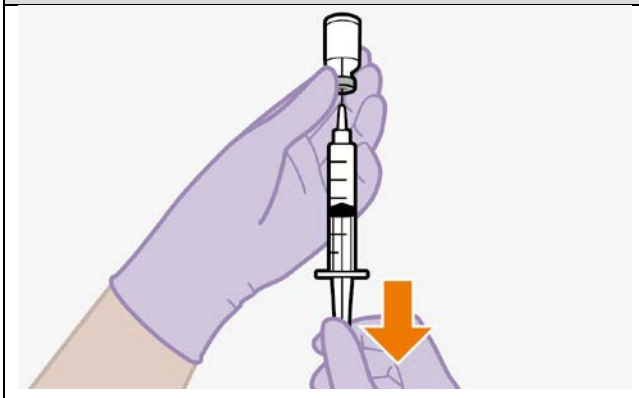
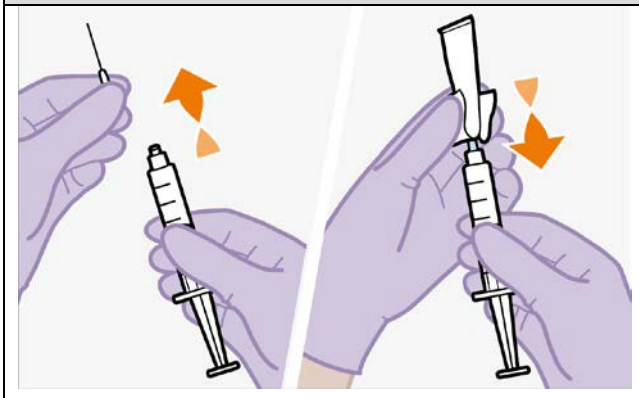
Note: The cabotegravir vial has a brown tint to the glass.
Do not use if the expiry date has passed.

2. Shake vigorously



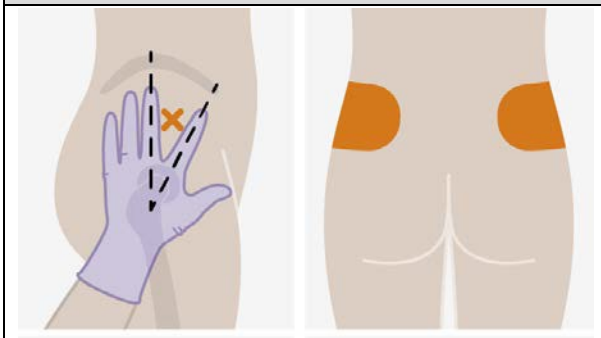
- Hold the vial firmly and vigorously shake for a full 10 seconds as shown.
- Invert the vial and check the resuspension. It should look uniform. If the suspension is not uniform, shake the vial again.
- It is also normal to see small air bubbles.
- Remove the cap from the vial.
- Wipe the rubber stopper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

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

3. Prepare syringe and needle	
	• Attach the aspiration needle to the syringe. Continue to prepare the injection in line with local guidelines. • Use the aspiration needle to perforate the rubber stopper of the vial. • It is recommended that you inject 1 mL of air into the vial to allow the required volume to be drawn off. • If using an aspiration device, follow device instructions to prepare the injection.
4. Slowly draw up dose	
	• Invert the syringe and vial, and slowly withdraw as much of the liquid as possible into the syringe. There might be more liquid than dose amount. **Note:** Check that the suspension looks uniform and white to light pink.
5. Attach injection needle	
	• Peel open the needle packaging part way to expose the needle base. • Keeping the syringe upright, firmly twist the syringe onto the injection needle. • Remove the needle packaging from the injection needle.

Injection

6. Prepare injection site

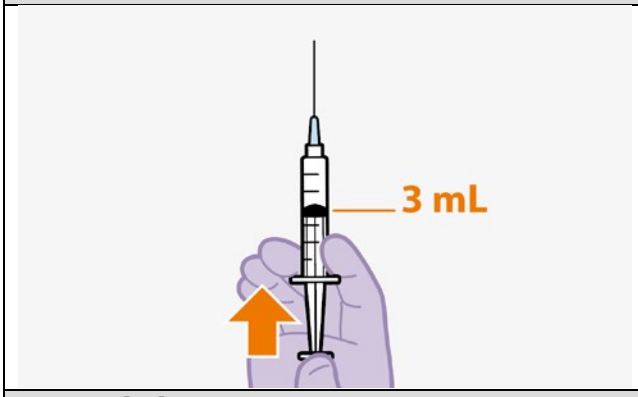


Injections must be administered to the gluteal sites. Select from the following areas for the injection:

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

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

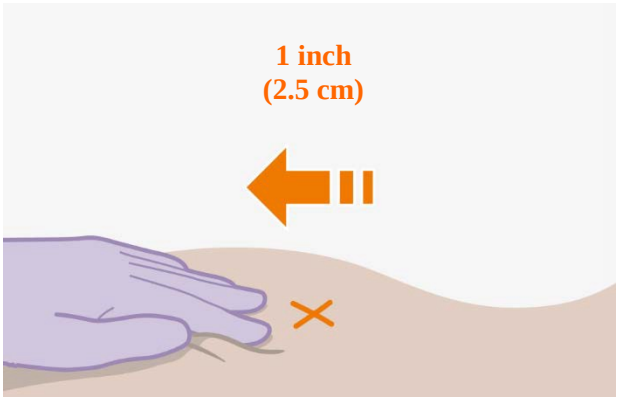
7. Remove extra liquid



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

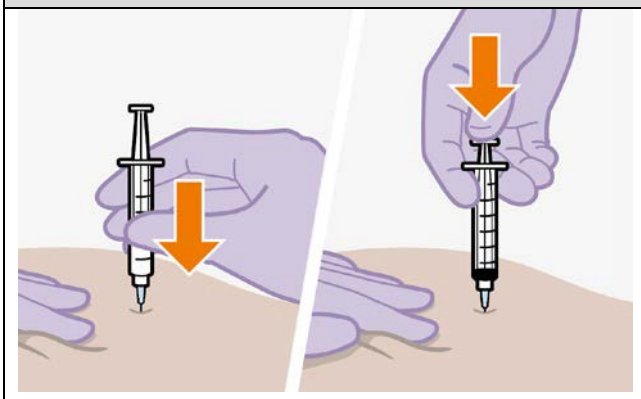
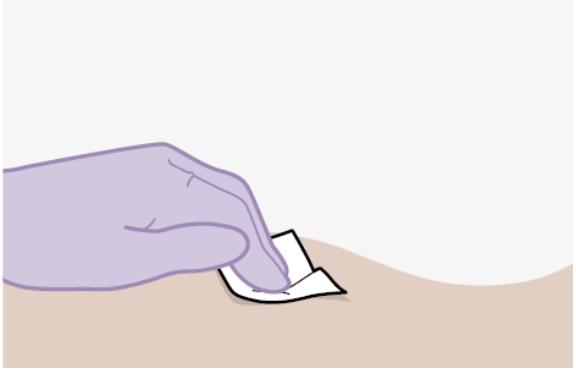
Note: Clean the injection site with an alcohol swab. Allow the skin to air dry before continuing.

8. Stretch skin



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

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

9. Inject dose	
	• Insert the needle to its full depth, or deep enough to reach the muscle. • Still holding the skin stretched – slowly press the plunger all the way down. • Ensure the syringe is empty. • Withdraw the needle and release the stretched skin immediately.
10. Assess the injection site	
	• Apply pressure to the injection site using a gauze. • A small bandage may be used if a bleed occurs. • Dispose of used needles, syringes and vials according to local health and safety laws. **Do not** massage the area.
Repeat for 2nd medicine	
 **Repeat all steps 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?

It is best to inject the (room temperature) medicine as soon as possible after drawing it up. However, the medicine can remain in the syringe for up to 2 hours before injecting.

If 2 hours are exceeded, the medicine, syringe and needle must be discarded.

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.