▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

CABENUVA cabotegravir prolonged-release suspension for injection and rilpivirine prolonged-release suspension for injection

1 NAME OF THE MEDICINE

Cabotegravir and rilpivirine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CABENUVA contains cabotegravir 200 mg/mL (400 mg/2 mL or 600 mg/3 mL) prolonged-release suspension for injection and rilpivirine 300 mg/mL (600 mg/2 mL or 900 mg/3 mL) prolonged-release suspension for injection.

List of excipients with known effect

None

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Cabotegravir prolonged-release suspension for injection is a white to light pink suspension.

Rilpivirine prolonged-release suspension for injection is a white to off-white suspension.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CABENUVA (cabotegravir prolonged-release suspension for injection and rilpivirine prolonged-release suspension for injection) is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies per mL) and have no known or suspected resistance to either cabotegravir or rilpivirine (see section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

4.2 DOSE AND METHOD OF ADMINISTRATION

CABENUVA should be prescribed by a physician experienced in the management of HIV infection.

Dosing for CABENUVA consists of 3 distinct phases: An oral lead-in with cabotegravir (VOCABRIA) and rilpivirine (EDURANT) tablets taken together, initiation injections of CABENUVA, and continuation injections with CABENUVA.

Prior to starting VOCABRIA tablets, healthcare professionals should carefully select 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.

Adults

The healthcare provider and patient may proceed directly to cabotegravir and rilpvirine prolonged-release suspension injections, CABENUVA. Alternatively, cabotegravir and rilpvirine oral tablets may be used as an oral lead-in prior to the initiation of CABENUVA injections to assess tolerability to cabotegravir and rilpvirine (see Table 1).

Oral lead-in dosing

When used for oral lead-in cabotegravir (VOCABRIA) 30 mg tablet and one rilpivirine (EDURANT) 25 mg tablet, co-administered once daily, should be used for approximately 1 month (at least 28 days) prior to the initiation of CABENUVA, to assess the tolerability of cabotegravir and rilpivirine. See Table 1 for recommended oral dosing.

Table 1: Oral lead-in dosing schedule in adults

	ORAL LEAD-IN
Drug	**For 1 month (at least 28 days), followed by the Initiation Injection**
Cabotegravir	30 mg once daily
Rilpivirine	25 mg once daily

[a] see Table 2 for monthly injection dosing schedule and Table 3 for every 2 month dosing schedule.

Monthly Dosing

Initiation injection (3 mL dosing)

Initiate injections on the final day of prior antiretroviral therapy or oral lead in therapy (see Table 1). The recommended initial injection doses of CABENUVA in adults are a single 3 mL (600 mg) intramuscular (IM) injection of cabotegravir and a single 3 mL (900 mg) IM injection of rilpivirine.

Continuation injection (2 mL dosing)

One month following the initiation injections, the recommended continuation injection doses of CABENUVA in adults are a single 2 mL (400 mg) IM injection of cabotegravir and a single 2 mL (600 mg) IM injection of rilpivirine, administered monthly (see Table 2).

Patients may be given CABENUVA up to 7 days before or after the date of the scheduled monthly 2 mL injection dosing visit (see Table 4).

Table 2: Recommended monthly dosing schedule in adult patients

	IM INITIATION INJECTION	IM CONTINUATION INJECTION
Medicinal product	**Direct to injection: month 1 or Following oral lead-in: month 2**	**One month after initiation injection and monthly onwards**
Cabotegravir	3 mL (600 mg)	2 mL (400 mg)
Rilpivirine	3 mL (900 mg)	2 mL (600 mg)

IM = Intramuscular Injection

[a] See full prescribing information for VOCABRIA (cabotegravir) and EDURANT (rilpivirine) for recommended oral dosing

Every 2 Month Dosing

Initiation injection (3 mL dosing)

Initiate injections on the final day of prior antiretroviral therapy or oral lead in therapy (see Table 2). The recommended initial injection doses of CABENUVA in adults are a single 3 mL (600 mg) IM injection of cabotegravir and a single 3 mL (900 mg) IM injection of rilpivirine. One month later, a second 3 mL (600 mg) IM injection of cabotegravir and 3 mL (900 mg) IM injection of rilpivirine should be administered. Patients may be given the second initiation doses up to 7 days before or after the scheduled dosing date.

Continuation Injection

After the second initiation injections the recommended continuation injection doses of CABENUVA in adults are a single 3 mL (600 mg) IM injection of cabotegravir and a single 3 mL (900 mg) IM injection of rilpivirine administered every 2 months. Patients may be given injections up to 7 days before or after the date of the every 2 month, 3 mL dosing schedule.

Table 3: Recommended every 2 month dosing schedule in adult patients

	IM INITIATION INJECTION	CONTINUATION INJECTIONS
Medicinal product	**Direct to injection: months 1 and 2 or Following oral lead-in: months 2 and 3**	**Two months after final initiation injection and every 2 months onwards**
Cabotegravir	3 mL (600 mg)	3 mL (600 mg)
Rilpivirine	3 mL (900 mg)	3 mL (900 mg)

IM = Intramuscular Injection

[a] See full prescribing information for VOCABRIA (cabotegravir) and EDURANT (rilpivirine) for recommended oral dosing

In the clinical trial (ATLAS 2M), a higher rate of confirmed virological failure (CVF, two consecutive plasma HIV-1 RNA ≥200 copies per mL) was seen with the 2 monthly injection

schedule (8/522, 1.5%) as compared to the 1 monthly schedule (2/523, 0.4%) (see Section 5.1 PHARMACODYNAMIC PROPERTIES**,** Resistance In Vivo**)**.

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) IM injection of cabotegravir and a single 3 mL (900 mg) IM injection of rilpivirine one month after the last 2 mL (400 mg) cabotegravir and 2 mL (600 mg) rilpivirine continuation injection doses and then 3 mL (600 mg) of cabotegravir and 3 mL (900 mg) of rilpivirine every 2 months thereafter.

Dosing recommendations when switching from every 2 month to monthly injections

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

Missed doses

Adherence to the injection dosing schedule is strongly recommended, to help maintain viral suppression, reduce the risk of viral rebound and potential development of resistance with missed doses. 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 injections

If a deviation of more than 7 days from a scheduled injection visit cannot be avoided, oral therapy (one cabotegravir 30 mg tablet (VOCABRIA) and one rilpivirine 25 mg tablet (EDURANT) once daily) may be used 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 approximately one month (+/- 7 days) after the last injection dose of CABENUVA. Injection dosing should be resumed on the day oral dosing completes, as recommended in Table 4.

Table 4: CABENUVA 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 injection dosing schedule as soon as possible
>2 months:	Re-initiate the patient on the 3 mL dose, and then continue to follow the monthly 2 mL injection dosing schedule.

Missed 2 month injection

If a deviation of more than 7 days from a scheduled injection visit cannot be avoided, oral therapy (one cabotegravir 30 mg tablet (VOCABRIA) and one rilpivirine 25 mg tablet (EDURANT) once daily) may be used 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 approximately two months (+/- 7 days) after the last injection dose of CABENUVA. Injection dosing should be resumed on the day oral dosing completes, as recommended in Table 5.

Table 5: CABENUVA 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) of cabotegravir and 3 mL (900 mg) of rilpivirine injection doses as soon as possible and continue with 2 month injection dosing schedule.
	>2 months	Re-initiate the patient on 3 mL (600 mg) of cabotegravir and 3 mL (900 mg) of rilpivirine injection doses, followed by a second 3 mL (600 mg) cabotegravir and 3 mL (900 mg) rilpivirine initiation injections one month later. Then follow the every 2 month injection dosing schedule.
Injection 3 or later	**≤3 months**	Resume with 3 mL (600 mg) of cabotegravir and 3 mL (900 mg) of rilpivirine injection doses as soon as possible and continue with 2 month injection dosing schedule.
	>3 months	Re-initiate the patient on 3 mL (600 mg) of cabotegravir and 3 mL (900 mg) of rilpivirine injection doses, followed by a second 3 mL (600 mg) cabotegravir and 3 mL (900 mg) rilpivirine initiation injections one month later. Then follow the every 2 month injection dosing schedule.

Elderly

No dose adjustment is required in elderly patients. There are limited data available on the use of cabotegravir in patients aged 65 years and over (see section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations).

Renal impairment

No dosage adjustment of CABENUVA is required for patients with mild to moderate renal impairment (CrCl ≥ 30 to < 90 mL/min). CABENUVA has not been studied in patients with severe renal impairment or end stage renal disease (CrCl <30 mL/min) or in patients on dialysis; increased monitoring for adverse events is recommended (see section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations).

Hepatic impairment

No dosage adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh score A or B). CABENUVA has not been studied in patients with severe hepatic impairment (Child-Pugh score C) (see section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations).

Paediatric and adolescent population
The safety and efficacy of CABENUVA in children and adolescents aged under 18 years has not been established.

Method of Administration
CABENUVA should be administered by a healthcare professional. Prior to administration, vials should be brought to room temperature (not to exceed 25°C).

For gluteal intramuscular (IM) injection use only. Do not inject intravenously.

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

A complete dose requires two (2) injections: one injection of cabotegravir and one injection of rilpivirine. Refer to the Instructions for Use for complete administration instructions with illustrations.

Cabenuva is for single use in one patient only.

When administering CABENUVA, healthcare professionals should take into consideration the Body Mass Index (BMI) of the patient to ensure that the needle length is sufficient to reach the gluteus muscle. The 1.5 inch length needle provided in the pack may not be sufficient for patients with high BMI. Longer needle lengths (not included in the dosing kit) may be required for patients with higher BMI (example: greater than 30 kg/m2).

4.3 CONTRAINDICATIONS

CABENUVA is contraindicated in patients with known hypersensitivity to cabotegravir or rilpivirine or to any of the excipients listed in section 6.1.

CABENUVA is contraindicated in combination with the following (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS):

- anticonvulsants: phenytoin, phenobarbital carbamazepine and oxcarbazepine
- antimycobacterials: rifabutin, rifampicin, rifapentine
- glucocorticoids: systemic dexamethasone (except as a single dose treatment)
- St John’s wort (*Hypericum perforatum*).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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

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 CABENUVA and other suspected medicinal products immediately, should signs or symptoms of hypersensitivity develop (including, but not limited to, severe rash, or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia or angioedema). Clinical status, including liver aminotransferases should be monitored and appropriate therapy initiated (see section 4.2 DOSAGE AND METHOD OF ADMINISTRATION, 4.3 CONTRAINDICATIONS, prolonged-release properties of CABENUVA below and 5.1 PHARMACODYNAMIC PROPERTIES).

Post-injection reactions

In clinical trials, serious post-injection reactions were reported within minutes after the injection of rilpivirine. These events included symptoms such as dyspnea, bronchospasm, agitation, abdominal cramping, rash/urticaria, dizziness, flushing, sweating, oral numbness, changes in blood pressure and pain (e.g. back and chest). These events were uncommon and began to resolve after the injection and some of the patients received supportive care. These events may have been associated with accidental intravenous administration during the intramuscular injection procedure.

Carefully follow the Instructions for Use when preparing and administering CABENUVA. Prior to administration the CABENUVA vial should be brought to room temperature. The suspension should be injected slowly, and care should be taken to avoid accidental intravenous administration. Observe patients briefly (approximately 10 minutes) after injection. If a patient experiences a post-injection reaction, monitor and treat as clinically indicated.

Hepatotoxicity

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

Monitoring of liver chemistries is recommended and treatment with CABENUVA should be discontinued if hepatotoxicity is suspected (see Prolonged-release properties of CABENUVA).

Prolonged-release properties of CABENUVA

Residual subtherapeutic concentrations of cabotegravir and rilpivirine may persist in the systemic circulation of patients for prolonged periods (up to 12 months or longer) following discontinuation of CABENUVA treatment. These pose no pharmacokinetic (PK) related limitations to alternative antiretroviral treatment (ART) selection. The prolonged-release characteristics of CABENUVA should be taken into consideration when the medicinal product is discontinued (see sections 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, 4.6 FERTILITY, PREGNANCY AND LACTATION, 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES and 4.9 OVERDOSE).

Interactions with medicinal products
Caution should be given to prescribing CABENUVA with other medicinal products that may result in known or potentially significant drug interactions (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Opportunistic infections
Patients receiving CABENUVA 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.

Use in hepatic impairment
See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations.

Use in renal impairment
See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations.

Use in the elderly
See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 PHARMACOKINETIC PROPERTIES, Special patient populations.

Paediatric use
The safety and efficacy of CABENUVA in children and adolescents aged under 18 years has not been established. No data is available.

Effects on laboratory tests
Small, non-progressive increases in total bilirubin (without clinical jaundice) were observed with treatment with CABENUVA. 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 CABENUVA during the clinical studies. 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 cabotegravir + rilpivirine; Grade 3 and 4 lipase increases occurred at a higher incidence with cabotegravir + 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 plus rilpivirine treatment.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Because CABENUVA is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended (see Section 4.1 INDICATIONS). There are no limitations on the use of other antiretroviral medications after discontinuing CABENUVA.

Effect of other medicinal products on the pharmacokinetics of cabotegravir and rilpivirine

Cabotegravir

Cabotegravir is primarily metabolised by uridine diphosphate glucuronosyl transferase (UGT) 1A1 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 section 4.3 CONTRAINDICATIONS).

Simulations using physiologically based pharmacokinetic (PBPK) modelling show that no clinically significant interaction is expected following co-administration of cabotegravir with medicines that inhibit UGT enzymes.

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

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

Rilpivirine

Rilpivirine is primarily metabolised by cytochrome P450 (CYP)3A, and medicinal products that induce or inhibit CYP3A may thus affect the clearance of rilpivirine (see Section 5.2 PHARMACOKINETIC PROPERTIES). Co-administration of rilpivirine and medicinal products that induce CYP3A may result in decreased plasma concentrations of rilpivirine which could potentially reduce the therapeutic effect of rilpivirine. Co-administration of rilpivirine and medicinal products that inhibit CYP3A may result in increased plasma concentrations of rilpivirine.

Effect of cabotegravir and rilpivirine on the pharmacokinetics of other medicinal products

Cabotegravir

In vivo, cabotegravir did not have an effect on midazolam, a cytochrome P450 (CYP) 3A4 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, BCRP, Bile salt export pump (BSEP), OCT1, OCT2, OATP1B1, OATP1B3, multidrug and toxin extrusion transporter (MATE) 1, MATE 2-K, multidrug resistance protein (MRP) 2 or MRP4.

Cabotegravir inhibited the organic anion transporters (OAT) 1 (IC_{50}=0.81 µM) and OAT3 (IC_{50}=0.41 µM) *in vitro*, however, based on 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 medicinal products 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 or ibalizumab.

Rilpivirine

Rilpivirine is not likely to have a clinically relevant effect on the exposure of medicinal products metabolised by CYP enzymes.

No drug interaction studies have been performed with cabotegravir or rilpivirine when administered as an IM injection. The drug interaction data provided in Table 6 is obtained from studies with oral cabotegravir and drug interaction data provided in Table 7 is obtained from studies with oral rilpivirine.

Table 6: Drug Interactions for cabotegravir

Medicinal products by therapeutic areas	**Interaction Geometric mean change (%)**	**Recommendations concerning co-administration**
HIV-1 Antiviral medicinal products		
Non-nucleoside Reverse Transcriptase Inhibitor: Etravirine	Cabotegravir ↔ AUC ↑ 1% C_{max} ↑ 4% C_T ↔ 0%	Etravirine did not significantly change cabotegravir plasma concentration. No dose adjustment of CABENUVA is necessary when co-administered with etravirine.
Anticonvulsants		
Carbamazepine Oxcarbazepine Phenytoin Phenobarbital	Cabotegravir ↓	Metabolic inducers may significantly decrease cabotegravir plasma concentration. Concomitant use is contraindicated (see Section 4.3 CONTRAINDICATIONS).
Antimycobacterials		

Medicinal products by therapeutic areas	Interaction Geometric mean change (%)	Recommendations concerning co-administration
Rifampicin	Cabotegravir ↓ AUC ↓ 59% C_{max} ↓ 6%	Rifampicin significantly decreased cabotegravir plasma concentration which is likely to result in loss of therapeutic effect. Dosing recommendations for co-administration of CABENUVA with rifampicin have not been established and co-administration of CABENUVA with rifampicin is contraindicated (see Section 4.3 CONTRAINDICATIONS).
Rifapentine	Cabotegravir ↓	Rifapentine may significantly decrease cabotegravir plasma concentrations. Concomitant use is contraindicated.
Rifabutin	Cabotegravir ↓ AUC ↓ 21% C_{max} ↓ 17% C_T ↓ 8%	Rifabutin may decrease cabotegravir injection plasma concentration. Concomitant use should be avoided.
Oral contraceptives		
Ethinyl estradiol (EE) and Levonorgestrel (LNG)	EE ↔ AUC ↑ 2% C_{max} ↓ 8% C_T ↔ 0% LNG ↔	Cabotegravir did not significantly change ethinyl estradiol and levonorgestrel plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with CABENUVA.

Abbreviations: ↑ = increase; ↓ = decrease; ↔ = no change ; AUC = area under the concentration versus time curve ; C_{max} = maximum observed concentration; C_T = concentration at end of dosing interval.

Table 7: Drug Interactions for rilpivirine

Medicinal products by therapeutic areas	Interaction Geometric mean change (%)	Recommendations concerning co-administration
HIV-1 Antiviral medicinal products		
Ribavirin	Not studied. No clinically relevant drug-drug interaction is expected.	No dose adjustment is required.
Anticonvulsants		
Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	Not studied. Significant decreases in rilpivirine plasma concentrations are expected. (induction of CYP3A enzymes)	Rilpivirine must not be used in combination with these anticonvulsants as co-administration may result in loss of therapeutic effect of rilpivirine (see Section 4.3 CONTRAINDICATIONS).
Azole antifungal agents		
Ketoconazole 400 mg once daily	ketoconazole AUC ↓ 24% ketoconazole C_{min} ↓ 66% ketoconazole C_{max} ↔ (induction of CYP3A due to high rilpivirine dose in the study) rilpivirine AUC ↑ 49% rilpivirine C_{min} ↑ 76% rilpivirine C_{max} ↑ 30% (inhibition of CYP3A enzymes)	No dose adjustment is required.

Medicinal products by therapeutic areas	Interaction Geometric mean change (%)	Recommendations concerning co-administration
Fluconazole Itraconazole Posaconazole Voriconazole	Not studied. Concomitant use of rilpivirine with azole antifungal agents may cause an increase in the plasma concentrations of rilpivirine. (inhibition of CYP3A enzymes)	No dose adjustment is required.
Antimycobacterials		
Rifabutin*# 300 mg once daily	rifabutin AUC ↔ rifabutin C_{min} ↔ rifabutin C_{max} ↔ 25-*O*-desacetyl-rifabutin AUC ↔ 25-*O*-desacetyl-rifabutin C_{min} ↔ 25-*O*-desacetyl-rifabutin C_{max} ↔	Rilpivirine must not be used in combination with rifabutin as specific dosing recommendations have not been established. Co-administration is likely to result in loss of therapeutic effect of rilpivirine (see Section 4.3 CONTRAINDICATIONS).
300 mg once daily (+ 25 mg once daily rilpivirine)	rilpivirine AUC ↓ 42% rilpivirine C_{min} ↓ 48% rilpivirine C_{max} ↓ 31%	
300 mg once daily (+ 50 mg once daily rilpivirine)	rilpivirine AUC ↑ 16%£ rilpivirine C_{min} ↔£ rilpivirine C_{max} ↑ 43%£ £ compared to 25 mg once daily rilpivirine alone (induction of CYP3A enzymes)	
Rifampicin 600 mg once daily	rifampicin AUC ↔ rifampicin C_{min} NA rifampicin C_{max} ↔ 25-desacetyl-rifampicin AUC ↓ 9% 25-desacetyl-rifampicin C_{min} NA 25-desacetyl-rifampicin C_{max} ↔ rilpivirine AUC ↓ 80% rilpivirine C_{min} ↓ 89% rilpivirine C_{max} ↓ 69% (induction of CYP3A enzymes)	Rilpivirine must not be used in combination with rifampicin as co-administration is likely to result in loss of therapeutic effect of rilpivirine (see Section 4.3 CONTRAINDICATIONS).
Rifapentine	Not studied. Significant decreases in rilpivirine plasma concentrations are expected. (induction of CYP3A enzymes)	Rilpivirine must not be used in combination with rifapentine as co-administration is likely to result in loss of therapeutic effect of rilpivirine (see Section 4.3 CONTRAINDICATIONS).
Macrolide antibiotics		
Clarithromycin Erythromycin	Not studied. Increased exposure of rilpivirine is expected. (inhibition of CYP3A enzymes)	Where possible, alternatives such as azithromycin should be considered.

Medicinal products by therapeutic areas	**Interaction Geometric mean change (%)**	**Recommendations concerning co-administration**
Glucocorticoids or corticosteroids		
Dexamethasone (systemic, except for single dose use)	Not studied. Dose dependent decreases in rilpivirine plasma concentrations are expected. (induction of CYP3A enzymes)	Rilpivirine should not be used in combination with systemic dexamethasone (except as a single dose) as co-administration may result in loss of therapeutic effect of rilpivirine (see Section 4.3 CONTRAINDICATIONS). Alternatives should be considered, particularly for long-term use.
Narcotic analgesics		
Methadone 60-100 mg once daily, individualised dose	R(-) methadone AUC ↓ 16% R(-) methadone C_{min} ↓ 22% R(-) methadone C_{max} ↓ 14% rilpivirine AUC ↔[£] rilpivirine C_{min} ↔[£] rilpivirine C_{max} ↔[£] [£] based on historic controls	No dose adjustments are required when initiating co-administration of methadone. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.
Antiarrhythmics		
Digoxin*	digoxin AUC ↔ digoxin C_{min} NA digoxin C_{max} ↔	No dose adjustment is required.
Antidiabetics		
Metformin	metformin AUC ↔ metformin C_{min} NA metformin C_{max} ↔	No dose adjustment is required.
Herbal products		
St John's wort *(Hypericum perforatum)*	Not studied. Significant decreases in rilpivirine plasma concentrations are expected. (induction of CYP3A enzymes)	Rilpivirine must not be used in combination with products containing St John's wort as co-administration may result in loss of therapeutic effect of rilpivirine (see Section 4.3 CONTRAINDICATIONS).
Analgesics		
Paracetamol 500 mg single dose	paracetamol AUC ↔ paracetamol C_{min} NA paracetamol C_{max} ↔ rilpivirine AUC ↔ rilpivirine C_{min} ↑ 26% rilpivirine C_{max} ↔	No dose adjustment is required.

Medicinal products by therapeutic areas	Interaction Geometric mean change (%)	Recommendations concerning co-administration
Oral contraceptives		
Ethinylestradiol* 0.035 mg once daily Norethindrone 1 mg once daily	ethinylestradiol AUC ↔ ethinylestradiol C_{min} ↔ ethinylestradiol C_{max} ↑ 17% norethindrone AUC ↔ norethindrone C_{min} ↔ norethindrone C_{max} ↔ rilpivirine AUC ↔£ rilpivirine C_{min} ↔£ rilpivirine C_{max} ↔£ £ based on historic controls	No dose adjustment is required.
HMG Co-A reductase inhibitors		
Atorvastatin 40 mg once daily	atorvastatin AUC ↔ atorvastatin C_{min} ↓ 15% atorvastatin C_{max} ↑ 35% rilpivirine AUC ↔ rilpivirine C_{min} ↔ rilpivirine C_{max} ↓ 9%	No dose adjustment is required.
Fluvastatin Lovastatin Pitavastatin Pravastatin Rosuvastatin Simvastatin	Not studied.	No dose adjustment is required.
Phosphodiesterase type 5 (PDE-5) inhibitors		
Sildenafil*# 50 mg single dose	sildenafil AUC ↔ sildenafil C_{min} NA sildenafil C_{max} ↔ rilpivirine AUC ↔ rilpivirine C_{min} ↔ rilpivirine C_{max} ↔	No dose adjustment is required.
Vardenafil Tadalafil	Not studied.	No dose adjustment is required.

* The interaction between rilpivirine and the medicinal product was evaluated in a clinical study. All other drug-drug interactions shown are predicted.

\# This interaction study has been performed with a dose higher than the recommended dose for rilpivirine assessing the maximal effect on the co-administered medicinal product. The dosing recommendation is applicable to the recommended dose of rilpivirine of 25 mg once daily.

QT prolonging drugs

There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and medicinal products that prolong the QTc interval of the electrocardiogram. In a study of healthy subjects, supratherapeutic doses of oral rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the electrocardiogram. Plasma rilpivirine concentrations after rilpivirine injections are comparable to those achieved with oral rilpivirine at a dose of 25 mg once daily (see section 5.1 PHARMACODYNAMIC PROPERTIES). Rilpivirine should be used with caution when co-administered with a medicinal product with a known risk of Torsade de Pointes.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Cabotegravir

There are no data on the effects of cabotegravir on human male or female fertility. Animal studies indicate no effects of cabotegravir on male or female fertility.

Cabotegravir when administered orally to male and female rats at 1,000 mg/kg/day (>30 times the exposure in humans at the Maximum Recommended Human Dose [MHRD] of 30 mg oral or 400 mg intramuscular (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 1,000 mg/kg/day.

Rilpivirine

There are no data on the effect of rilpivirine on human male or female fertility.

In a study conducted in rats, there were no effects on mating or fertility with oral rilpivirine up to 400 mg/kg/day.

Use in pregnancy
(Pregnancy Category B1)

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

CABENUVA should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

Cabotegravir and rilpivirine have been detected in systemic circulation for up to 12 months or longer after an injection, therefore, consideration should be given to the potential for fetal exposure during pregnancy (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Lower exposures of oral rilpivirine were observed during pregnancy, therefore viral load should be monitored closely.

Cabotegravir crossed the placenta in pregnant rats and could be detected in fetal tissues. Cabotegravir was not teratogenic in rats at oral 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) but caused a delay in delivery that was associated with reduced survival and viability of rat offspring; there was no effect on survival when fetuses were delivered by caesarean section. Exposures at the NOAEL were at least 11 times the exposure in humans at the MRHD of 30 mg oral or 400 mg IM dose. The relevance to human pregnancy is unknown

Studies in animals have shown no evidence of relevant embryonic or fetal toxicity or an effect on reproductive function with rilpivirine. There was no teratogenicity with oral rilpivirine in rats and rabbits. The exposures at the embryo-fetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectively 15 and 70 times higher than the exposure in humans at the recommended dose of 25 mg once daily.

To monitor maternal-fetal outcomes of pregnant women, an Antiretroviral Pregnancy Registry has been established (http://www.apregistry.com) for rilpivirine and cabotegravir.

This is a voluntary prospective, exposure-registration, observational study designed to collect and evaluate data on the outcomes of pregnancy exposures to antiretroviral products. For rilpivirine, sufficient first trimester exposures are available to allow detection of at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date.

Use in lactation
Health experts recommend that where possible HIV 1 infected women should not breastfeed their infants in order to avoid transmission of HIV-1. 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 and rilpivirine will be secreted into human milk based on animal data, although this has not been confirmed in humans. Cabotegravir and rilpivirine may be present in human milk for up to 12 months or longer after the last cabotegravir or rilpivirine injection.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial data
The safety assessment of CABENUVA given monthly in HIV-1-infected, virologically suppressed patients is based on pooled primary Week 48 analyses of data from two international, multicenter open-label studies: FLAIR and ATLAS.

In FLAIR and ATLAS, a total of 1,182 HIV-1 infected patients were randomized to receive either a cabotegravir plus rilpivirine regimen or remain on their baseline antiretroviral regimen. Patients randomized to receive the cabotegravir plus rilpivirine regimen, initiated treatment with daily oral lead-in dosing with one 30 mg cabotegravir tablet (VOCABRIA) plus one 25 mg rilpivirine tablet (EDURANT) for at least 4 weeks followed by treatment with cabotegravir injection plus rilpivirine injection for at least an additional 44 weeks.

The safety assessment of CABENUVA given every 2 months, is based on Week 48 analyses of data from one Phase IIIb international, multicentre open-label study, ATLAS-2M.

In ATLAS-2M, 1045 HIV-1 infected, ART experienced, virologically suppressed subjects were randomised 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 (VOCABRIA) plus one rilpivirine 25 mg tablet (EDURANT), daily, for at least 4 weeks. Subjects randomised to monthly cabotegravir injections and rilpivirine injections received treatment for an additional 44

weeks. Subjects randomised to every 2 month cabotegravir injections and rilpivirine injections for an additional 44 weeks.

Adverse events

For many of the adverse events listed in Table 8, it is unclear whether they are related to the active substance, the wide range of other medicinal products used in the management of HIV infection, or whether they are a result of the underlying disease process

The most common adverse events reported in greater than 10% of subjects in the group that received CABENUVA in the FLAIR and ATLAS studies were injection site pain, nasopharyngitis, upper respiratory tract infection, headache, diarrhoea, injection site nodule and injection site induration.

Table 8: Summary of adverse events reported in ≥3% of subjects in any treatment group by overall frequency in ATLAS and FLAIR (Week 48 pooled analysis)

Preferred Term	Cabotegravir plus rilpivirine N=591 n(%)	Current antiretroviral therapy N=591 n(%)
Infections and Infestations		
Nasopharyngitis	108 (18%)	90 (15%
Upper respiratory tract infection	70 (12%	53 (9%)
Influenza	42 (7%)	34 (6%)
Respiratory tract infection, viral	24 (4%)	29 (5%)
Pharyngitis	23 (4%)	21 (4%)
Gastroenteritis	20 (3%)	21 (4%)
Gastrointestinal disorders		
Diarrhoea	54 (9%)	40 (7%)
Nausea	30 (5%)	16 (3%)
Haemorrhoids	20 (3%)	5 (<1%)
Nervous system disorders		
Headache	73 (12%)	38 (6%)
Dizziness	24 (4%)	8 (1%)
Musculoskeletal and connective		
Back pain	43 (7%)	23 (4%)
General disorders and administration site conditions		
Injection site pain	458 (77%)	-
Injection site nodule	81 (14%	-
Injection site induration	68 (12%)	-
Injection site swelling	46 (8%)	-
Pyrexia	43 (7%)	13 (2%)
Injection site pruritis	23 (4%)	-
Fatigue	29 (5%)	14 (2%)
Respiratory, thoracic and mediastinal disorders		
Cough	26 (4%)	26 (4%)
Metabolism and nutrition disorders		

Preferred Term	Cabotegravir plus rilpivirine N=591 n(%)	Current antiretroviral therapy N=591 n(%)
Vitamin D deficiency	31 (5%)	25 (4%)

Adverse events leading to discontinuation and occurring in more than 1 subject were injection site reactions, hepatitis A, acute hepatitis B, headache, and diarrhea which occurred with an incidence of ≤1%. The incidence of serious adverse events was 5% in subjects receiving CABENUVA and 4% for subjects remaining on current antiretroviral therapy.

Adverse drug reactions

ADRs are adverse events that are considered to be reasonably associated with the use of a drug based on the comprehensive assessment of the available adverse event information. A causal relationship cannot be reliably established in individual cases.

Adverse drug reactions for CABENUVA were identified from pivotal Phase III clinical studies (FLAIR and ATLAS) based on an analysis of pooled data (N=591) and ATLAS-2M at Week 48.

CABENUVA was administered as a combination regimen of cabotegravir and rilpivirine (monthly and every 2 month dosing) and associated adverse drug reactions are listed in Table 9.

Adverse drug reactions 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 9.

The most frequently reported adverse drug reactions from monthly dosing studies were injection site reactions (up to 84%), headache (up to 12%) and pyrexia[4] (10%).

The most frequently reported adverse drug reactions from ATLAS-2M every 2 month dosing were injection site reactions (76%), headache (7%) and pyrexia[4] (7%).

The adverse reactions considered at least possibly related to cabotegravir are listed in Table 7 by body system, organ, class and frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), including isolated reports.

Table 9: Tabulated summary of adverse drug reactions

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

[1] Abdominal pain includes the following grouped MedDRA preferred term: 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] Injection site reactions listed in the table have been reported in 2 subjects or more.

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

The overall safety profile at Week 96 and Week 124 in the FLAIR study was consistent with that observed at Week 48, with no new safety findings identified. In the extension phase of the FLAIR study, initiating the CAB prolonged-release suspension for injection plus RPV prolonged-release suspension for injection regimen with Direct to Injection did not identify any new safety concerns related to omitting the Oral Lead-in phase (see section 5.1 PHARMACODYNAMIC PROPERTIES).

Description of selected adverse reactions

Local injection site reactions

In each of the three Phase III studies, approximately ≤1% of subjects discontinued treatment with CABENUVA 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 the FLAIR and ATLAS studies, who received CABENUVA gained a median of 1.5 kg in weight; those in the current antiretroviral therapy (CAR) group gained a median of 1.0 kg (pooled analysis). In the individual FLAIR and ATLAS studies, the median weight gains in the CABENUVA group were 1.3 kg and 1.8 kg respectively, compared to 1.5 kg and 0.3 kg in the CAR group. At the 48 week timepoint, in ATLAS-2M the median weight gain in both the monthly and 2-monthly CABENUVA group was 1.0 kg.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is currently no experience with overdosage of CABENUVA.

There is no specific treatment for overdose with CABENUVA. 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 and rilpivirine are known to be highly protein bound in plasma; therefore, dialysis is unlikely to be helpful in removal of cabotegravir or rilpivirine from the body. Management of overdose with CABENUVA should take into consideration the prolonged

exposure to the medicine following an injection (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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.

Rilpivirine is a diarylpyrimidine non-nucleoside reverse transcriptase inhibitor (NNRTI) of HIV-1. Rilpivirine activity is mediated by non-competitive inhibition of HIV-1 reverse transcriptase (RT). Rilpivirine does not inhibit the human cellular DNA polymerases α, β and γ.

Pharmacodynamic effects

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

Rilpivirine exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median EC_{50} value for HIV-1/IIIB of 0.73 nM (0.27 ng per mL). Although rilpivirine demonstrated limited *in vitro* activity against HIV-2 with EC_{50} values ranging from 2,510 to 10,830 nM (920 to 3970 ng per mL), treatment of HIV-2 infection with rilpivirine is not recommended in the absence of clinical data.

Rilpivirine also demonstrated antiviral activity against a broad panel of HIV-1 group M (subtype A, B, C, D, F, G, H) primary isolates with EC_{50} values ranging from 0.07 to 1.01 nM (0.03 to 0.37 ng/mL) and group O primary isolates with EC_{50} values ranging from 2.88 to 8.45 nM (1.06 to 3.10 ng/mL).

Antiviral Activity in combination with other medicinal products
In *in vitro* combination studies, cabotegravir had weak synergistic antiviral effects with nucleoside reverse transcriptase inhibitors (lamivudine, tenofovir disoproxil fumarate, emtricitabine) and additive effects with the non-nucleoside reverse transcriptase inhibitor, rilpivirine.

Rilpivirine showed additive antiviral activity in combination with the N(t)RTIs: abacavir, didanosine, emtricitabine, stavudine and tenofovir.; the protease inhibitors (PIs): amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir; the NNRTIs: efavirenz, etravirine and nevirapine; the fusion inhibitor enfuvirtide; and the entry inhibitor maraviroc. Rilpivirine showed additive to synergistic antiviral activity in combination with the NRTIs lamivudine and zidovudine, and the integrase inhibitor raltegravir.

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 EC_{50} were not observed during the 112-day passage of strain IIIB. The following integrase (IN) mutations emerged after passaging wild type HIV-1 (with T124A polymorphism) in the presence of cabotegravir: Q146L (fold-change range 1.3-4.6), S153Y (fold-change range 2.8-8.4), and I162M (fold-change = 2.8). As noted above, the detection of T124A is selection of a pre-existing minority variant that does not have differential susceptibility to cabotegravir. 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 known integrase resistant mutants tested, mild resistance (≥ 5-fold but <10-fold resistance) was seen with E92Q/N155H, G118R, G140S/Q148H, Y143H/N155H, Q148K, Q148R, T66K/L74M and G140S/Q148K. High resistance (≥10-fold resistance) was seen with E138K/Q148K, V72I/E138K/Q148K, E138K/Q148R, E138K/G140S/Q148R, L74M/V75A/G140S/Q148H, G140C/Q148R, Q148R/N155H and G140S/Q148R.

Taking into consideration all of the available *in vitro* and *in vivo* data generated with oral rilpivirine in previously untreated patients, the following amino acid substitutions, when present at baseline, may affect the activity of rilpivirine: K101E, K101P, E138A, E138G, E138K, E138Q, E138R, V179L, Y181C, Y181I, Y181V, Y188L, H221Y, F227C, M230I, and M230L, and the combination of L100I and K103N.

Cross-resistance: In a panel of 67 HIV-1 recombinant laboratory strains, with one amino acid substitution at RT positions associated with NNRTI resistance, including the most commonly found K103N and Y181C, rilpivirine showed antiviral activity against 64 (96%) of these strains. The single amino acid substitutions associated with a loss of susceptibility to rilpivirine were: K101P, Y181I and Y181V. The K103N substitution did not result in reduced susceptibility to rilpivirine by itself, but the combination of K103N and L100I resulted in a 7-fold reduced susceptibility to rilpivirine.

Rilpivirine retained sensitivity (FC ≤ BCO) against 62% of 4786 HIV-1 recombinant clinical isolates resistant to efavirenz and/or nevirapine.

Resistance in vivo

The number of subjects who met CVF criteria was low across the pooled FLAIR and ATLAS studies. 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 3 CVFs on

cabotegravir plus rilpivirine in 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 of the 3 CVFs had treatment-emergent integrase inhibitor resistance associated substitution Q148R while 1 of the 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 of the 3 showed reduced phenotypic susceptibility to rilpivirine. The 3 CVFs in 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 of the 3 CVFs carried the INI resistance-associated substitution N155H at SVF. All 3 CVFs had treatment-emergent rilpivirine resistance-associated substitution: E138A, E138E/K or E138K, and showed reduced phenotypic susceptibility to rilpivirine while 1 of the 3 also showed reduced phenotypic susceptibility to cabotegravir. In 2 of these 3 CVFs, the rilpivirine resistance-associated substitutions observed at failure were also observed at baseline in PBMC HIV-1 DNA. The seventh CVF (FLAIR) never received an injection.

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

In the ATLAS-2M study 10 subjects met CVF criteria through Week 48: 8 subjects (1.5%) in the every 2 month dose arm and 2 subjects (0.4%) in the monthly dose 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 every 2 month dose 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 every 2 month dose 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 clinical 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, 0.2 to 2.2 for dolutegravir and 0.8 to 1.7 for bictegravir.

In the monthly dose 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 randomised 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), and 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 post-dose.

Clinical trials

Monthly Dosing

The efficacy of CABENUVA 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)-naïve subjects received a dolutegravir integrase strand transfer inhibitor (INSTI) containing regimen for 20 weeks (either dolutegravir/abacavir/lamivudine or dolutegravir plus 2 other nucleoside reverse transcriptase inhibitors if subjects were HLA-B*5701 positive). Subjects who were virologically suppressed (HIV-1 RNA <50 copies per mL, n=566) were then randomised (1:1) to receive either the CABENUVA regimen or remain on the current antiretroviral (CAR) regimen. Subjects randomised to receive the CABENUVA regimen, initiated treatment with oral lead-in dosing with a cabotegravir 30 mg (VOCABRIA) tablet plus a rilpivirine 25 mg (EDURANT) 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 the CABENUVA regimen or remained on the CAR regimen. Subjects randomised to receive the CABENUVA regimen, initiated treatment with oral lead-in dosing with a cabotegravir 30 mg (VOCABRIA) tablet plus a rilpivirine 25 mg (EDURANT) 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 medicine class prior to randomisation and this was similar between treatment arms.

At baseline, in the pooled analysis, for the CABENUVA 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 per mL at week 48 (snapshot algorithm for the ITT-E population).

In a pooled analysis of the two pivotal studies, CABENUVA 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 CABENUVA plus rilpivirine and CAR (0.2; 95% CI: -1.4, 1.7) for the pooled analysis met the non-inferiority criterion (upper bound of the 95% CI below 4%). Furthermore, in the pooled analysis, CABENUVA was non-inferior to CAR on the proportion of subjects having plasma HIV-1 RNA < 50 copies per mL (93.1% and 94.4%, respectively) at Week 48. The adjusted treatment difference between CABENUVA 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 10]).

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

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

Table 10: Virologic Outcomes of Randomised 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, CAB = cabotegravir, RPV = rilpivirine.

Table 11: 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, baseline third agent treatment class) were comparable.

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

Week 96 FLAIR

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

Week 124 FLAIR Direct to Injection

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

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

Every 2 Month Dosing

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

In ATLAS-2M, 1045 HIV-1 infected, ART experienced, virologically suppressed subjects were randomised (1:1) and received a cabotegravir plus rilpivirine injection regimen administered either every 2 months or monthly. Subjects initially on non- cabotegravir plus rilpivirine 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) for an additional 44 weeks. Prior to randomisation, 63%, 13% and 24% of subjects received cabotegravir plus rilpivirine for 0 weeks, 1 to 24 weeks and >24 weeks, respectively.

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

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

In ATLAS-2M, cabotegravir and rilpivirine administered every 2 months was non-inferior to cabotegravir and rilpivirine administered every month on the proportion of subjects having plasma HIV-1 RNA ≥50 c/mL (1.7% and 1.0% respectively) at Week 48. The adjusted treatment difference between cabotegravir and rilpivirine administered every 2 months and every month (0.8; 95% CI: -0.6, 2.2) met the non-inferiority criterion (upper bound of the 95% CI below 4%). Furthermore, cabotegravir and rilpivirine dosed every 2 months was non-inferior to cabotegravir plus rilpivirine 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 and 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 12].

Table 12 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 13 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)

		Number of HIV-1 RNA ≥50 c/mL/ Total Assessed (%)	
		2 Month Dosing (Q8W)	**Monthly dosing (Q4W)**
	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 [See Table 13].

Post-hoc analysis:

Multivariable analyses of pooled phase 3 studies (ATLAS, FLAIR and ATLAS-2M), including data from 1039 HIV-infected adults with no prior exposure to CABENUVA, 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/m2 (associated with cabotegravir pharmacokinetics). Other variables including Q4W or Q8W dosing, female gender, or other viral subtypes (non A6/A1) had no significant association with CVF. No baseline factor, when present in isolation, was predictive of virologic failure. However, a combination of at least 2 of the following baseline factors was associated with an increased risk of CVF: rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI≥30 mg/m2 (see Table 14).

Table 14 Week 48 outcomes by presence of key baseline factors of RPV RAM, Subtype A6/A11[1], BMI ≥30 kg/m2

Baseline Factors (number)	Virologic Successes (%)[2]	Confirmed Virologic Failure (%)[3]
0	694/732 (94.8)	3/732 (0.41)
1	261/272 (96.0)	1/272 (0.37)[4]
≥2	25/35 (71.4)	9/35 (25.7)[5]
TOTAL (95% Confidence Interval)	980/1039 (94.3) (92.74%, 95.65%)	13/1039 (1.25) (0.67%, 2.13%)

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

2 Based on the FDA Snapshot algorithm of RNA <50 copies/mL.

3 Defined as two consecutive measurements of HIV RNA >200 copies/mL.
4 Positive Predictive Value (PPV) <1%; Negative Predictive Value (NPV) 98%; sensitivity 8%; specificity 74%
5 PPV 26%; NPV 99.6%; sensitivity 69%; specificity 97.5%
RAM: resistance-associated mutations

Patient reported outcomes

Patient reported outcomes were assessed by several distinct measures.

Treatment satisfaction significantly improved in the CABENUVA group compared with daily oral antiretroviral therapy (CART) group (mean difference [95% CI] in HIV Treatment Satisfaction Questionnaire (HIVTSQs) at weeks 24 and 44 was 3.9 [3.0, 4.7] ($p<0.001$) and 3.3 [2.5, 4.2] ($p<0.001$) respectively, in the pooled ATLAS and FLAIR analysis). Key items driving this difference were "satisfaction to continue with treatment" as well as "flexibility" and "convenience".

Treatment acceptance also significantly improved in the CABENUVA group compared with CART group (mean difference [95% CI] in ACCEPT General Dimension at weeks 24 and 44 was 4.9 [2.4, 7.5] ($p<0.01$) and 6.8 [4.3, 9.4]($p<0.001$) respectively, in the pooled ATLAS and FLAIR analysis). Items were assessing acceptability based on advantages and disadvantages of treatment option.

Acceptability of injection site reactions (including pain) significantly improved from Week 5 (2.09 points) to weeks 24 (1.66 points; $p<0.001$) and 48 (1.61 points; $p<0.001$) in a pooled ATLAS and FLAIR analysis for participants in the CABENUVA group according to "Acceptability of ISRs" dimension of Perception of Injection Questionnaire (PIN) (adapted from the Vaccinees' Perception of Injection (VAPI) Questionnaire) with 86% and 84% of participants in ATLAS and FLAIR finding pain following injections as "totally" or "very acceptable" at week 48.

According to the three dimensions of the HIV/AIDS Targeted Quality of Life (HAT-QoL) included in the study, "medication concerns" significantly improved in the CABENUVA group compared with cART (mean difference [95% CI] at weeks 24 and 48 was 3.4 [1.9, 4.9]($p <0.001$) and 3.5 [1.8, 5.2]($p <0.001$) respectively, in the pooled ATLAS and FLAIR analysis) mostly driven by the improvement in "treatment burden" scores. "Life satisfaction" and HIV "disclosure worries" showed no significant difference between treatment groups, indicating no impact of either treatment options on those concepts.

SF-12 mental and physical component scores showed no significant difference in change from baseline between treatment groups at weeks 24 and 48, which indicates no improvement or worsening in mental or physical health status of participants in both groups.

5.2 PHARMACOKINETIC PROPERTIES

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 prolonged-release cabotegravir injection.

Table 15. Pharmacokinetic parameters following cabotegravir orally once daily, and initiation, monthly and every 2 month continuation intramuscular injections

Dosing Phase	Dosage Regimen	Geometric Mean (5th, 95th Percentile)[a]		
		$AUC_{(0\text{-}tau)}$[b] (µg*h/mL)	C_{max} (µg/mL)	C_{tau} (µg/mL)
Oral lead-in[c]	30 mg once daily	145 (93.5, 224)	8.0 (5.3, 11.9)	4.6 (2.8, 7.5)
Initial injection[d]	600 mg IM Initial Dose	1591 (714, 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

Cabotegravir

Cabotegravir injection exhibits absorption-limited pharmacokinetics because cabotegravir is slowly absorbed into the systemic circulation from the gluteal muscle resulting in sustained plasma concentrations. Following a single intramuscular (IM) 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.

Rilpivirine

Rilpivirine injection exhibits absorption-limited (flip-flop) kinetics resulting from slow absorption from the gluteal muscle into the systemic circulation resulting in sustained plasma concentrations. Following a single intramuscular (IM) dose, plasma rilpivirine concentrations are detectable on the first day and gradually rise to reach maximum plasma concentration with a median T_{max} of 3-4 days. Rilpivirine has been detected in plasma for longer than 52 weeks after administration of a single injection. About 80% of the rilpivirine steady-state exposure is reached by 48 weeks. After that, there is limited accumulation, with pharmacokinetic steady-state reached after approximately 2 years.

Plasma rilpivirine exposure increases in proportion or slightly less than in proportion to dose following single and repeat IM injection of doses ranging from 300 to 1200 mg.

Distribution

Cabotegravir

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

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

Cabotegravir is present in cerebrospinal fluid (CSF). In HIV-infected subjects receiving a regimen of cabotegravir injection plus rilpivirine injection, the cabotegravir CSF to plasma concentration ratio [median (range)] (n=16) was 0.003 (0.002 to 0.004) one week following a steady-state prolonged-release cabotegravir (monthly does or every 2 month dose) 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.

Rilpivirine

Rilpivirine is approximately 99.7% bound to plasma proteins *in vitro*, primarily to albumin. Based on population pharmacokinetics analysis, the typical apparent volume of the central compartment (Vc/F) for rilpivirine after IM administration was estimated to be 132 L, reflecting a moderate distribution to peripheral tissues.

Rilpivirine is present in cerebrospinal fluid (CSF). In HIV-1-infected patients receiving a regimen of rilpivirine injection plus cabotegravir injection, the median rilpivirine CSF to plasma concentration ratio (n=16) was 1.07 to 1.32% (range: not quantifiable to 1.69%). Consistent with therapeutic antiretroviral concentrations in the CSF, CSF HIV-1 RNA (n=16) was <50 c/mL in 100% and <2 c/mL in 15/16 (94%) patients. At the same time point, plasma HIV-1 RNA (n=18) was <50 c/mL in 100% of patients and <2 c/mL in 12/18 (66.7%) patients.

Metabolism

Cabotegravir

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

Twenty-seven percent of the total oral dose is excreted in the urine, primarily as a glucuronide metabolite (75% of urine radioactivity, 20% of total dose).

Rilpivirine
In vitro experiments indicate that rilpivirine primarily undergoes oxidative metabolism mediated by the cytochrome P450 (CYP) 3A system.

Excretion
Cabotegravir
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 based on population pharmacokinetic analysis.

Rilpivirine
The rilpivirine apparent terminal elimination half-life after IM injection is absorption-rate limited and estimated to be 13 to 28 weeks. The apparent plasma clearance (CL/F) of rilpivirine after IM administration was 5.08 L/h. After single-dose oral administration of ^{14}C-rilpivirine, on average 85% and 6.1% of the radioactivity could be retrieved in faeces and urine, respectively. In faeces, unchanged rilpivirine accounted for on average 25% of the administered dose. Only trace amounts of unchanged rilpivirine (< 1% of dose) were detected in urine.

Polymorphisms
In a meta-analysis of healthy and HIV-infected subject trials, HIV-infected subjects with UGT1A1 genotypes conferring poor cabotegravir metabolism had a 1.2-fold mean increase in steady-state cabotegravir AUC, C_{max}, and C_{tau} following prolonged-release injection administration compared with subjects with genotypes associated with normal metabolism via UGT1A1. No dose adjustment is required in subjects with UGT1A1 polymorphisms

Special patient populations
Gender
Population pharmacokinetic analyses revealed no clinically relevant effect of gender on the exposure of cabotegravir or rilpivirine, 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 or rilpivirine, therefore no dosage adjustment is required on the basis of race.

Body Mass Index (BMI)
Population pharmacokinetic analyses revealed no clinically relevant effect of BMI on the exposure of cabotegravir or rilpivirine, 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 or rilpivirine exposure. Pharmacokinetic data for cabotegravir and rilpivirine in subjects of >65 years old are limited.

Renal impairment

Cabotegravir: 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.

Rilpivirine: The pharmacokinetics of rilpivirine have not been studied in patients with renal insufficiency. Renal elimination of rilpivirine is negligible. Therefore, the impact of renal impairment on rilpivirine elimination is expected to be minimal. As rilpivirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis.

Hepatic impairment

Cabotegravir: 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.

Rilpivirine: Rilpivirine is primarily metabolised and eliminated by the liver. In a study comparing 8 patients with mild hepatic impairment (Child-Pugh score A) to 8 matched controls, and 8 patients with moderate hepatic impairment (Child-Pugh score B) to 8 matched controls, the multiple dose exposure of rilpivirine was 47% higher in patients with mild hepatic impairment and 5% higher in patients with moderate hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of rilpivirine has not been studied.

HBV/HCV Co-infected Patients

Cabotegravir plus rilpivirine has not been studied in patients with hepatitis B co-infection. There is limited experience in patients with hepatitis C coinfection without evidence of advanced liver disease receiving cabotegravir and rilpivirine.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Cabotegravir was not mutagenic or clastogenic using *in vitro* tests in bacteria and cultured mammalian cells, and an *in vivo* rodent micronucleus assay.

Rilpivirine has tested negative in the in vitro Ames reverse mutation assay, in vitro chromosomal aberration assay in human lymphocyte and in vitro clastogenicity mouse

lymphoma assay, tested in the absence and presence of a metabolic activation system. Rilpivirine did not induce chromosomal damage in the in vivo micronucleus test in mice.

Carcinogenicity
Cabotegravir was not carcinogenic in long term oral studies in the mouse and rat at doses resulting in up to 7–8 and 26 times, respectively (75 mg/kg/day in male mice and rats and 35 mg/kg/day in female mice), the maximum AUC in patients.

Rilpivirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 20, 60 and 160 mg/kg/day were administered to mice and doses of 40, 200, 500 and 1500 mg/kg/day were administered to rats. An increase in the incidences of hepatocellular adenomas and carcinomas was observed in mice and rats. An increase in the incidences of follicular cell adenomas and/or carcinomas in the thyroid gland was observed in rats. Administration of rilpivirine did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed hepatocellular findings in mice and rats are considered to be rodent-specific, associated with liver enzyme induction. A similar mechanism does not exist in humans; hence, these tumors are not relevant for humans. The follicular cell findings are considered to be rat-specific, associated with increased clearance of thyroxine and are not considered to be relevant for humans. At the lowest tested doses in carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were >17 times relative to those observed in humans at the recommended doses (25 mg once daily orally or 600 mg IM injection monthly).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Cabotegravir prolonged-release suspension for injection

Mannitol
Polysorbate 20
Macrogol 3350
Water for injections

Rilpivirine prolonged-release suspension for injection

Citric acid monohydrate
Glucose monohydrate
Poloxamer
Monobasic sodium phosphate monohydrate
Sodium hydroxide
Water for Injections

6.2 INCOMPATIBILITIES

In the absence of compatibility studies cabotegravir and rilpivirine injections must not be mixed with other medicinal products

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

In use shelf life:

Prior to administration, vials should be brought to room temperature (not to exceed 25°C). Vials may remain in the carton at room temperature for up to 6 hours. If not used after 6 hours, they must be discarded.

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C.

Do not freeze.

Prior to administration, vials should be brought to room temperature (not to exceed 25°C).

6.5 NATURE AND CONTENTS OF CONTAINER

2mL CABENUVA contains:

- One 2 mL single-dose vial of cabotegravir prolonged-release suspension for injection containing 400 mg of cabotegravir.
- One 2 mL single-dose vial of rilpivirine prolonged-release suspension for injection containing 600 mg of rilpivirine.
- 2 syringes, 2 vial adaptors, and 2 needles (23-gauge, 1½ inch).

3 mL CABENUVA contains:

- One 3 mL single-dose vial of cabotegravir prolonged-release suspension for injection containing 600 mg of cabotegravir.
- One 3 mL single-dose vial of rilpivirine prolonged-release suspension for injection containing 900 mg of rilpivirine.
- 2 syringes, 2 vial adaptors, and 2 needles (23-gauge, 1½ inch).

The vials are Type I clear glass vials, sealed with bromobutyl rubber stoppers and an aluminum overseal with a removeable plastic cap.

Not all strengths may be distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

Full instructions for use and handling of CABENUVA is provided in the Instructions for Use included as a package insert.

6.7 PHYSICOCHEMICAL PROPERTIES

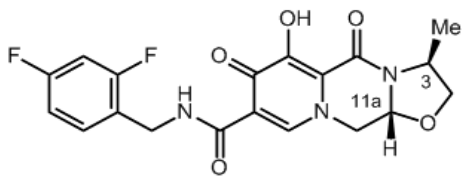
Cabotegravir

Chemical name: (3S,11aR)-N-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide

Molecular formula: $C_{19}H_{17}F_2N_3O_5$

Molecular weight: 405.35 g/mol

Chemical structure



CAS number: 1051375-10-0

Cabotegravir is a white to almost white solid.

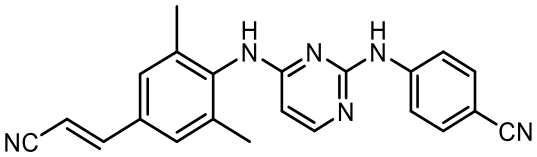
Rilpivirine

Chemical name: 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile

Molecular formula: $C_{22}H_{18}N_6$

Molecular weight: 366.42 g/mol

Chemical structure



CAS number: 500287-72-9

Rilpivirine is a white to off white powder.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

ViiV Healthcare Pty Ltd

Level 4, 436 Johnston Street,

Abbotsford, Victoria, 3067

9 DATE OF FIRST APPROVAL

23 February 2021

10 DATE OF REVISION

08 August 2022

Section Changed	Summary of new information
4.2	Addition of patient selection statement. Change of dosing instructions to reflect the change to the optional oral lead-in.
4.4	Removal of recommendation of oral lead in dosing.
4.8	Addition of Week 96 and Week 124 FLAIR safety statements.
5.1	Editorial changes to Pharmacodynamics. Addition of Week 124 FLAIR data.
5.2	Editorial changes.

Version 3.0