Date: 11 March 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Vocabria

International non-proprietary name: cabotegravir
Pharmaceutical forms: prolonged release suspension for injection
Dosage strength: 600 mg/3 ml, 400 mg/2 ml
Route(s) of administration: intramuscular
Marketing Authorisation Holder: ViiV Healthcare GmbH
Marketing Authorisation No.: 67740
Decision and Decision date: approved on 8 October 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of the SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

3TC	Lamivudin
ABC	Abacavir
ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
AEs	Adverse events
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ARV	Antiretroviral
ART	Antiretroviral therapy
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BMI	Body mass index
CAB	Cabotegravir
CAR	Continued oral standard antiretroviral regimen
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
DTG	Dolutegravir
EFV	Efavirenz
ERA	Environmental Risk Assessment
FTC	Emtricitabine
GC	Gas Chromatography
GLP	Good Laboratory Practice
HIV	Human immunodeficiency virus
HPLC	High Pressure Liquid Chromatography
IC_{50}	Half Maximal Inhibitory Concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IM	Intramuscular
INI	Integrase inhibitor
INN	International Nonproprietary Name
INSTI	Integrase strand transfer inhibitor
IR	Infrared Spectrometry
ISRs	Injection site reactions
ITT-E	Intention to treat exposed population
IUPAC	International Union of Pure and Applied Chemistry
LAIs	Long acting injections
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NAS	New active substance
NO(A)EL	No Observed (Adverse) Effect Level
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTIs	Nucleoside reverse transcriptase inhibitors
PD	Pharmacodynamics
Ph. Eur.	Pharmacopoea europaea
PI	Protease inhibitor

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PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
Q4W	Every four weeks
Q8W	Every eight weeks/every two months
QD	Once daily
RMP	Risk Management Plan
RNA	Ribonucleic acid
RPV	Rilpivirine
SAEs	Serious adverse events
SC	Subcutaneous
SOC	Standard of care
SwissPAR	Swiss Public Assessment Report
t1/2	Elimination half -life
TDF	Tenofovir
Tmax	Time to reach the maximum concentration
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
UGT	Uridine 5'-diphospho-glucuronosyltransferase
UV	Ultraviolet spectrometry
Vc/F	Apparent central volume of distribution
Vp/F	Apparent peripheral volume of distribution
XRPD	X-ray powder diffraction

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance cabotegravir of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Vocabria injections are indicated, in combination with rilpivirine injections, for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) and have no known or suspected resistance to either cabotegravir or rilpivirine.

2.2.2 Approved Indication

Vocabria injections are indicated in combination with rilpivirine injections for treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/ml) on a stable antiretroviral treatment for at least 6 months prior to the switch to the cabotegravir-rilpivirine combination and have no known or suspected resistance to or no history of virological failure with agents of the NNRTI and INI class (see Clinical Efficacy).

2.2.3 Requested Dosage

Therapy should be initiated by a physician experienced in the management of HIV infection.
Vocabria injection is indicated for the treatment of HIV-1 in combination with rilpivirine injection; therefore, the prescribing information for rilpivirine injection should be consulted for recommended dosing.

Adults
Oral lead-in
Vocabria tablets are recommended for approximately one month (at least 28 days) in virologically suppressed patients prior to the initiation of Vocabria injections to assess tolerability of cabotegravir. One Vocabria tablet (30 mg) should be taken with one rilpivirine tablet (25 mg) once daily. When administered with rilpivirine, Vocabria tablets should be taken with a meal (see Vocabria tablets information for healthcare professionals).
Initiation injection (3 mL [600 mg] dose)

Initiation injection
On the final day of oral lead-in therapy, the recommended initial dose of Vocabria injection in adults is a single 3 mL (600 mg) intramuscular injection. Vocabria injection and rilpivirine injection should be administered at separate gluteal injection sites at the same visit.

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

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Recommended dosing schedule in adults

	ORAL LEAD-IN		INITIATION INJECTION		CONTINUATION INJECTION
Medicinal product	**Month 1 (at least 28 days)**		**Month 2**		**Month 3 onwards**
Cabotegravir	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

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	25 October 2019
Formal control completed	18 November 2019
List of Questions (LoQ)	18 March 2020
Answers to LoQ	16 June 2020 and 17 August 2020
2. List of Questions	13 November 2020
Answers to 2. LoQ	11 February 2021
Predecision	12 May 2021
Answers to Predecision	9 July 2021
Labelling corrections	29 September 2021
Answers to Labelling corrections:	3 October 2021
Final Decision	8 October 2021
Decision	approval

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3 Medical Context

Human Immunodeficiency Virus-1 (HIV-1) infection is a life-threatening and serious disease that is of major public health interest. If left untreated or treated sub-optimally, the course of HIV-1 infection is characterised by deterioration in immune function, with the subsequent occurrence of opportunistic infections and malignancies, ultimately resulting in death.

Epidemiology

Worldwide there are 37.9 million people living with HIV (2018). In 2018, 770,000 people died of Acquired Immune Deficiency Syndrome (AIDS). There were approximately 1.7 million new HIV infections around the world in 2018.

In Switzerland, around 17,000 people are living with HIV. In 2018, 425 new HIV diagnoses were made in Switzerland.

Treatment

Generally, the initial antiretroviral treatment regimen for a treatment-naive patient consists of a three-drug regimen containing

- two nucleoside reverse transcriptase inhibitors (NRTIs), also called an NRTI backbone,

plus a third drug from one of the following three drug classes (anchor drug):

- an integrase strand transfer inhibitor (INSTI),
- a non-nucleoside reverse transcriptase inhibitor (NNRTI),
- or a boosted protease inhibitor (PI).

Recently, two-drug regimens for the treatment of people with HIV have also been approved:

- DTG (dolutegravir) plus 3TC (lamivudine)
- DTG (dolutegravir) plus RPV (rilpivirine)

However, up to now there are no long-acting injections (LAIs) available for the treatment of HIV-1-infection.

Vocabria/Rekambys is a novel 2-drug antiretroviral (ARV) regimen for HIV-1 infection. Vocabria, oral film-coated tablets contain the new active substance (NAS) cabotegravir sodium in one strength of 30 mg. Vocabria, suspension for intramuscular (IM) injection, contains the NAS cabotegravir as a free acid in two different strengths: a 600 mg loading dose and a 400 mgmaintenance dose. Rekambys suspension for IM injection contains the known active substance rilpivirine as a free base in this new pharmaceutical formulation for this new route of administration.

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4 Quality Aspects

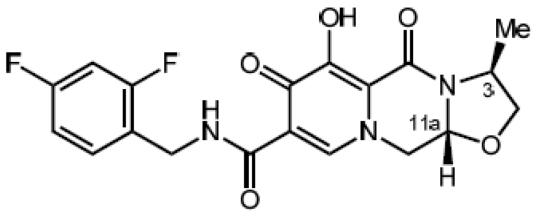
4.1 Drug Substance

Vocabria prolonged release suspension for injection contains cabotegravir free acid.

The chemical IUPAC name for cabotegravir is (*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.

The molecular formula of cabotegravir is $C_{19}H_{17}F_2N_3O_5$ and the corresponding molecular weight is 405.35 g/mol.

The chemical structure of cabotegravir is as follows:



The synthesis of the drug substance cabotegravir has been adequately described and the process is controlled with appropriate tests for isolated intermediates.

The drug substance specification includes tests for description (visual), identification (IR), solid state form (XRPD), cabotegravir content (HPLC), impurities (HPLC), enantiomer content (chiral HPLC), diastereomer content (chiral HPLC), residual solvents (GC), water content (Karl Fischer titration), bacterial endotoxins (Ph. Eur.) and bioburden (Ph. Eur.). The specification is in line with the recommendations of the relevant ICH guidelines and is considered appropriate in order to ensure a consistent drug substance quality.

Appropriate stability data have been presented and justify the proposed re-test period.

4.2 Drug Product

Vocabria is presented as a prolonged release suspension for injection containing 200 mg/ml cabotegravir free acid, intended for intramuscular (IM) injection. The drug product is a white to light pink, free flowing suspension. Each sterile, single-use vial of the drug product is intended to provide a dose of 400 mg or 600 mg, available in two nominal fill presentations: 2 ml for the 400 mg and 3 ml for the 600 mg dose. No dilution is required prior to IM administration. The packaging of the suspension is a clear glass vial with a rubber injection stopper and sealed with an aluminium overseal with a removable plastic cap. The labelling and the colours of the plastic caps differentiate the two fill presentations. The clear glass vial becomes brown as a result of sterilisation by gamma irradiation.

The composition of the drug product is adequately described, qualitatively and quantitatively.

The manufacturing process is described in sufficient detail and consists of sterilisation of the drug substance cabotegravir by gamma irradiation, compounding and filtration of the formulation vehicle,

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compounding of the bulk suspension for milling, milling of the suspension and transfer of the milled suspension to a filling tank, filling into vials, stoppering and oversealing, vial inspection, terminal sterilisation by gamma irradiation and vial inspection.

For the control of the finished product, adequate tests and acceptance criteria for release and at shelf life are established. The specifications include the parameters description (visual), identification (HPLC, UV), cabotegravir content (HPLC), impurities (HPLC), uniformity of dosage units (Ph. Eur.), extractable volume (Ph. Eur.), particulate contamination (Ph. Eur.), pH (Ph. Eur.), particle size (laser diffraction), dissolution (Ph. Eur., HPLC), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.).
The proposed parametric release for sterility is justified and accepted.
The corresponding test procedures are validated according to international guidelines. Batch data show consistent quality of the drug product.

Appropriate stability data have been generated in the packaging material intended for commercial use and following the relevant international guidelines. Based on these data, a shelf life of 24 months was established for Vocabria prolonged release suspension for injection. The storage recommendation is “Do not store above 30°C. Do not freeze.”

4.3 Quality Conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

Pharmacodynamics
Cabotegravir (CAB) blocked the Human Immunodeficiency Virus (HIV) DNA strand transfer with half maximal inhibitory concentration (IC_{50}) values of 3-13 nM. At low nanomolar concentrations, CAB inhibited replication of various HIV-1 and HIV-2 subtypes, and HIV mutants resistant to nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNTRI), protease inhibitors and integrase inhibitors. Human serum reduced antiviral activity in MT4 cells several hundred-fold with an extrapolated IC_{50} of 101-218 nM. *In vitro*, CAB selected for multiple highly resistant mutants starting from Q148K, Q148R and Q148H mutants. CAB induced few mutations in the integrase region, i.e. T124A, S153Y, T124A/S153Y and Q146L (less than 10-fold resistance increase).
CAB was additive or weakly synergistic when administered with marketed NRTIs and rilpivirine.

In secondary pharmacodynamics studies, CAB had > 50% activity on the melanocortin-4 (MC_4) receptor at 10 µM. As protein binding is > 99%, clinical relevance is considered unlikely but cannot be fully excluded.

In safety pharmacology studies, hERG current was inhibited by 28.5% at a concentration > 100-fold the clinical $C_{max\ unbound}$ at the maximum recommended human dose (MRHD) of 30 mg. Rats showed no effects on respiratory and central nervous system function at clinical exposures approx. 4-fold the C_{max} in humans. A slight decrease in blood pressure and increased heart rate were noted in conscious monkeys at 1,000 mg/kg/day. No ECG changes were noted at the same dose in a 14-day oral toxicity study in monkeys at exposures 8.3-fold the clinical C_{max}.

Pharmacokinetics
Oral bioavailability of CAB solutions was 43-83% and that of capsules and suspensions was ≤ 8% in dogs and monkeys and ≤ 28% in rats, and was probably limited by dissolution and/or solubility. T_{max} was 1-10 hours after oral administration. Elimination half-lives were long after intramuscular (IM) administration ($t_{1/2}$ up to 26 days in monkeys and 14 days in rats). C_{max} und AUC increased much less than dose proportional after single or repeated oral and IM dosing. In rats, exposure was usually greater after repeated dosing, independent of the route, but there was no accumulation in mice and monkeys.
Exposures (C_{max} and AUC) decreased up to 39% in rats (IM route) as well as in humans with increasing particle size. PK changes were noted upon co-administration of CAB and rilpivirine in monkeys and in rats but not in humans.

As is known from other integrase inhibitors, CAB chelates various metal cations *in vitro,* and absorption is likely to decrease upon co-administration of cation antacids. Appropriate recommendations are included in the information for healthcare professionals. Plasma protein binding was ≥ 99.5% in all species. Orally administered [^{14}C]-CAB was slowly absorbed but widely distributed in rats with high levels in the blood and lungs, bulbourethral gland, renal medulla and adrenal medulla detectable up to 28 days and detectable levels in the brain up to 7 days after administration. There was no preferential binding to melanin in the eyes and skin or to cellular blood components. CAB crossed the placenta in rats and rabbits. No data on distribution and metabolism were provided for the IM route. A study in cannulated rats demonstrated the presence of CAB in lymph fluid and lymph nodes 7 days after IM administration.
Upon IM administration of formulations with 1 µm particles, dipotassium-adducts of CAB were localised in macrophages and multinucleated giant cells in the periphery of the injection site in rats. CAB was very stable in rat, dog, monkey and human S9 liver fractions, liver microsomes and hepatocytes. At higher concentrations, CAB was metabolised (< 10 %) to glucuronidated CAB in rat, monkey and human hepatocytes, but not in dog hepatocytes. The major circulating [^{14}C]-CAB component was unchanged CAB (>92% in all species). In animals, no metabolites could be identified

in plasma. The glucuronide of CAB (M1) was present in human urine (20% of total radioactive dose) and in low amounts in rodent and monkey urine and/or bile. The glucose adduct (M2) was detected in all species except mice. Rodents and monkeys excreted 1-2 minor metabolites that were not detected in humans.
Excretion was predominantly via faeces in rodents and monkeys, mainly as unchanged CAB, whereas in humans both faecal and renal excretion was observed. No conversion to the enantiomer or the diastereomer was seen in hepatocytes in any species.

Toxicity
Species selection (rat, monkey), dosing scheme and treatment duration were appropriate to support the proposed clinical treatment regimen (1-month oral dosing followed by chronic IM administration). Exposure increases were limited due to low solubility of the oral formulation, but exposures at maximum doses and/or NOAELs covered the clinical exposures. Single dose and repeated-dose oral toxicity studies with CAB sodium salt were conducted up to 13 weeks in mice, 26 weeks in rats, and 39 weeks in monkeys with doses up to 2,000 mg/kg/day (mice) and 1,000 mg/kg/day (rats, monkeys). Parenteral weekly subcutaneous (SC) or monthly (SC, IM) administration of the free acid form was assessed in rats with doses up to 75 mg/kg/dose (IM) and 100 mg/kg/dose (SC) over 3 months. The chronic oral toxicity studies along with the parenteral studies were considered as providing appropriate information about chronic IM administration.
Repeated oral administration of 1,000 mg/kg/day in a 14-day study was not tolerated by male monkeys due to gastrointestinal toxicity and resulted in morbidity. In contrast, administration of 500 mg/kg/day up to 39 weeks with similar systemic exposures was not associated with major toxicities. In mice and rats given 1,000 mg/kg/day, inflammation, degeneration of the epithelium and/or apoptosis were noted in the non-glandular stomach and nasal cavity (due to gastric reflux) and were not related to exposure. Changes in clinical parameters indicative of renal or liver toxicity generally did not correlate with histopathological findings (only in mice, but in single animals only). The only toxicities after parenteral administration were injection site reactions (oedema and erythema) accompanied by histopathological changes.
In the pivotal oral toxicity studies, exposures ($AUC_{0\text{-}24h}$) at the NOAELs of 500 mg/kg/day in monkeys, 75 mg/kg/day in mice and 1,000 mg/kg/day in rats were 3.7-fold, 9.2-fold and 27-fold the AUC at the 30 mg oral dose in humans. In the 3-month study with IM administration in rats, exposure ($AUC_{d60\text{-}d90}$) at the systemic NOAEL of 75 mg/kg/dose was 92 mg*h/mL, i.e. 37-fold the AUC at the clinical maintenance dose of 400 mg.
Toxicological combination studies with rilpivirine (RPV) were not conducted. It is agreed that the toxicological profile of CAB does not raise concerns with regard to additive or synergistic effects with RPV. Known toxicities of RPV are not expected to be substantially changed, including liver or kidney toxicities.
CAB was not genotoxic in a standard testing battery. CAB was not carcinogenic after oral dosing in 2-year studies in rats and mice with exposures up to 7-fold (mice) and 26-fold (rats) human exposure. Fertility of male and female rats was not affected up to oral doses of 1,000 mg/kg/day. Foetal weight was reduced by 6% in female rats given 1,000 mg/kg/day orally. Apart from a transient bodyweight gain reduction in pregnant rabbits (16%), there were no effects in dams and their offspring up to 2,000 mg/kg/day. The exposure multiples at the NOAELs for embryofoetal toxicity were 30-fold in rats and 0.65-fold in rabbits. In a pre- and postnatal development study and in a subsequent cross-fostering study in rats, slight delays in parturition, higher incidences of stillborn pups and increased foetal death at postnatal days 2-4 (10-17%) were noted at exposures 30-fold the human exposure. The cross-fostering study and additional toxicokinetics studies showed that the findings were associated with *in utero* exposure rather than with exposure through milk.
Juvenile studies were not conducted in agreement with the EU PIP.
No effect on T-cell-dependent antibody responses were observed in rats.
CAB absorbs light at a wavelength > 290 nm. Non-clinical studies were not conducted, which can be accepted as clinical data did not point to a risk of phototoxicity.
There are no concerns with regard to excipients and impurities.

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The environmental studies did not identify a risk at anticipated exposures. The non-clinical information is appropriately stated in the RMP and the information for healthcare professionals.

Conclusion:
The submitted non-clinical documentation was considered sufficient to conduct a risk assessment. There were no preclinical issues identified that would preclude approval of CAB for the requested indication in combination with RPV.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

Biopharmaceutics
Tablet: The tablet formulation used in all Phase 3 trials is intended for the market. Thus, no bridging is required for the Phase 3 material to the commercial material. Successful bridging was performed to the Phase 3 tablet from earlier studies (Phase 1 and Phase 2)

IM injection: The IM injection consists of size-reduced particles in an isotonic aqueous medium. There is no additional coating of the drug particles or special excipients that would cause a further delay in release following IM administration. The IM injection formulation used in the Phase 3 studies is intended for the market. The same formulation was also used in the Phase 2 studies.

ADME
Tablet
Cabotegravir is rapidly absorbed following oral administration. The median T_{max} at steady state, based on the popPK analysis is 3 h (range: 2 to 4 h) following the proposed dosing regimen. In view of the poor aqueous solubility of cabotegravir, information on the absolute bioavailability is absent. However, in the mass balance study, urinary recovery was 26.8%. Despite the absence of a food effect, cabotegravir, when combined with rilpivirine, is to be given with a meal (according to the Edurant® label).

Cabotegravir exposure increases in proportion to the dose or slightly less than dose proportional in the dose range 10 mg to 60 mg. Steady state following administration of 30 mg once daily (QD) is reached on Day 7 with an accumulation factor of approximately 2.5.

IM injection
Cabotegravir absorption is markedly delayed following IM administration compared to the oral route. The median T_{max} at steady state, based on the popPK analysis is 5 days (range: 4 to 7 days) following the proposed dosing regimen with high individual variability (T_{max}, range: 2 – 213 days), which is of limited clinical concern as desired target C_{trough} levels are maintained to ensure maximum HIV suppression. In addition, since maximum cabotegravir concentrations following IM administration are well within the range observed after oral administration, there are also no safety concerns.

The substantially delayed cabotegravir absorption (compared to oral administration) is the rate limiting step in the absorption, distribution and elimination of cabotegravir, with a resultant marked prolongation of the terminal half-life (see Elimination / Excretion).

In view of the poor aqueous solubility of cabotegravir, no information on the absolute bioavailability is available.

Cabotegravir exposure increases in proportion to the dose or slightly less than dose proportional in the dose range 100 mg to 800 mg by IM administration.

Distribution
Cabotegravir is highly bound to human plasma proteins based on *ex vivo* and *in vitro* data. In healthy subjects with normal organ function and HIV-1 infected patients, median protein binding was 99.8 to 99.9%. Protein binding occurs via albumin. Binding sites are not saturated, with a resultant low potential for displacement from plasma protein binding sites.

There is minimal association of cabotegravir with red blood cells. Cabotegravir is detectable in cervical, vaginal and rectal tissues. Cabotegravir also enters the cerebrospinal fluid.

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In humans, the estimate of plasma cabotegravir Vc/F is 5.27 L and Vp/F is 2.43 L based on the results of the popPK analysis.

Metabolism
Cabotegravir is primarily metabolised by glucuronidation via UGT1A1 and to a lesser extent via UGT1A9 to form the pharmacologically inactive metabolite M1. There is no clinically relevant impact of UGT1A1 and UGT1A9 genotypes (“poor” vs. “fast” metabolisers) on cabotegravir exposure and tolerability based on a meta-analysis of Phase 1 and Phase 2 study data.

Elimination / Excretion
Following single dose administration of [^{14}C]-cabotegravir 30 mg oral solution in humans, 85.3% of the administered dose was recovered, with 58.5% of the dose recovered in faeces and 26.8% recovered in urine. Unchanged cabotegravir is the predominant species in plasma (>90% of the species in plasma) and in faeces (80% of the faecal radioactivity). In urine, the metabolite M1 represents the majority of the radioactivity (75% of the urinary radioactivity). Both cabotegravir and M1 were detected in human bile.

The terminal half-life for cabotegravir is markedly prolonged after IM injection vs oral administration (5.6 (males) to 11.5 (females) weeks vs 41 h according to the popPK analysis) due to the depot effect of the muscular site. There is a statistically but not clinically relevant gender effect on the absorption rate constant following IM administration, which results in a 50% slower absorption rate in female patients with a subsequent increase of $T_{1/2}$ to 11.5 weeks vs. 5.6 weeks in male subjects. This is likely the consequence of greater subcutaneous fat thickness above the gluteus medius muscle in females and resulting slower absorption from adipose tissue due to lower blood flow than from muscle.
The IM depot is not depleted for prolonged periods of time following cessation of treatment and instead continues to release cabotegravir at low concentrations into the main circulation with limited clinical consequence.

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Summary of Cabotegravir Exposure Following Administration of the Proposed CAB + RPV Regimens in HIV-1-infected Subjects

CAB Regimen	Dose	Statistics	Plasma CAB Exposure (n=647)			
			AUC(0-τ) (µg × h/mL)	Cmax (µg/mL)	Cτ (µg/mL)	Tmax (hour)
30 mg PO QD	Steady state	Geometric mean (95% CI)	150.6 (147.4,153.9)	8.21 (8.05,8.38)	4.82 (4.70,4.93)	1.9 [a] (1.6,2.8)
		Median [5th-95th percentile]	150.2 [94.33-243.4]	8.19 [5.28-12.93]	4.82 [2.87-8.09]	1.9 [a] [1.8-2.0]
Q4W: 600 mg IM initiation injection + 400 mg IM monthly	Initiation injection	Geometric mean (95% CI)	1708.1 (1649.2,1769.1)	8.21 [b] (8.04,8.38)	1.57 (1.52,1.63)	0.0 [a,b] (0.0,72.0)
		Median [5th-95th percentile]	1790.9 [778.1-3476.7]	8.19 [b] [5.27-12.92]	1.69 [0.64-2.97]	0.0 [b] [0.0-0.0]
	11th LA IM injection (40-44 weeks after initiation injection)	Geometric mean (95% CI)	2484.9 (2434.8,2536.1)	4.32 (4.23,4.42)	2.9 (2.84,2.97)	5.0 [a,c] (4.0,7.0)
		Median [5th-95th percentile]	2456.0 [1592.1-3860.0]	4.35 [2.61-6.76]	2.93 [1.84-4.64]	5.0 [c] [4.0-6.0]
Q8W: 600 mg IM initiation injection + one month later + every 2 months	Initiation injection	Geometric mean (95% CI)	1708.1 (1649.2,1769.1)	8.21 [b] (8.04,8.38)	1.57 (1.52,1.63)	0.0 [a,b] (0.0,72.0)
		Median [5th-95th percentile]	1790.9 [778.1-3476.7]	8.19 [b] [5.27-12.92]	1.69 [0.64-2.97]	0.0 [b] [0.0-0.0]
	6th LA IM injection (36-44 weeks after initiation injection)	Geometric mean (95% CI)	3764.1 (3689.0,3840.8)	4.02 (3.92,4.12)	1.61 (1.56,1.66)	6.0 [a,c] (4.0,9.0)
		Median [5th-95th percentile]	3716.8 [2430.8-5856.9]	4.04 [2.26-6.83]	1.64 [0.80-2.99]	6.0 [c] [5.0-8.0]

AUC(0-τ) = area under concentration-versus-time curve from time 0 to the end of the dosing interval; Cτ = plasma concentration at the end of the dosing interval; Cmax = maximum plasma concentration; CAB = cabotegravir; CI = confidence interval; HIV = Human Immunodeficiency Virus; IM = intramuscular; PK = pharmacokinetic(s); PO = oral; PopPK = population pharmacokinetics; QD = daily; RPV = rilpivirine; Tmax = time to reach maximum plasma concentration.

Note: PK sampling schedule in the simulation:

1. following PO doses: one sample every 0.1 hour within 6 hours, and one sample every 2 hours after 6 hours. This sampling schedule is more intensive than the previous tNDA PopPK analysis [1].
2. following IM injections: one sample every 24 hours.

a. Median (minimum, maximum).
b. The Cmax and Tmax following the first CAB LA injection is likely determined by the last oral dose instead of the initiation LA dose.
c. The unit is day.

Data source: p. 46 of the popPK report 2019N421460_00 207966

Special Populations

As a result of dedicated studies in patients with renal or hepatic impairment, no dose adjustments are warranted in patients with mild or moderate (Child Pugh A and B) hepatic impairment or in patients with mild, moderate or severe (not requiring dialysis) renal impairment. Patients with severe hepatic impairment or with severe renal impairment requiring dialysis were not investigated.

The popPK analysis indicated that no dose adjustments are necessary with respect to BMI, weight, race, age, smoker status or UGT1A1 polymorphism. In addition, the PK of cabotegravir is similar in healthy subjects and HIV-1 infected patients.

Interactions

The PK-based interaction potential for cabotegravir as a perpetrator and a victim was investigated comprehensively by means of *in vitro* analyses, modelling approaches and 6 dedicated *in vivo* studies. The results of these investigations and respective dosing recommendations are included in the information for healthcare professionals. The combined administration of cabotegravir with

UGT1A1 inducers such as rifampicin is contraindicated due to the 59% decrease in cabotegravir AUC and loss of antiviral activitiy.

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

The proposed dosing regimens ensure the maintainance of cabotegravir levels throughout the entire dosing interval well above the protein-adjusted IC_{90} (PA IC_{90}) value of 0.167 µg/mL, which is derived from *in vitro* experiments to ensure maximum antiviral effects.

One dedicated QT/QTc study was submitted, which was placebo-controlled with a positive control (moxifloxacin). Supratherapeutic cabotegravir oral doses (150 mg every 12 hours for 3 doses) resulted in C_{max} values 3 – 6 times those observed following the oral and IM portions of the proposed dosing regimen. The study indicated the absence of a QT/QTc prolongation potential for cabotegravir.

6.2 Dose Finding and Dose Recommendation

Two main dose-finding studies have been conducted pertinent to the Applicant's request: a) the oral dose finding LATTE study (LAI116482); b) the IM injection dose-finding LATTE-2 study (200056).

LATTE Study(LAI116482)

The oral dose-finding LATTE study was a Phase IIb, dose-ranging study of oral cabotegravir (CAB) in combination with oral rilpivirine (RPV) in HIV-1 infected, antiretroviral therapy (ART)-naive adult subjects.

The study design was a multicentre, randomised, partially (only cabotegravir dose)-blinded, parallel group study in HIV-1 infected ART-naive adults. A total of n=244 eligible patients were randomised into 4 treatment arms (n=60, 60, 61 and 62) with 3 different oral CAB doses (10, 30 or 60 mg) or 600 mg efavirenz (EFV), all of them in combination with a 2-NRTI backbone of either ABC/3TC (abacavir/lamivudine) or TDF/FTC (tenofovir/emtricitabine). In case of viral suppression (HIV-1 RNA <50 c/mL) at the end of a 24 week induction phase, patients in the CAB groups continued their respective CAB dose but discontinued the 2-NRTI backbone and instead initiated a daily oral 25 mg RPV dose, resulting in a new 2-drug regimen. Subjects in the EFV group continued their assigned EFV-based 3-drug ARV regimen.

The *primary endpoint* was the proportion of subjects with HIV-1 RNA <50 c/mL at Week 48. *Dose selection* was based primarily on antiviral activity, in conjunction with safety, tolerability and immunologic, virologic resistance and PK measures.

The *results* showed that the 10 and 30 mg CAB dose groups had similar response rates (80% each), whereas the 60 mg CAB dose groups had a higher response rate (87%); all 3 CAB dose groups had higher response rates than the EFV control group (71%).

LATTE-2 Study (200056)

The IM injection dose-finding LATTE-2 study (200056) was a Phase IIb study evaluating a long-acting intramuscular regimen of cabotegravir (CAB) plus rilpivirien (RPV) for the maintenance of virologic

suppression following an induction of virologic suppression on an oral regimen of CAB plus abacavir/lamivudine in HIV-1 infected, antiretroviral therapy (ART)-naive adult subjects.

The study design was a Phase IIb multicentre, randomised, open-label, parallel group study in HIV-1 infected ART-naive adults. A total of n=309 patients entered a 5 month-induction period with an oral treatment regimen of CAB 30 mg plus ABC/3TC 600 mg/300 mg once daily, plus an additional 25 mg oral RPV in Month 5. Following viral suppression (HIV-1 RNA <50 c/mL) in the induction period, n=286 patients were *randomised* in a 2:2:1 ratio into 3 treatment arms (n=115, 115 and 56):
1) every 4 weeks (Q4W) IM long-acting injections of CAB 400 mg + RPV 600 mg,
2) every 8 weeks (Q8W) IM long-acting injections of CAB 600 mg + RPV 900 mg, and
3) continuation of QD oral CAB 30 mg plus ABC/3TC 600 mg/300 mg.
The long-acting injection treatment arms started with loading doses.

The *primary objective* was to select an IM long-acting dosing regimen of CAB plus RPV based on a comparison of the Week 32 antiviral activity, tolerability and safety data with the oral once-daily dosing regimen of CAB 30 mg plus ABC/3TC 600 mg/300 mg. The *primary endpoint* for this study was the proportion of patients that maintained viral suppression with HIV-1 RNA <50 c/mL at Week 32 (i.e. after 20 weeks of induction and 32 weeks of randomised treatment).

The Week 32 results showed that similar proportions of the patients that received the 2 different IM long-acting injections achieved the primary endpoint (HIV-1 RNA <50 c/mL): 95% (Q8W IM arm), 94% (Q4W IM arm) and 91% (QD oral treatment arm), respectively.
By contrast, virologic failure (HIV-1 RNA >50 c/mL) was observed in 4% (Q8W IM arm), 4% (QD oral treatment arm) and only <1% (Q4W IM arm), respectively.

The Week 48 results showed a similar picture: 92% (Q8W IM arm), 91% (Q4W IM) and 89% (QD oral treatment arm) of the patients maintained viral suppression (HIV-1 RNA <50 c/mL), whereas 7% (Q8W IM arm), 2% (QD oral treatment arm) and <1% (Q4W IM) of the patients experienced virologic failure (HIV-1 RNA >50 c/mL).

The decision to initiate the Phase 3b ATLAS-2M study was based on the Week 96 outcomes of the LATTE-2 study.
The Week 96 results showed a clearer advantage for the Q8W treatment arm compared to the other two treatment arms in terms of maintained viral suppression (HIV-1 RNA <50 c/mL): 94% (Q8W IM arm), 87% (Q4W IM) and 84% (QD oral treatment arm), respectively. At the same time, there was no further increase in virologic failures (HIV-1 RNA >50 c/mL): 4% (Q8W IM arm), 0% (Q4W IM) and 2% (QD oral treatment arm), respectively.

In summary, the dose finding conducted in LATTE and LATTE 2 was acceptable from a regulatory point of view.

6.3 Efficacy

Three pivotal Phase 3(b) studies have been conducted: study 201584 (FLAIR), study 201584 (ATLAS) and study 207966 (ATLAS-2M), which are summarised below.

Study 201584 (FLAIR)

FLAIR was a Phase III study to evaluate the efficacy, safety and tolerability of long-acting intramuscular cabotegravir (CAB) and rilpivirine (RPV) for maintenance of virologic suppression following a switch from a standard oral antiretroviral treatment (ART) including dolutegravir in HIV-1 infected ART-naive adult patients.

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The *primary objective* was to demonstrate the non-inferior antiviral activity of switching to monthly intramuscular long-acting injections (LAI) of CAB and RPV (Q4W) compared to the continued oral standard antiretroviral regimen (CAR) over 48 weeks in HIV-1 infected ART-naive adult patients.

FLAIR was designed as multi-centre, multi-phase, randomised, open label, active-controlled, parallel-group study. The study design and study treatments are described in the *Properties/Effects/Clinical Efficacy* section of the Swiss Information for healthcare professionals.

A total of n=809 subjects were screened and n=629 subjects were eligible to receive the standard oral antiretroviral treatment (ART) including dolutegravir for 20 weeks to induce viral suppression, defined as confirmed HIV-1 RNA <50 c/mL. After successful induction of viral suppression, n=566 subjects were randomised 1:1, either to the investigational treatment with CAB+RPV (n=283 subjects) or to continuation of the standard oral ART regimen (CAR, n=283).

Efficacy results: The primary efficacy endpoint was “the proportion of subjects with a ‘virologic failure’ endpoint as per FDA Snapshot algorithm at Week 48 (ITT-E Population)”. A secondary efficacy analysis was performed at Week 96.
The Week 48 primary efficacy analysis demonstrated that monthly (Q4W) intramuscular long-acting injections of CAB+RPV were non-inferior to continuation of the standard oral ART regimen (CAR) in maintaining virologic suppression: Only few subjects had virologic failure with plasma HIV-1 RNA >50 c/mL at Week 48: n=6/283 (2.1%) in the CAB+RPV group compared to n=7/283 (2.5%) in the control group (CAR). The Week 96 secondary efficacy analysis demonstrated that monthly (Q4W) intramuscular long-acting injections of CAB+RPV continued to be non-inferior to CAR, with only few subjects experiencing a loss of virologic suppression (plasma HIV-1 RNA >50 c/mL) in both groups (3.2% versus 3.2%).

Overall, the primary endpoint was met and the study demonstrated that the Q4W CAB+RPV treatment regimen was non-inferior to the standard oral 3-drug ART regimen.

Study 201585 (ATLAS)

ATLAS was a Phase III study to evaluate the efficacy, safety and tolerability of switching to long-acting cabotegravir (CAB) plus long-acting rilpivirine (RPV) from current standard INI-, NNRTI- or PI-based antiretroviral treatment regimens (ART) in HIV-1-infected adults who are virologically suppressed.

The *primary objective* was to demonstrate the non-inferior antiviral activity of switching to monthly (Q4W) intramuscular long-acting injections of CAB and RPV compared to continuation of standard oral antiretroviral regimens (CAR) over 48 weeks in HIV-1 infected treatment-experienced adult subjects who were on a stable suppressive, uninterrupted ART with a 2-NRTI backbone plus an INI, NNRTI or a PI as third agent for at least 6 months.

ATLAS was designed as multi-centre, multi-phase, randomised, open label, active-controlled, parallel-group study. The study design and study treatments are described in the *Properties/Effects/Clinical Efficacy* section of the Swiss Information for healthcare professionals.

A total of n=705 subjects were screened and n=616 subjects were randomised 1:1, either to the investigational treatment CAB+RPV (n=308) or to continuation of the standard oral ART regimen (CAR, n=308).

Efficacy results: The primary efficacy endpoint was “the proportion of subjects who met the Snapshot virologic failure criteria, defined as plasma HIV-1 RNA >50 c/mL, at Week 48”. The analysis

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of the primary endpoint demonstrated that monthly (Q4W) co-administration of CAB+RPV as an intramuscular long-acting injection was non-inferior to continuation of standard oral ART regimens (consisting of a 2-NRTI backbone plus an INI, a NNRTI or a PI) in maintaining virologic suppression: Only few subjects had virologic failure with plasma HIV-1 RNA >50 c/mL at Week 48: n=5/308 (1.6%) in the CAB+RPV treatment group compared to n=3/303 (1%) in the control group.

Overall, the primary endpoint was met and the study demonstrated that the Q4W CAB+RPV treatment regimen was non-inferior to standard oral ART regimens.

Study 207966 (ATLAS-2M)

ATLAS-2M was a Phase IIIb study to evaluate the efficacy, safety and tolerability of long-acting cabotegravir (CAB) plus long-acting rilpivirine (RPV) administered every 8 weeks (Q8W) or every 4 weeks (Q4W) in HIV-1-infected adults who are virologically suppressed.

The *primary objective* of this study was “to demonstrate the non-inferior antiviral activity of intramuscular CAB 600 mg + RPV 900 mg administered every 8 weeks (Q8W; every 2 months) compared with intramuscular CAB 400 mg + RPV 600 mg administered every 4 weeks (Q4W; monthly) over a 48-week treatment period”.

ATLAS-2M was designed as multicentre, randomised, open-label, active-controlled, parallel-group study. The study design and study treatments are described in the *Properties/Effects/Clinical Efficacy* section of the Swiss Information for healthcare professionals.

The *patients* were HIV-1-infected male and female adult subjects who were virologically suppressed, with approx. 50% from the ongoing ATLAS 2tudy (201585) and the remainder from routine care on oral standard of care (SOC) for HIV-1 infection.

A total of n=1,049 subjects were randomised 1:1, either to the Q8W (n=522 subjects) or the Q4W (n=523 subjects) treatment regimen with intramuscular long-acting injections of CAB and RPV.

Efficacy results: The primary efficacy endpoint was “the proportion of subjects with plasma HIV RNA $\underline{\geq}$50 copies/mL as per FDA Snapshot algorithm at Week 48 (ITT-E population)”. The analysis of the primary endpoint demonstrated that the Q8W was non-inferior to the Q4W intramuscular long-acting injection of CAB+RPV in maintaining virologic suppression: Only few subjects had a plasma HIV-1 RNA $\underline{\geq}$50 c/mL at Week 48: n=9/522 (1.7%) in the Q8W group compared to n=5/523 (1%) in the Q4W group.

Overall, the primary endpoint was met and the study demonstrated that the Q8W treatment regimen was non-inferior to the Q4W treatment regimen. However, no direct comparison to oral antiretroviral standard of care was performed.

6.4 Safety

The most common adverse events (≥10%) under the Q4W treatment regimen were injection site pain, nasopharyngitis, injection site nodule, upper respiratory tract infection, headache and injection site induration.
The most common adverse events (≥10%) under the Q8W treatment regimen were injection site pain, nasopharyngitis, injection site nodule and upper respiratory tract infection.

Deaths (Q4W, Q8W)
Two deaths were reported as drug-related:

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One patient in the Q4W arm of the LATTE-2 study died from myocardial infarction and one patient in the Q8W arm of the ATLAS-2M study died from acute complicated pancreatitis. Considering all aspects of the medical history and the course of the event, the latter case seems unlikely to be related.

SAEs (Q4W vs oral SOC)
Serious adverse events (SAEs) occurred more frequently under the Q4W CAB+RPV treatment regimen than under oral SOC through to Week 48 in the FLAIR and ATLAS pool: 10% vs 9%, respectively.
This difference through to Week 48 was mainly driven by treatment-naive patients (FLAIR study: 6% vs 4% of patients, ATLAS study: 4% vs 5% of patients), but through to Week 100, this difference in treatment-naive FLAIR patients had levelled out (8% vs 8%, Q4W vs SOC).
Due to the different durations of controlled phases of the FLAIR and ATLAS studies, no Week 100 comparison is available for treatment-experienced ATLAS patients.
The higher risk for treatment-naive patients in the first year of treatment may be regarded as acceptable as no higher risk of fatal SAEs was observed.

SAEs (Q8W vs Q4W)
More SAEs occurred under the Q8W vs the Q4W treatment regimen in the ATLAS-2M study: 5% vs. 4% of patients, respectively.

SAEs (Q8W vs oral SOC)
A post-hoc indirect comparison of the Q8W and QD oral SOC regimens showed that the risk If SAEs is higher for the Q8W treatment regimen than for oral SOC (odds ratio 1.8) (excluding injection site reactions). However, the differences between the treatment groups are considered small enough to be acceptable for approval.

Grade 3-4 AEs (Q4W vs oral SOC):
More grade 3-4 adverse events (AEs) were observed through to Week 48 in the investigational treatment group than in the control group: 11% versus 6% patients of the pooled FLAIR and ATLAS studies, respectively.
Through to Week 100, 14% vs 6% patients of the FLAIR study suffered 3-4 AEs.

Grade 3-4 AEs (Q8W vs Q4W):
Similar proportions of patients in the two long-acting injection treatment groups experienced grade 3-4 AEs when excluding injections site reactions (4.9% vs 4.6% patients, respectively).

AEs (Q4W vs oral SOC)
Overall, the frequency of AEs was distinctly higher in the Q4W CAB+RPV groups than in the control groups on standard oral ART in both pivotal Phase 3 studies, FLAIR (94% vs 80%) and ATLAS (95% vs 71%). The picture remained similar after exclusion of the high rates of injection site reactions and was principally consistent over all categories of AEs, including adverse drug reactions. See also Table 6 in *Adverse* Reactions section of the Swiss information for healthcare professionals.

AEs (Q8W vs Q4W)
Slightly fewer subjects from the Q8W than from the Q4W treatment group suffered non-serious AEs including injection site reactions in the ATLAS-2M study (91% vs 92%). However, this is more than with oral SOC (see below) and is probably due to the less frequent injection site reactions (ISRs). An analysis of AEs excluding ISRs was not provided.

AEs (Q8W vs oral SOC)
Across the studies, the slightly lower AE frequency (including ISRs) under the Q8W versus the Q4W treatment regimen is still much higher when compared with the oral SOC arms in the FLAIR and ATLAS studies (91% vs 71-80%, see above).

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A post-hoc anchored indirect comparison of the Q8W treatment regimen with QD oral SOC, which used the Q4W treatment regimen as the common comparator, showed that – even when excluding ISRs - the risk of AEs, grade 3-5 AEs and discontinuations due to AEs is higher for the Q8W treatment regimen than for QD oral SOC ART regimens (odds ratios 1.2, 1.7 and 1.5, respectively).

Greater use of pain killers was observed in patients on the long-acting injection treatment regimens compared to oral SOC.

The adverse drug reactions of the Q4W and Q8W treatment regimens with CAB+RPV (including oral lead-in or bridging phases) are listed and described in the *Warnings and Precautions* section of the Swiss information for healthcare professionals.

6.5 Final Clinical and Clinical Pharmacology Benefit-Risk Assessment

Beneficial effects

PK Vocabria (oral and IM):
The PK characteristics of cabotegravir are adequately characterised; the prolongation of the terminal half-life following IM administration is well understood. Therapeutically targeted cabotegravir plasma concentrations are maintained during all phases of treatment following the Q4W or the Q8W dosing regimen.The PK of cabotegravir was assessed in patients with mild and moderate (Child Pugh A and B) hepatic impairment and in patients with mild, moderate and severe (not requiring dialysis) renal impairment. Patients with severe hepatic impairment or with severe renal impairment requiring dialysis were not investigated. The interaction potential was comprehensively assessed and results of these assessments and respective dosing recommendations are included in the information for healthcare professionals.There was no QT/QTc prolongation potential for cabotegravir at supratherapeutic cabotegravir oral doses.

Q4W treatment regimen
Efficacy of the Q4W CAB+RPV treatment regimen was demonstrated in two pivotal Phase 3 studies, FLAIR and ATLAS, in treatment-naive and treatment-experienced HIV-1-infected patients who were virologically suppressed for 5-6 months prior to start of treatment with CAB+RPV. Non-inferiority to oral standard of care (DTG/ABC/3TC in the FLAIR study; a dual NRTI backbone plus INI, NNRTI or PI as a third drug in the ATLAS study) was shown with respect to loss of virologic suppression, the parameter of interest in switch trials.

Q8W treatment regimen
Efficacy of the Q8W CAB+RPV treatment regimen was demonstrated in the pivotal Phase 3b ATLAS-2M study in HIV-1-infected patients who were virologically suppressed prior to study start for at least 6 months (either by Q4W CAB+RPV LAI or by oral SOC). Non-inferiority to the Q4W CAB+RPV treatment regimen was shown with respect to loss of virologic suppression, the parameter of interest in switch trials.

Uncertainties about the beneficial effects

Although Vocabria/Rekambys is a long-term treatment, no pivotal data on efficacy, development of HIV resistances and safety are available beyond 2 years.

Unfavourable effects (risks)

PK: The combined administration of cabotegravir with UGT1A1 inducers such as rifampicin is contraindicated due to the 59% decrease in cabotegravir AUC and loss of antiviral activitiy.

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Long persisting drug release after IM injection (Q4W and Q8W)
The long persistence of the drug release is especially relevant after end of treatment with Vocabria/Rekambys. There is neither a mechanism by which the drug release from the IM depots can be stopped, nor a mechanism by which the IM depots can be removed or accessed by aspiration. Furthermore, once the drugs have reached the systemic circulation, there are no known neutralising drugs or antibodies, and even if there were a short-term mechanism to reduce systemic concentrations, these would be subsequently replaced by drug released from the IM depots. Lastly, both CAB and RPV are heavily protein bound molecules and are not expected to be susceptible to removal via hemodialysis. See also the *Warnings and Precautions* section of the Swiss information for healthcare professionals.

In conclusion, the single death cases, the slightly higher risk of SAEs, the higher frequencies of non-serious AEs under the Q4W and Q8W treatment regimens with cabotegravir and rilpivirine in comparison to the daily oral standard of care and any individual (S)AEs were not considered as prohibitive for approval.

Conclusion

1. *Q4W treatment regimen*

Vocabria & Rekambys, a complete treatment regimen combining only the two antiretrovirals cabotegravir (CAB) and rilpivirine (RPV), is a new treatment option with a new route of administration (intramuscular long-acting injections, IM LAI) and a reduced dosing frequency (monthly, Q4W). In terms of efficacy, this treatment regimen has been proven to be non-inferior to standard oral antiretroviral regimens (SOC) in treatment-naive HIV-1-infected patients after a 5 month induction of virologic suppression with SOC as well as in treatment-experienced HIV-1-infected patients who were virologically suppressed for at least 6 months and had no history of virologic failure.

In terms of safety, the Q4W CAB+RPV IM LAI regimen appears to be associated with more risks than oral SOC regimens because of a) the long persistence of drug release after IM injection, b) a slightly higher frequency of SAEs (at least for treatment-naive patients in the first treatment year), c) a distinctly higher frequency of grade 3-4 AEs and of AEs in general (with and without injection site reactions) and d) more frequent use of analgetics due to the very common ISRs.
All these above-mentioned uncertainties and risks can be regarded as acceptable as a) there was no higher risk of fatal SAEs compared to oral SOC, b) the patients are free to switch back to oral SOC and c) all relevant information is provided in the Swiss information for healthcare professionals and patient information.

In summary, the benefit-risk ratio for the Q4W CAB+RPV IM LAI regimen is positive.

2. *Q8W treatment regimen*

Vocabria & Rekambys, a complete treatment regimen combining only the two antiretrovirals cabotegravir (CAB) and rilpivirine (RPV), is a new treatment option with a new route of administration (intramuscular long-acting injections, IM LAI) and a reduced dosing frequency (monthly, Q4W).
In terms of efficacy, this treatment regimen has been proven non-inferior to the Q4W treatment regimen (with a very small numerical disadvantage) in HIV-1-infected patients who were virologically suppressed for at least 6 months.
The Q8W treatment regimen was, however, not directly compared to standard oral antiretroviral regimens (SOC), which is considered acceptable based on the totality of the data. A cross-study comparison of the Q8W treatment regimen with oral SOC suggests a virologic failure rate

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in the same order of magnitude. A post-hoc indirect comparison with oral SOC, which used the Q4W treatment regimen as the common comparator, revealed only slightly more treatment failures in the Q8W treatment regimen, which is acceptable because a switch back to one of numerous oral antiretroviral regimens is possible.

In terms of safety, the Q8W CAB+RPV IM LAI regimen appears to be associated with more risks than oral SOC regimens because of a) the long persistence of drug release after IM injection, and b) a higher risk of SAEs, grade 3-5 AEs, AEs leading to discontinuation and AEs in general (with and without ISRs) – as suggested by a post-hoc indirect comparison between the Q8W treatment regimen and oral SOC.

When comparing the Q8W with the Q4W treatment regimen, the Q8W regimen seems to be associated with a slightly higher risk of SAEs and injection site reactions (ISRs). However, there was no difference in the frequency of grade 3 AEs, and a slightly lower frequency of grade 3 ISRs, slightly lower use of analgesics and a slightly lower frequency of non-serious AEs (including ISR). As the safety differences between the two long-acting injection regimens were rather small (mostly 1% of patients), the two treatment regimens are considered interchangeable.

In summary, the benefit-risk ratio for the Q8W CAB+RPV IM LAI regimen is positive.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Vocabria, prolonged release suspension for injection was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Vocabria

Composition

Active Ingredients:

cabotegravir

Excipients:

Mannitol (E421), Polysorbate 20, Macrogol 3350, water for injection ad solutionem per 1 ml.

Pharmaceutical form and active ingredient quantity

Prolonged-release suspension for IM injection:

Each 2 ml vial contains 400 mg cabotegravir (200 mg/ml) as free acid.

Each 3 ml vial contains 600 mg cabotegravir (200 mg/ml) as free acid.

Indications

Vocabria injections are indicated in combination with rilpivirine injections for treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/ml*)* on a stable antiretroviral treatment for at least 6 months prior to the switch to the cabotegravir-rilpivirine combination and have no known or suspected resistance to or no history of virological failure with agents of the NNRTI and INI class (see *Clinical Efficacy*)**.**

Dosage and Administration

Therapy should be initiated by a physician experienced in the management of HIV infection.
Vocabria injections should always be given in combination with rilpivirine injections for the treatment of HIV-1. Therefore, also refer to the prescribing information for rilpivirine injections.
Prior to starting Vocabria injection, 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.

Posology

Adults

Oral lead in

To assess tolerability to cabotegravir, cabotegravir tablets are recommended for approximately one month (at least 28 days, up to a maximum of 2 months) in virologically suppressed patients prior to the initiation of cabotegravir injections. One Vocabria tablet (30 mg) should be taken with one rilpivirine tablet (25 mg) once daily. When administered with rilpivirine, Vocabria tablets should be taken with a meal (see prescribing information for Vocabria 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. Cabotegravir and rilpivirine injections should be administered at separate gluteal injection sites (opposite sides) during the same visit.
If opposite sides are not possible, the injections should be given at least 2 cm apart.

Continuation Injections

After the initiation injection, the recommended Vocabria continuation injection dose in adults is a single 2 ml (400 mg) intramuscular injection, administered monthly. The cabotegravir injection and rilpivirine injection should be administered at separate gluteal injection sites (opposite sides) during the same visit. If opposite sides are not possible, the injections should be given at least 2 cm apart. A 2 cm space should also be kept from previous injection sites or any reactions at previous injection sites. 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 Dosing Schedule for monthly intramuscular administration in Adults

	ORAL LEAD IN	**INITIATION INJECTION IM**	**CONTINUATION INJECTION IM**
Drug	**once daily (at least 28 days, up to 2 months) followed by initiation injection**	**Following oral lead-in: One-time**	**One month after initiation injection and monthly onwards**
Vocabria	30 mg	3 ml (600 mg)	2 ml (400 mg)
Rilpivirine	25 mg	3 ml (900 mg)	2 ml (600 mg)

Every 2 Month Dosing (Suspension for Injection)

Initiation Injections

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

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

	ORAL LEAD-IN	**INITIATION INJECTIONS IM**	**CONTINUATION INJECTIONS IM**
Drug	**once daily (at least 28 days, up to 2 months) followed by initiation injections**	**Following oral lead-in and 1 month afterwards**	**Two months after final initiation injection and every two months onwards**
Vocabria	30 mg	3 ml (600 mg)	3 ml (600 mg)
Rilpivirine	25 mg	3 ml (900 mg)	3 ml (900 mg)

Dosing recommendations when Switching from Monthly to Every 2 Month Injections
Patients switching from a monthly continuation injection schedule to an every 2 month continuation injection 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 Injections to Monthly injections
Patients switching from every 2 month continuation injection dosing schedule to a monthly dosing schedule in the maintenance phase should receive a single intramuscular injection of 2 ml (400 mg) of Vocabria two months after the last 3 ml (600 mg) Vocabria injection and 2 ml (400 mg) monthly thereafter.

Missed Injections

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
Oral bridging treatment and resumption of monthly injections:
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. 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. If more than two consecutive monthly injections are missed and need to be replaced, an alternative oral treatment should be started one month after the last injection of Vocabria.

Table 3: Injection Dosing Recommendations for the Resumption of monthly Injections After Missed Injections or After Oral Bridging Therapy

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

Oral bridging treatment and resumption of every 2-month injections:

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. 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 for the Resumption of every 2 month Injections After Missed Injections or After Oral Bridging Therapy

Missed Injection Visit	**Time since last injection**	**Recommendation (all injections are 3 ml)**
Injection 2 (Month 3)	**≤ 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 (Month 5 onwards)	**≤ 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.

Special Dosing Recommendations

Hepatic impairment

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

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 Pharmacokinetics – Special Patient Populations*).

Adolescents and Children

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

Method of Application

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

The cabotegravir and rilpivirine injections should be administered at separate gluteal injection sites (opposite sides) during the same visit. If opposite sides are not possible, the injections should be given at least 2 cm apart. A 2 cm space should also be kept from previous injection sites or any reactions at previous injection sites.

Please follow the detailed step-by-step instructions for injection in the instructions for use in the package.

Vocabria injection should be administered by a healthcare professional.

When administering the cabotegravir 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.

Contraindications

Cabotegravir is contraindicated in patients:

- with known hypersensitivity to cabotegravir or to any of the excipients of the injection formulation.
- receiving strong UGT1A1 inducers e.g. rifampicin, rifapentine, phenytoine, phenobarbital, carbamazepine and oxcarbazepine as they are expected to decrease cabotegravir plasma concentrations and may result in loss of virologic response.

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

Warnings and Precautions

Long acting properties of cabotegravir injection

Residual concentrations of cabotegravir injection may remain in the systemic circulation of patients for prolonged periods (up to 12 months or longer), therefore, the prolonged release characteristics of cabotegravir beyond the active dosing period has to be taken into consideration in the individual benefit/risk assessment and into consideration when the medicinal product is discontinued (see *Warnings and Precautions (Hypersensitivity Reactions, Hepatoxicity), Interactions, Pregnancy and Lactation, Undesirable effects, Pharmacokinetics and Overdosage)*

There is no mechanism by which the release of cabotegravir after intramuscular injection can be stopped or neutralised or removed from the muscle (e.g. by aspiration) or the blood (e.g. by haemodialysis) due to strong protein binding.

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. While no such reactions have been observed to date in association with cabotegravir, physicians should remain vigilant and should discontinue cabotegravir 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. Administration of oral lead-in is recommended to help identify patients who may be at

risk of a hypersensitivity reaction (see *Dosing and Administration, Contraindications and Long acting properties of cabotegravir injection*).

Hepatotoxicity

Hepatotoxicity has been reported in a limited number of patients receiving cabotegravir with or without known pre-existing hepatic disease (see *Adverse reactions*).
Monitoring of liver chemistries is recommended and treatment with cabotegravir should be discontinued if hepatotoxicity is suspected (see *Long acting properties of cabotegravir injection)*.

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 cabotegravir when dosed every two months.

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

Opportunistic infections
Patients receiving cabotegravir 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.

Immune reconstitution and inflammation syndrome
Immune reconstitution and inflammatory syndrome have been reported in patients receiving combination antiretroviral therapy. In the initial phase of combination antiretroviral therapy, patients whose immune systems respond to treatment may develop an inflammatory reaction against indolent or residual opportunistic infections (e.g. with Mycobacterium avium complex, cytomegalovirus, Pneumocystis jiroveci pneumonia and tuberculosis), which may require further evaluation and treatment. There have also been reports of autoimmune diseases (such as Graves' disease and autoimmune hepatitis) occurring as part of an immune reconstitution and inflammatory syndrome. However, the timing of onset is more variable, and these events may occur many months after the start of treatment.

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-1 in combination with rilpivirine, therefore, the prescribing information for rilpivirine should be consulted.

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

Concomitant use of Vocabria injection with rifabutin is not recommended (see *Interactions*).

Patients with hepatitis B and hepatitis C virus co-infection
Patients with a hepatitis B co-infection were excluded from participating in the studies with Vocabria. It is not recommended that patients with hepatitis B co-infection start treatment with Vocabria. The current treatment guidelines for HIV infection in patients with hepatitis B virus co-infection must be followed, as well as the section on *Interaction*s (see below).
Very limited data are available on the use of Vocabria in patients with hepatitis C virus co-infection. If hepatitis C infection occurs during treatment with Vocabria, the current treatment guidelines for HIV infection in patients with hepatitis C virus co-infection must be followed, as well as the section on *Interactions* (see below).

Interactions

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

Effect of Vocabria on 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, 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 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 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, and ibalizumab.

Effect of other agents on Vocabria

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 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 OATP1B1, OATP1B3 or 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.

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

Effect of Coadministered Drugs on the Pharmacokinetics of Cabotegravir[1]				
Coadministered Drug Class + Drug(s) and Dose(s)	**Effects on drug concentration GMR (90% CI) No Effect = 1.00**			**Recommendation for concomitant use**
	C_{max}	**AUC**	**C_τ or C_{24}**	
HIV-1 Antiviral Agents				
NNRTI Etravirine 200 mg twice daily	1.04 (0.99, 1.09)	1.01 (0.96, 1.06)	1.00 (0.94, 1.06)	Etravirine did not significantly change cabotegravir plasma concentration. No dose adjustment is necessary when co-administered with etravirine.
NNRTI Rilpivirine 25 mg once daily	1.05 (0.96, 1.15)	1.12 (1.05, 1.19)	1.14 (1.04, 1.24)	Rilpivirine did not significantly change cabotegravir plasma concentration. No dose adjustment is necessary when co-administered with rilpivirine.
Other agents				
Rifabutin 300 mg once daily	0.83 (0.76, 0.90)	0.77 (0.74, 0.83)	0.74 (0.70, 0.78)	As rifabutin can significantly reduce the plasma concentration of cabotegravir, concomitant administration should be avoided.
Rifampicin 600 mg once daily	0.94 (0.87, 1.02)	0.41 (0.36, 0.46)	0.50 (0.44, 0.57)	Rifampicin significantly decreased cabotegravir plasma concentrations due to induction of UGT metabolism which is likely to result in loss of therapeutic effect. Dosing recommendations for co-administration of Vocabria with rifampicin have not been established and co-administration of Vocabria with rifampicin is contraindicated.
Effect of Cabotegravir[1] on the Pharmacokinetics of Coadministered Drugs				
Coadministered Drug Class + Drug(s) and Dose(s)	**Effects on drug concentration GMR (90% CI) No Effect = 1.00**			**Recommendation for concomitant use**
	C_{max}	**AUC**	**C_τ or C_{24}**	
HIV-1 Antiviral Agents				
Rilpivirine 25 mg once daily	0.96 (0.85, 1.09)	0.99 (0.89, 1.09)	0.92 (0.79, 1.07)	Cabotegravir did not significantly change rilpivirine plasma concentrations. No dose adjustment of rilpivirine is necessary when co-administered with Vocabria.

Other agents				
Ethinyl estradiol 0.03 mg once daily	0.92 (0.83, 1.03)	1.02 (0.97, 1.08)	1.00 (0.92, 1.10)	Cabotegravir did not significantly change ethinyl estradiol/ levonorgestrel plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with Vocabria.
Levonorgestrel 0.15 mg once daily	1.05 (0.96, 1.15)	1.12 (1.07, 1.18)	1.07 (1.01, 1.15)	Cabotegravir did not significantly change levonorgestrel plasma concentrations to a clinically relevant extent. No dose adjustment of oral contraceptives is necessary when co-administered with Vocabria.
Midazolam 3 mg	1.09 (0.94, 1.26)	1.10 (0.95, 1.26)	Not Available	Cabotegravir did not significantly change midazolam plasma concentrations to a clinically relevant extent. No dose adjustment of CYP3A substrates is necessary when co-administered with Vocabria.

1 Cabotegravir 30 mg administered orally once daily for all studies except for Rifampicin where cabotegravir 30 mg was administered as single dose

Other Agents Expected to Decrease Cabotegravir Concentrations without Clinical Data		
Class of Concomitant Agent	**Drug Name(s)**	**Recommendation for concomitant use**
Antimycobacterials	Rifapentine	Rifapentine, a metabolic inducer, may significantly decrease cabotegravir plasma concentrations, concomitant use is contraindicated.
Anticonvulsants	Carbamazepine, Oxcarbazepine, Phenytoin, Phenobarbital	Metabolic inducers may significantly decrease cabotegravir plasma concentrations, concomitant use is contraindicated.

GMR = Geometric Mean Ratio

Pregnancy, Lactation

Pregnancy

There are no studies of cabotegravir in pregnant women. The effect of cabotegravir 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 *Preclinical data*).

The significance of these findings for human pregnancy is not known.

Vocabria should not be used during pregnancy or in women who are planning to become pregnant or who do not use a reliable contraceptive method, unless the expected benefits justify the possible risks to the foetus or unborn child.

Women should be counselled about the use of effective contraception. Cabotegravir and oestrogen

and/or progesterone-based contraceptives can be used concomitantly without dose adjustment (*see Interactions*).
After cabotegravir injections, residual concentrations have been detected in the body of patients for up to 12 months or longer (see *Warnings and Precautions*) which should be considered for the duration of effective contraception.

Lactation

Based on animal studies, it can be assumed that cabotegravir passes into breast milk, although this has not been proven for humans.
After cabotegravir therapy, residual concentrations may be present in breast milk for up to 12 months or longer after the last injection.
It is recommended that HIV-positive women do not breastfeed their babies to avoid HIV transmission and the possibility of adverse effects in the breastfed infant.

Fertility

Animal studies indicate no effects of cabotegravir on male or female fertility (*see Preclinical Data*).

Ability to perform tasks that require Judgement, Motor or Cognitive Skills

There have been no studies to investigate the effect of cabotegravir on driving performance or the ability to operate machinery. Vocabria can cause dizziness, headaches and nausea. 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) associated with cabotegravir alone or combination therapy of cabotegravir plus rilpivirine (monthly dosing or dosing every 2 months) are listed in Table 6.
ADRs listed include those attributable to both the oral and injectable formulations of cabotegravir and rilpivirine.

Frequencies were calculated from Phase III clinical studies and where they differed between monthly and every 2 month treatment regimens, 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% of patients), headache (up to 12% of patients) and pyrexia[3] (10% of patients).

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

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	**Frequency**	**ARs for Vocabria + rilpivirine regimen**
Metabolic and nutritional disorders	Common	Weight increased
Psychiatric disorders	Common	Depression Anxiety Abnormal dreams Insomnia
Nervous system disorders	Very common	Headache (12%)
	Common	Dizziness
	Uncommon	Somnolence Vasovagal reactions (in response to injections)
Gastrointestinal disorders	Common	Nausea Vomiting Abdominal pain[1] Flatulence Diarrhoea Lipase increased (grades 3-4)
Hepatobiliary Disorders	Uncommon	Hepatotoxicity Transaminases increased (AST/ALT)
Skin and subcutaneous tissue disorders	Common	Rash[2]
Musculoskeletal and	Common	Myalgia

connective tissue disorders		Creatine phosphokinase increased (grades 3-4)
General disorders	Very Common	Pyrexia[3] (10%)
	Common	Fatigue Asthenia Malaise
Administrative site conditions: Reactions at the injection site[4] (84%)	Very common	Pain (79%) Nodules (17%) Induration (12%)
	Common	Discomfort Swelling Erythema Pruritus Bruising Warmth Haematoma
	Uncommon	Cellulitis Abscess Anaesthesia Haemorrhage Discolouration

[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 generalized, rash macular, rash maculo-papular, rash morbilliform, rash popular, rash pruritic.
[3] Pyrexia includes the following grouped MedDRA preferred terms: pyrexia, feeling hot, body temperature increased.
[4] Injection site reactions listed in the table have been reported in 2 subjects or more.

Description of selected adverse reactions and additional information

Frequent Adverse Drug Reactions under Vocabria/Rekambys once monthly compared to standard daily oral therapy (CAR).

Table 7. Systemic Adverse Reactions Reported in ≥1% of Virologically Suppressed Subjects with HIV-1 Infection in Pooled FLAIR and ATLAS Trials (Week 48)

Adverse Reaction	CAB+RPV (N=591)	CAR (N=591)
Headache	12%	6%
Pyrexia[3]	10%	2%
Diarrhoea	9%	7%

Creatine phosphokinase increased (grades 3-4)	8%	4%
Lipase increased (grades 3-4)	6%	3%
Nausea	5%	3%
Fatigue	5%	2%
Rash[2]	5%	3%
Dizziness	4%	1%
Myalgia	4%	1%
Abdominal pain[1]	4%	2%
Insomnia	4%	1%
Anxiety	4%	2%
Asthenia	3%	<1%
Vomiting	2%	1%
Depression	2%	2%
Malaise	2%	<1%
Abnormal dreams	1%	<1%
Flatulence	1%	<1%

[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 generalized, rash macular, rash maculo-papular, rash morbilliform, rash popular, rash pruritic.
[3] Pyrexia includes the following grouped MedDRA preferred terms: pyrexia, feeling hot, body temperature increased.
CAR = current antiretroviral regimen

It should be noted that the FLAIR and ATLAS were open label switch studies (see details also in section *Clinical efficacy*). Higher frequencies of ARs have been reported in the cabotegravir and rilpivirine arm which may either be attributed to the treatment regimen or due to bias caused by the study design.

Local injection site reactions (ISR)

Monthly dosing

In Phase III studies (ATLAS, FLAIR and ATLAS-2M monthly dosing), up to 1% of subjects discontinued treatment with Vocabria plus rilpivirine because of ISRs. Out of 30393 injections, 6815 ISRs were reported and the severity of the reactions was generally mild (Grade 1, 75% of subjects) or moderate (Grade 2, 36% of subjects). 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 (1 days to 341 days), with up to 11% of subjects reporting unresolved ISRs at the time of their next injection. The percentage of subjects reporting ISRs decreased over time from 70% at Week 4 to 19% at week 48.

Every 2-month dosing
In ATLAS-2M, less than 1% of subjects discontinued treatment with Vocabria plus rilpivirine because of ISRs. Out of out of 8470 injections, 2507 ISRs were reported and the severity of the reactions was generally mild (Grade 1, 71% of subjects) or moderate (Grade 2, 27% of subjects). 3% of subjects experienced severe (Grade 3) ISRs, and no subjects experienced Grade 4 ISRs.
The median duration of overall ISR events was 3 days (1 days to 424 days), with 5% of subjects reporting unresolved ISRs at the time of their next injection.
The percentage of subjects reporting ISRs decreased over time from 70% at Week 4 to 20% at Week 48.

Weight increased
At the Week 48 time point, subjects in studies FLAIR and ATLAS, who received cabotegravir plus 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 plus rilpivirine arms were 1.3 kg and 1.8 kg respectively, compared to 1.5 kg and 0.3 kg in the CAR arms. At the 48 week timepoint, in ATLAS-2M the median weight gain in both the monthly and 2-monthly 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 plus rilpivirine. These changes are not considered clinically relevant as they likely reflect competition between cabotegravir and unconjugated bilirubin for a common clearance pathway (UGT1A1).

Elevated transaminases (ALT/AST) were observed in subjects receiving cabotegravir plus 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 (see *Warnings and Precautions*).

Asymptomatic creatine phosphokinase elevations, mainly in association with exercise, have also been

reported with cabotegravir plus rilpivirine treatment.

Additional information on special patient groups
The safety and efficacy of cabotegravir in children and adolescents aged under 18 years have not been established.

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

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the EIViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdosage

Symptoms and signs
There is currently no experience of overdose with Vocabria.
Treatment
There is no specific treatment for cabotegravir overdose. 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 toxicological information centre.
Cabotegravir is known to be highly protein bound in plasma; therefore, dialysis is unlikely to be helpful in removal of medicinal product from the body. Management of overdose with cabotegravir injection should take into consideration the prolonged exposure to the medicine following an injection (see *Warnings and Precautions*).

Properties/Effects

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.

Pharmacodynamics

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 to 1.4 nM in peripheral blood mononuclear cells (PBMCs) and 293T 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 four HIV-2 clinical isolates ranged from 0.10 nM to 0.14 nM.

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 in MT4 cells 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 PBMC.

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 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, G140S/Q148R and N155H/Q148R resulted in a 22-, 12- and 61-fold decrease in susceptibility to cabotegravir, respectively. While N155H did not alter susceptibility to cabotegravir more than 6-fold for other N155H double mutants.

Resistance in vivo

The number of subjects who met Confirmed Virologic Failure (CVF) criteria (two consecutive plasma HIV-1 RNA levels ≥200 c/ml after prior suppression to <200 c/m) was low across the pooled FLAIR and ATLAS phase III trials (see also section *Clinical Efficacy*). In the pooled analysis, there were 7 CVFs on cabotegravir plus rilpivirine (7/591, 1.2%) and 7 CVFs with continuation of current standard antiretroviral regimen (CAR) (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 and had no resistance mutations.

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 phase IIIb ATLAS-2M study (see also section *Clinical Efficacy*) 10 subjects met CVF criteria through Week 48: 8 subjects (1.5%) in the Q8W arm and 2 subjects (0.4%) in the Q4W arm. Eight subjects met CVF criteria at or before the Week 24 timepoint.

At Baseline in the Q8W arm, 5 subjects had 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 Y181Y/C + H221H/Y 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 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. Cabotegravir FCs (Fold Change in IC_{50}) for these subjects ranged from 1.8 to 9.1. All subjects remained sensitive to dolutegravir and bictegravir.

In the Q4W arm, neither subject with CVF 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 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. All subjects remained sensitive to dolutegravir and bictegravir.

Effects on Electrocardiogram

In a randomized, 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 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.

Clinical Efficacy

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 the FLAIR study, 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 about one month (at least 28 days, maximum 77 days), 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 up to 96 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 their 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 about one month (at least 28 days, maximum 73 days), 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) 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. This distribution remained similar after randomisation in the control arm (CAR).

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 studies FLAIR and ATLAS, 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%).

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. <5 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 N (%)	**CAR N=283 N (%)**	**CAB + RPV N=308 N (%)**	**CAR N=308 N (%)**	**CAB+RPV N=591 N (%)**	**CAR N=591 N (%)**
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)
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 n(%)	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 n(%)	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 n(%)	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, CAB = Cabotegravir, RPV = Rilpivirine, 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 (Third agent treatment class)	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 not clinically meaningful.

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

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).

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 the ATLAS-2M study, 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 about one month (at least 4 weeks, maximum 85 days). 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 cabotegravir + 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 + 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 copies/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%).

Table 10: Virologic Outcomes of Randomized Treatment for ATLAS-2M at 48 Weeks (Snapshot analysis)

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

Table 11: Proportion of Subjects with Plasma HIV-1 RNA ≥50 copies/ml at Week 48 for key baseline factors of patients (Snapshot Outcomes).

Baseline factors of patients		**Number of HIV-1 RNA ≥50 copies/ml/ Total Assessed (%)**	
		2 Month Dosing (Q8W) n/N (%)	**Monthly dosing (Q4W) n/N (%)**
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, CAB = cabotegravir, RPV = rilpivirine

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

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 Vocabria plus rilpivirine, examined the influence of baseline viral and participant characteristics, dosing regimen (Q4W or Q8W), and post-baseline plasma drug concentrations on confirmed virologic failure (CVF) using regression modelling with a variable selection procedure. Through Week 48 in these studies, 13/1039 (1.25%) participants had CVF while receiving cabotegravir and rilpivirine.

Four covariates were significantly associated (P<0.05 for each adjusted odds ratio) with increased risk of CVF: rilpivirine resistance mutations at baseline identified by proviral DNA genotypic assay, HIV-1 subtype A6/A1 (associated with integrase L74I polymorphism), rilpivirine trough concentration 4 weeks following initial injection dose, body mass index of at least 30 kg/m^2 (associated with cabotegravir pharmacokinetics). Other variables including Q4W or Q8W dosing, female gender, or other viral

subtypes (non A6/A1) had no significant association with CVF. No baseline factor, when present in isolation, was predictive of virologic failure. However, a combination of at least 2 of the following baseline factors was associated with an increased risk of CVF: rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI ≥30 kg/m^2 (see Table 12).

Table 12: Week 48 outcomes by presence of key baseline factors of rilpivirine resistance associated mutations, Subtype A6/A1[1] and BMI ≥30 kg/m^2

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%

Pharmacokinetics

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 65 to 76% was observed with single dose administration of long-acting cabotegravir injection.

Absorption

Cabotegravir injection exhibits absorption-limited pharmacokinetics because cabotegravir is slowly absorbed into the systemic circulation from the gluteal muscle resulting in sustained plasma concentrations. Following a single intramuscular dose, plasma cabotegravir concentrations are detectable on the first day and gradually rise to reach maximum plasma

concentration with a median T_{max} of 7 days. Cabotegravir has been detected in plasma up to 52 weeks or longer after administration of a single injection. Pharmacokinetic steady-state is achieved by 44 weeks.
Plasma CAB exposure increases in proportion or slightly less than in proportion to dose following single and repeat IM injection of doses ranging from 100 to 800 mg.

Distribution
Cabotegravir is highly bound (approximately >99%) to human plasma proteins, based on *in vitro* data. Following administration of oral tablets, the mean apparent oral volume of distribution (Vz/F) in plasma was 12.3 l. In humans, the estimate of plasma cabotegravir Vc/F was 5.27 l and Vp/F was 2.43 l. These volume estimates, along with the assumption of high F, suggest some distribution of cabotegravir to the extracellular space.
Cabotegravir is present in the female and male genital tract. Median cervical and vaginal tissue:plasma ratios ranged from 0.16 to 0.28 and median rectal tissue:plasma ratios were ≤0.08 following a single 400mg 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 + 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 copies/ml in 100% and <2 copies/ml in 15/16 (94%) of subjects. At the same time point, plasma HIV-1 RNA (n=18) was <50 copies/ml in 100% and <2 copies/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 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).

Elimination

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

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.

HBV and HCV Co-infected Patients

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

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.

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.

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.

Genetic Polymorphisms

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 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.

Preclinical Data

Repeat-dose toxicity (or toxicity after repeated administration)

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 at ~27 times the Maximum Recommended Human Dose [MHRD] of 30 mg oral dose or 500 mg/kg/day at ~3.7 times the MHRD of 30 mg oral, respectively.

In the 14 day oral 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 oral 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 systemic 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). Local inflammatory reactions (erythema and oedema graded very slight to severe) were noted in animals given 75 mg/kg/dose (monthly IM injections, >30 times the exposure in humans at the MRHD of 400 mg IM dose). Treatment-related histology findings were limited to granulomatous inflammation and mixed inflammatory cell infiltration at the corresponding injection sites, with correlating macroscopic changes.

Mutagenesis/Carcinogenesis

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 at ~7 times and the rat at ~26 times the MHRD of 30 mg oral.

Reproductive Toxicology

Cabotegravir when administered orally to male and female rats at 1000 mg/kg/day (>25 times the exposure in humans at the [MHRD] of 30 mg oral) for up to 26 weeks did not cause adverse effects on male or female reproductive organs or spermatogenesis and had no functional effects on male or female mating or fertility.

In embryo-foetal development studies there was no teratogenicity following oral administration of cabotegravir to pregnant rats and rabbits at doses up to 1000 or 2000mg/kg/day (30-fold or 0.66 times the exposure in humans at the MRHD of 30 mg oral)

A reduction in foetal body weight occurred in caesarean-delivered rats at 1,000 mg/kg/day; however, as there was no reproducible effect at this dose on the birth weights or postnatal growth and development of natural delivered pups, the foetal finding was not considered adverse. Cabotegravir was shown to cross the placenta of rats and was detected in foetal tissue. In rat pre- and postnatal (PPN) studies, cabotegravir at 1000 mg/kg/day reproducibly delayed the onset of delivery and was associated with increases in stillbirths and neonatal mortalities; there was no effect on survival when foetuses were delivered by caesarean section. A lower dose of 5 mg/kg/day (approximately 14 times the MRHD at 30 mg oral) was not associated with delayed delivery or neonatal mortality.

Other Information

Incompatibilities

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

Shelf-life

Vocabria may only be used up to the date marked "Exp." on the pack.

Special storage precautions

Do not store above 30°C. Do not freeze. Store in the original package and keep out of the sight and reach of children.

Shelf life in the syringe

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

Licence Number

67740 (Swissmedic)

Packs

Vocabria 400 mg prolonged-release suspension for injection: 2 ml (A)
Vocabria 600 mg prolonged-release suspension for injection: 3 ml (A)

Marketing authorization holder

ViiV Healthcare GmbH, 3053 Münchenbuchsee

Status of Information

May 2021

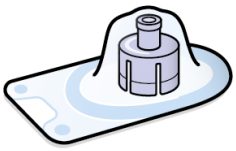
Injection Instructions for use of Vocabria 2 ml suspension for injection:

Overview
A complete dose requires two injections: 2 ml Cabotegravir and 2 ml Rilpivirine. 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 suspensions for injection are for intramuscular use only. Both injections must be administered to the gluteal sites. The ventrogluteal site is recommended. The administration order is not important.

Cabotegravir vial

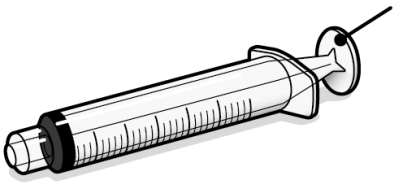
Vial cap (rubber stopper)

Vial adaptor



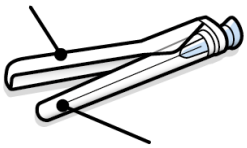
Syringe

Plunger



Injection needle

Needle guard



Needle cap

Your pack contains

- 1 vial of Cabotegravir
- 1 vial adaptor
- 1 syringe
- 1 injection needle (0.65 mm, 38 mm [23G, approx. 3.8 cm])

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

You will also need

- Non-sterile gloves
- 2 alcohol wipes
- 2 gauze pads
- A suitable sharps container
- 1 pack of Rilpivirine 2 ml prolonged-release suspension

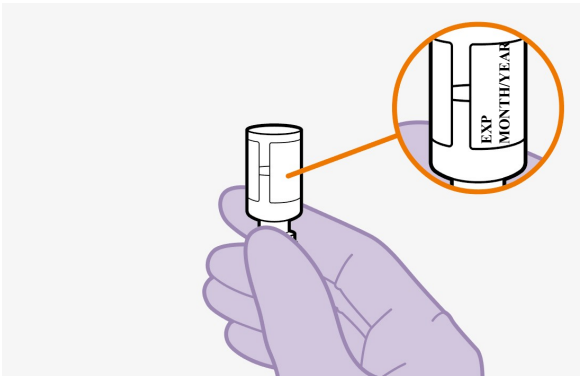
Preparation

1. Inspect both vials

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

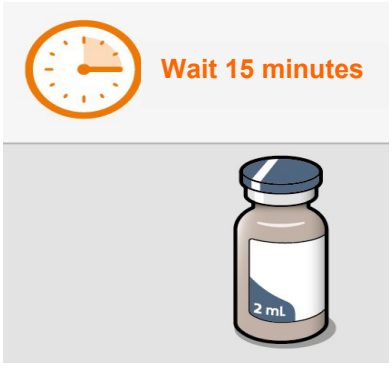
Note: The Cabotegravir vial has a brown tint to the glass.

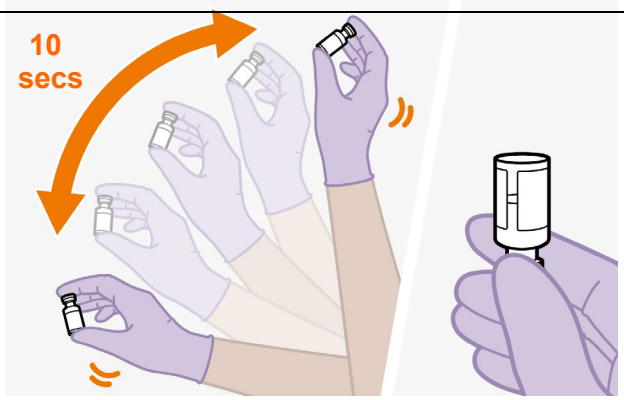
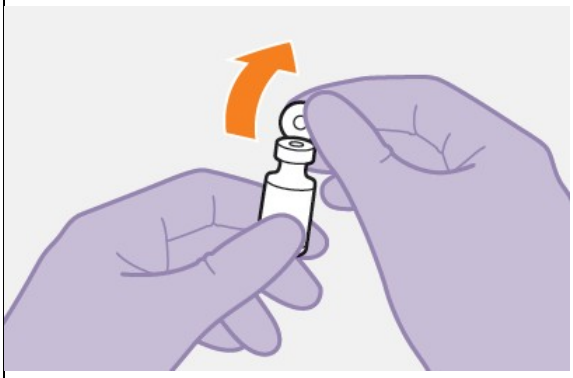
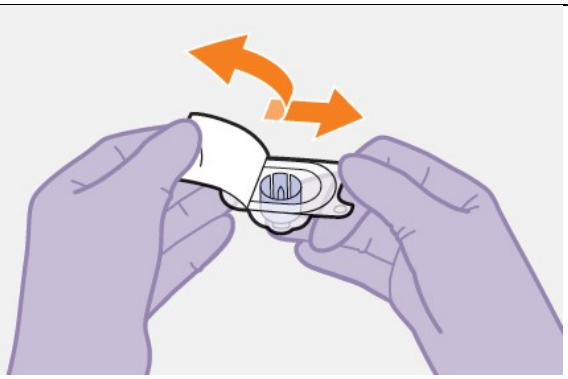
Do not use if the expiry date has passed.

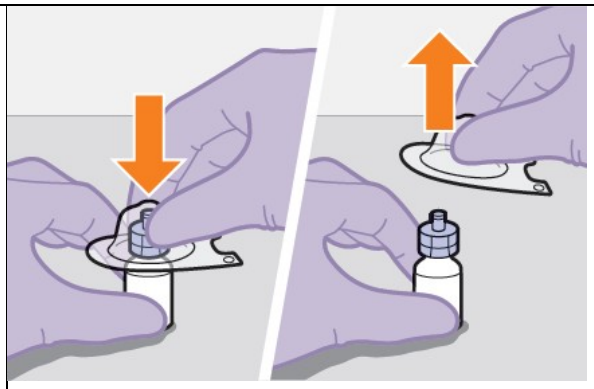
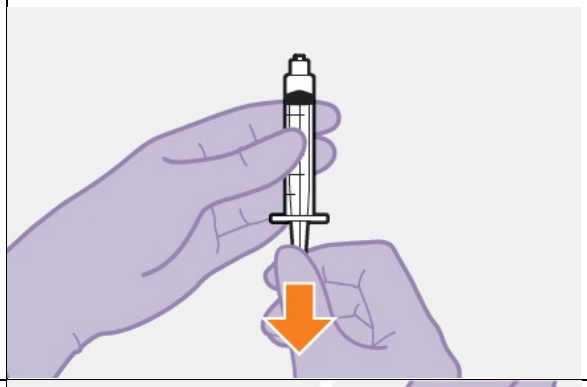
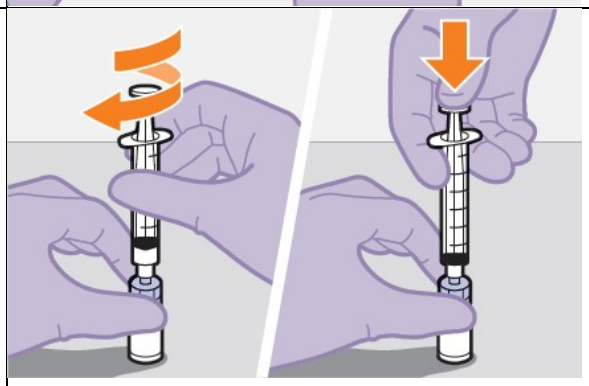


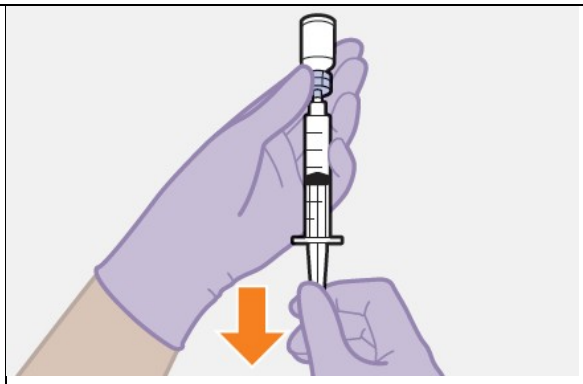
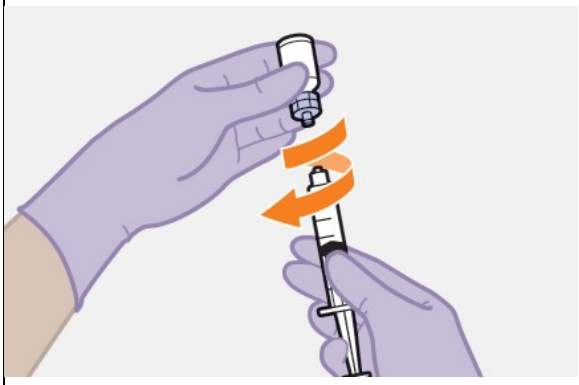
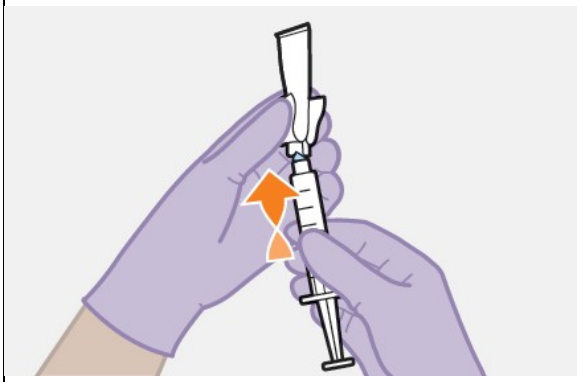
2. Wait 15 minutes

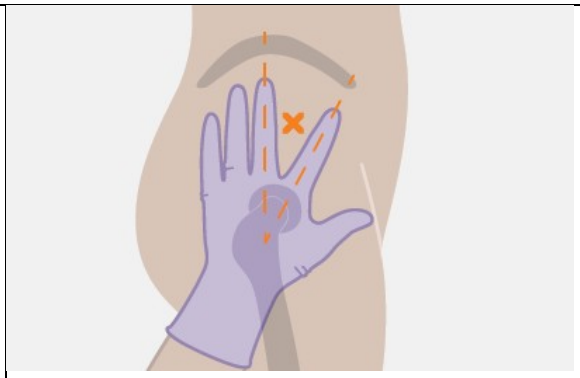
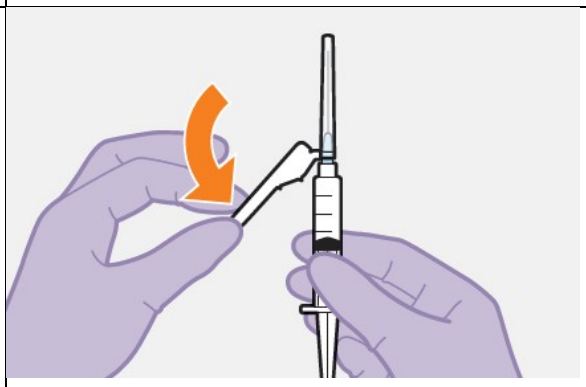
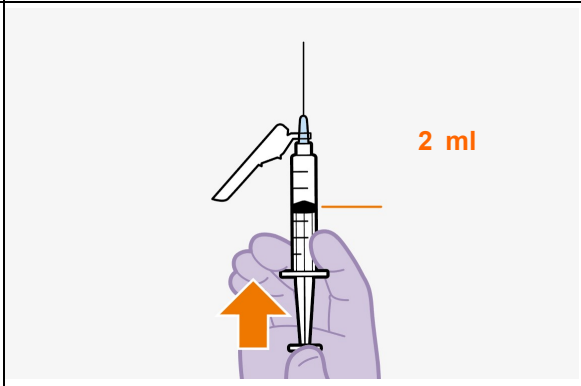
- If the pack has been stored in a fridge, wait at least 15 minutes before injecting to allow the medicine to come to room temperature.

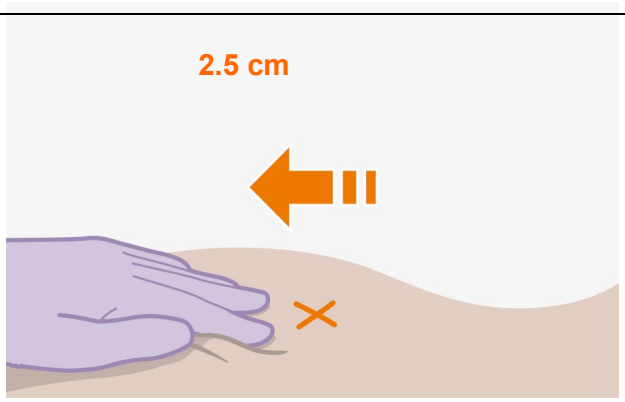
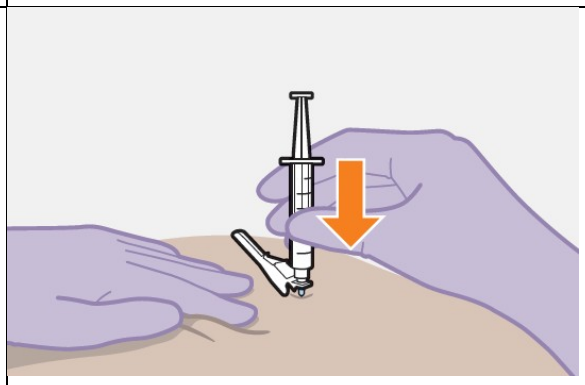
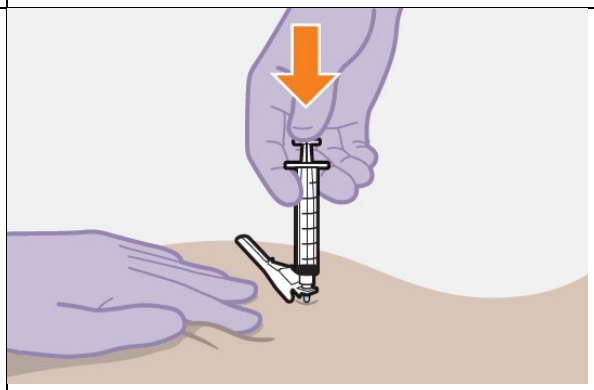


3. Vigorously shake • Hold the vial firmly, and vigorously shake for a full 10 seconds. • Invert the vial and check the resuspension. It should look uniform. If the suspension is not uniform, shake the vial again. • It is also normal to see small air bubbles.	
4. Remove vial cap • Remove the cap from the vial. • Wipe the rubber stopper with an alcohol wipe. **Do not** allow anything to touch the rubber stopper after wiping it.	
5. Peel open vial adaptor • Peel off the paper backing from the vial adaptor packaging. **Note**: Keep the adaptor in place in its packaging for the next step.	

6. Attach vial adaptor • Press the vial adaptor straight down onto the vial using the packaging, as shown. The vial adaptor should snap securely into place. • When you are ready, lift off the vial adaptor packaging as shown.	
7. Prepare syringe • Remove the syringe from its packaging. • Draw 1 ml of air into the syringe. This will make it easier to draw up the liquid later.	
8. Attach syringe • Hold the vial adaptor and vial firmly, as shown. • Screw the syringe firmly onto the vial adaptor. • Press the plunger all the way down to push the air into the vial.	

9. Slowly draw up dose • Invert the syringe and vial, and slowly withdraw as much of the liquid as possible into the syringe. There may be more liquid than the dose amount.	
10. Unscrew syringe • Screw the syringe off the vial adaptor, holding the vial adaptor as shown. **Note:** Keep the syringe upright to avoid leakage. Check that the suspension looks uniform and white to light pink.	
11. Attach needle • Peel open the needle packaging part way to expose the needle base. • Keeping the syringe upright, firmly twist the syringe onto the needle. • Remove the needle packaging from the needle.	

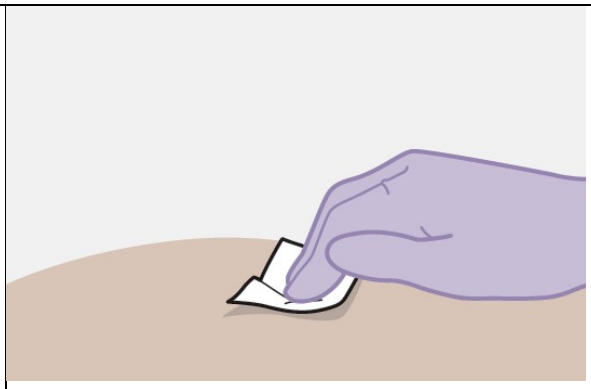
Injection	
12. Prepare Injection site Injections must be administered to the gluteal sites. Select from the following areas for the injection: Ventrogluteal, as shown (recommended) Dorsogluteal (upper outer quadrant) **Note:** For intramuscular use only. **Do not** inject intravenously.	
13. Remove cap • Fold the needle guard away from the needle. • Pull off the injection needle cap.	
14. Remove extra liquid • Hold the syringe with the needle pointing up. Press the plunger to the correct dose to remove extra liquid and any air bubbles. **Note:** Clean the injection site with an alcohol wipe. Allow the skin to air dry before continuing.	

15. Stretch skin Use the z-track injection technique to minimise medicine leakage from the injection site. • Firmly drag the skin covering the injection site, displacing it by about 2.5 cm. • Keep it held in this position for the injection.	
16. Insert needle • Insert the needle to its full depth, or deep enough to reach the muscle.	
17. Inject dose • Still holding the skin stretched – slowly press the plunger all the way down. • Ensure the syringe is empty. • Withdraw the needle and release the stretched skin immediately.	

18. Assess the injection site

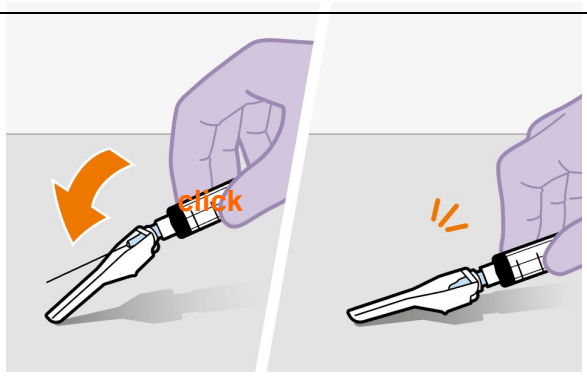
- Apply pressure to the injection site using a gauze.
- A small bandage may be used if a bleed occurs.

Do not massage the area.



19. Make needle safe

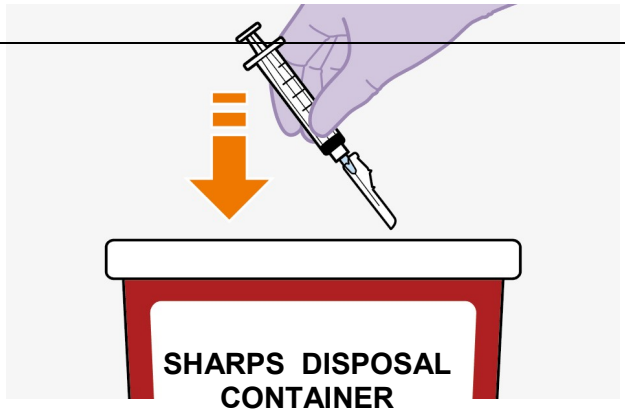
- Fold the needle guard over the needle.
- Gently apply pressure using a hard surface to lock the needle guard in place.
- The needle guard will make a click when it locks.



After Injection

20. Dispose safely

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



Repeat for 2nd medicine If you have only injected one of the two drugs, repeat all preparation steps and the injection again for the second drug.	

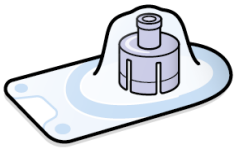
Injection Instructions for use of Vocabria 3 ml suspension for injection:

Overview
A complete dose requires two injections: 3 ml Cabotegravir and 3 ml Rilpivirine. 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 suspensions for injection are for intramuscular use only. Both injections must be administered to the gluteal sites. The ventrogluteal site is recommended. The administration order is not important.

Cabotegravir vial

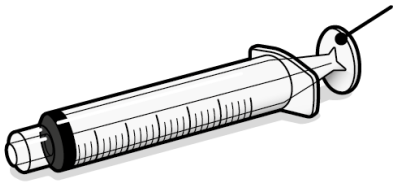
Vial cap (rubber stopper)

Vial adaptor



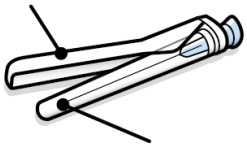
Syringe

Plunger



Injection needle

Needle guard



Needle cap

Your pack contains

- 1 vial of Cabotegravir
- 1 vial adaptor
- 1 syringe
- 1 injection needle (0.65 mm, 38 mm [23G, approx. 3.8 cm])

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

You will also need

- Non-sterile gloves
- 2 alcohol wipes
- 2 gauze pads
- A suitable sharps container
- 1 pack of Rilpivirine 3 ml prolonged-release suspension

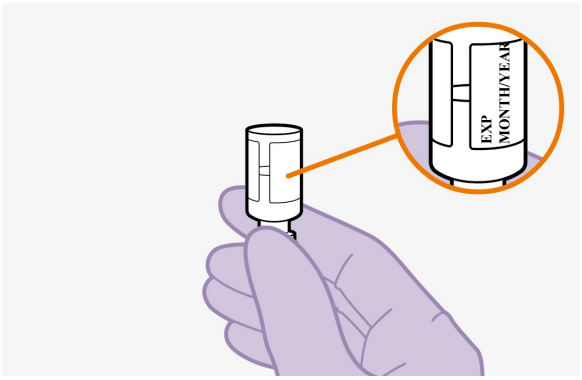
Preparation

1. Inspect both vials

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

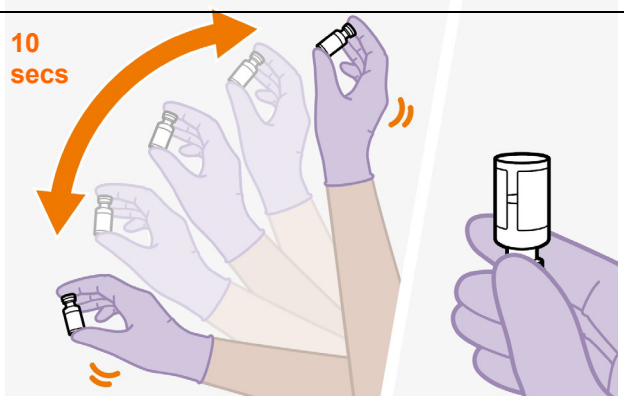
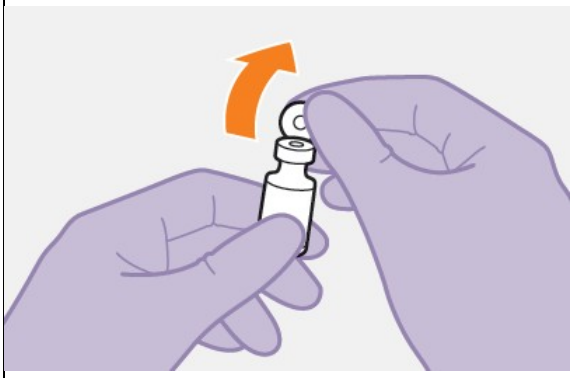
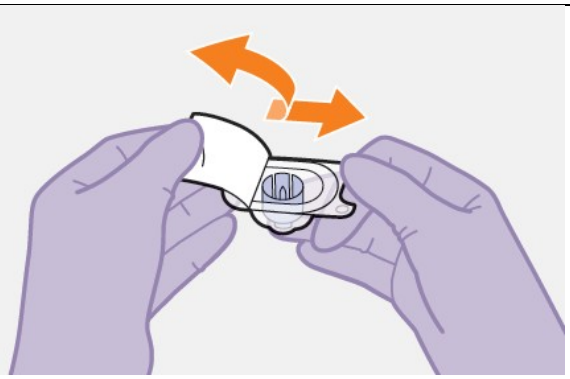
Note: The Cabotegravir vial has a brown tint to the glass.

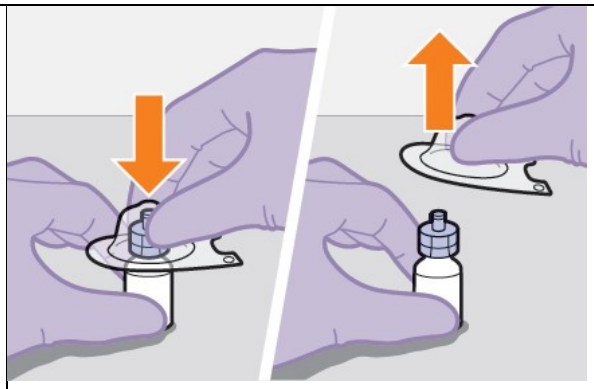
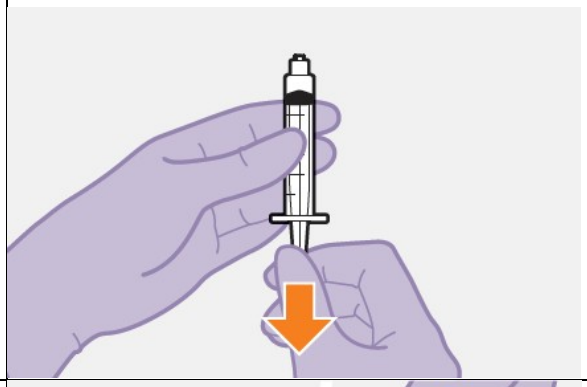
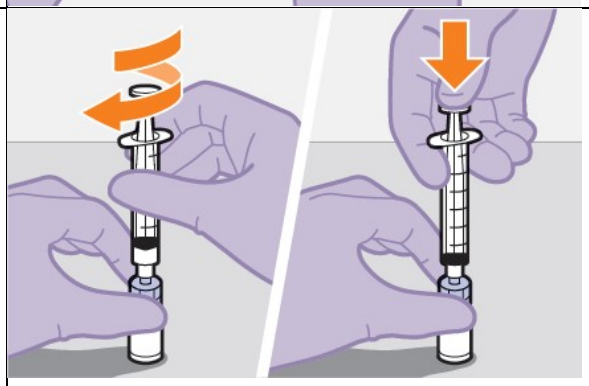
Do not use if the expiry date has passed.

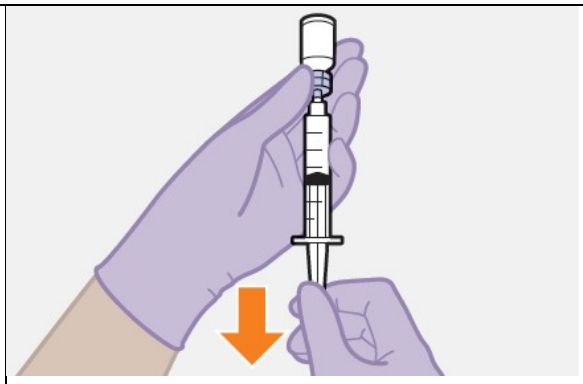
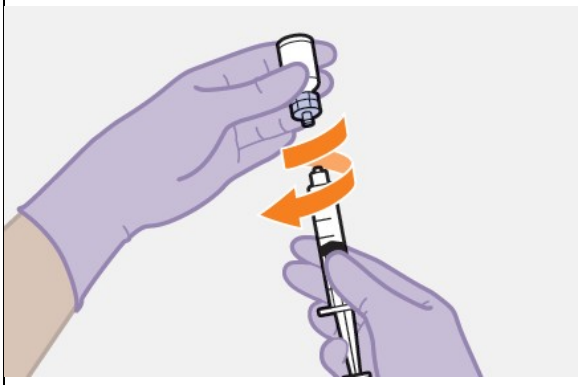
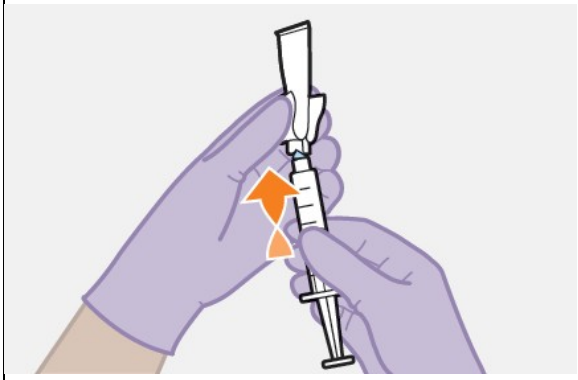


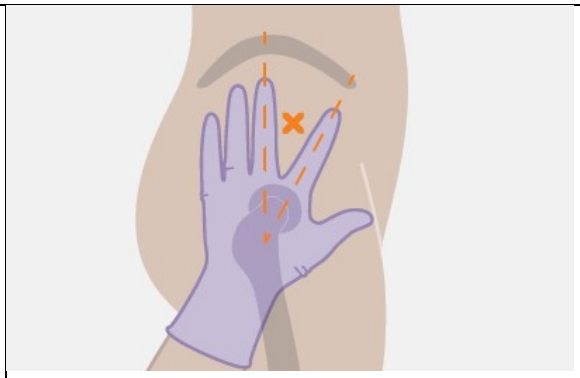
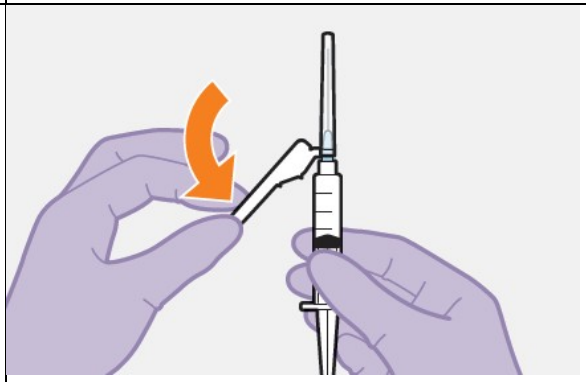
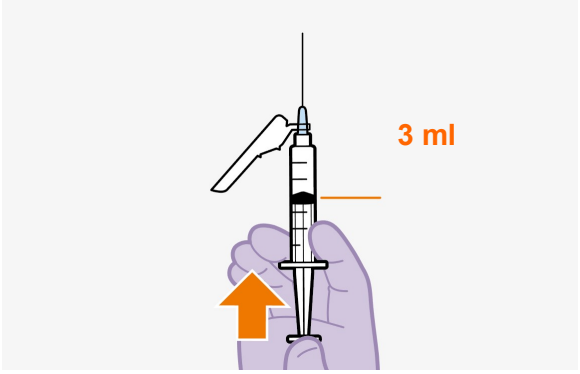
2. Wait 15 minutes

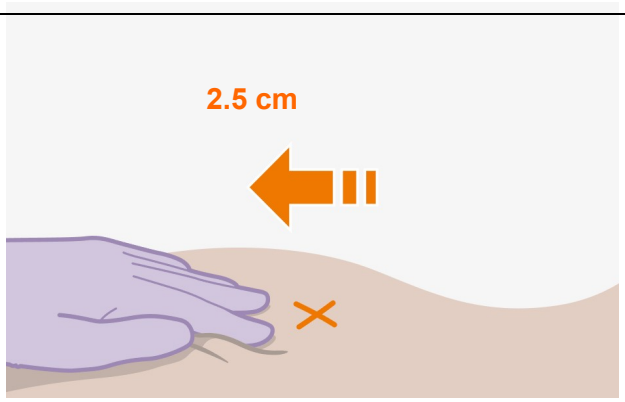
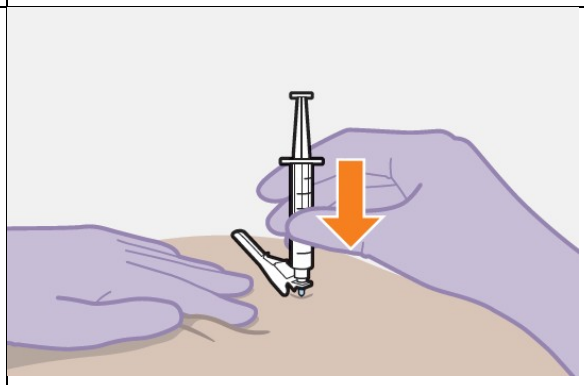
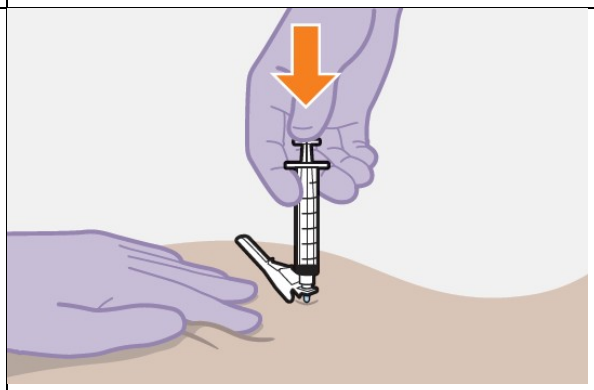
- If the pack has been stored in a fridge, wait at least 15 minutes before injecting to allow the medicine to come to room temperature.

3. Vigorously shake • Hold the vial firmly, and vigorously shake for a full 10 seconds. • Invert the vial and check the resuspension. It should look uniform. If the suspension is not uniform, shake the vial again. • It is also normal to see small air bubbles.	
4. Remove vial cap • Remove the cap from the vial. • Wipe the rubber stopper with an alcohol wipe. **Do not** allow anything to touch the rubber stopper after wiping it.	
5. Peel open vial adaptor • Peel off the paper backing from the vial adaptor packaging. **Note**: Keep the adaptor in place in its packaging for the next step.	

6. Attach vial adaptor • Press the vial adaptor straight down onto the vial using the packaging, as shown. The vial adaptor should snap securely into place. • When you are ready, lift off the vial adaptor packaging as shown.	
7. Prepare syringe • Remove the syringe from its packaging. • Draw 1 ml of air into the syringe. This will make it easier to draw up the liquid later.	
8. Attach syringe • Hold the vial adaptor and vial firmly, as shown. • Screw the syringe firmly onto the vial adaptor. • Press the plunger all the way down to push the air into the vial.	

9. Slowly draw up dose • Invert the syringe and vial, and slowly withdraw as much of the liquid as possible into the syringe. There may be more liquid than the dose amount.	
10. Unscrew syringe • Screw the syringe off the vial adaptor, holding the vial adaptor as shown. **Note:** Keep the syringe upright to avoid leakage. Check that the suspension looks uniform and white to light pink.	
11. Attach needle • Peel open the needle packaging part way to expose the needle base. • Keeping the syringe upright, firmly twist the syringe onto the needle. • Remove the needle packaging from the needle.	

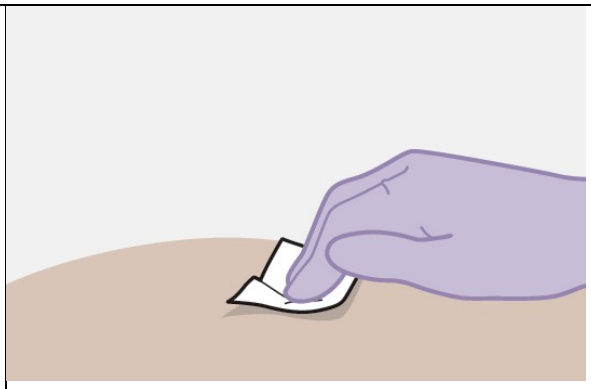
Injection	
12. Prepare Injection site Injections must be administered to the gluteal sites. Select from the following areas for the injection: Ventrogluteal, as shown (recommended) Dorsogluteal (upper outer quadrant) **Note:** For intramuscular use only. **Do not** inject intravenously.	
13. Remove cap • Fold the needle guard away from the needle. • Pull off the injection needle cap.	
14. Remove extra liquid • Hold the syringe with the needle pointing up. Press the plunger to the correct dose to remove extra liquid and any air bubbles. **Note:** Clean the injection site with an alcohol wipe. Allow the skin to air dry before continuing.	

15. Stretch skin Use the z-track injection technique to minimise medicine leakage from the injection site. • Firmly drag the skin covering the injection site, displacing it by about 2.5 cm. • Keep it held in this position for the injection.	
16. Insert needle • Insert the needle to its full depth, or deep enough to reach the muscle.	
17. Inject dose • Still holding the skin stretched – slowly press the plunger all the way down. • Ensure the syringe is empty. • Withdraw the needle and release the stretched skin immediately.	

18. Assess the injection site

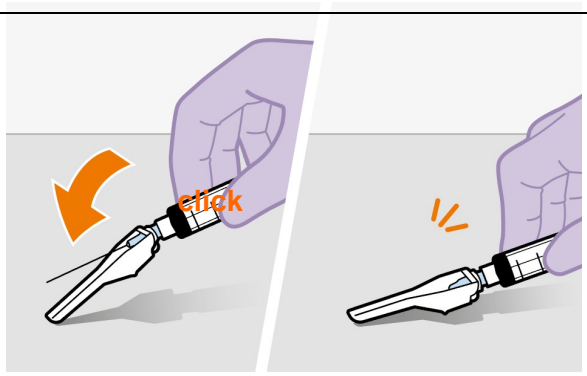
- Apply pressure to the injection site using a gauze.
- A small bandage may be used if a bleed occurs.

Do not massage the area.



19. Make needle safe

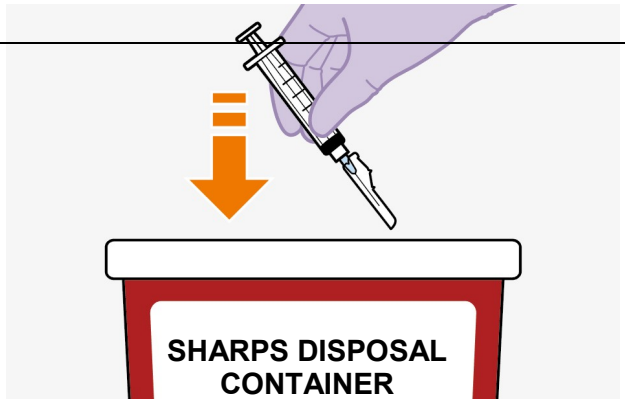
- Fold the needle guard over the needle.
- Gently apply pressure using a hard surface to lock the needle guard in place.
- The needle guard will make a click when it locks.



After Injection

20. Dispose safely

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



Repeat for 2nd medicine If you have only injected one of the two drugs, repeat all preparation steps and the injection again for the second drug.