# Swiss Summary of the Risk Management Plan (RMP)

# for Vocabria (cabotegravir)

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| Marketing Authorisation Holder: | ViiV Healthcare GmbH |
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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Vocabria is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Vocabria in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. ViiV Healthcare GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Vocabria.

# SUMMARY OF THE RISK MANAGEMENT PLAN

## Summary of risk management plan for Vocabria 30 mg Film-coated tablets (cabotegravir)

This is a summary of the risk management plan (RMP) for Vocabria 30 mg film-coated tablets. The RMP details important risks of Vocabria 30 mg film-coated tablets, how these risks can be minimised, and how more information will be obtained about Vocabria 30 mg film-coated tablets risks and uncertainties (missing information).

Vocabria 30 mg film-coated tablets' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Vocabria 30 mg film-coated tablets should be used.

This summary of the RMP for Vocabria 30 mg film-coated tablets should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Vocabria 30 mg film-coated tablets' RMP.

## I. The medicine and what it is used for

Vocabria 30 mg film-coated tablets are authorised in combination with rilpivirine tablets for the short-term treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class for:

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

See SmPC for the full indication. It contains cabotegravir as the active substance and it is given by the oral route.

Further information about the evaluation of Vocabria 30 mg film-coated tablets' benefits can be found in Vocabria 30 mg film-coated tablets' EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/documents/rmp-summary/vocabria-epar-risk-management-plan-summary_en.pdf

## II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Vocabria 30 mg film-coated tablets, together with measures to minimise such risks and the proposed studies for learning more about Vocabria 30 mg film-coated tablets' risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Vocabria 30 mg film-coated tablets is not yet available, it is listed under 'missing information' below.

## II.A List of important risks and missing information

Important risks of Vocabria 30 mg film-coated tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Vocabria 30 mg film-coated tablets. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

| **List of important risks and missing information** | |
|---|---|
| Important identified risks | Hepatotoxicity |
| Important potential risks | Medication errors including treatment non-compliance |
| Missing information | Use in Pregnancy |

## II.B Summary of important risks

| **Important identified risk: Hepatotoxicity** | |
|---|---|
| Evidence for linking the risk to the medicine | Clinical trials have shown that transient elevations of liver enzymes (transaminitis) can potentially occur with a CAB-containing regimen for a variety of reasons; these events are uncommon. Clinical study data from the development programme with CAB provide the evidence for this risk. |
| Risk factors and risk groups | None identified, as reports have been received involving a limited number of subjects receiving cabotegravir in clinical studies, with or without known pre-existing hepatic disease |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>• SmPC section 4.4, 4.8<br>• PL section 2 & 4<br>• Recommendation for liver chemistry monitoring are included in SmPC sections 4.4<br>• This is a prescription only medicine.<br>• Prescribed by physicians experienced in the treatment of HIV<br><br>**Additional risk minimisation measures***:* None |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>**Study short name:** A prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients initiating cabotegravir containing antiretroviral regimen<br>*See section II.C of this summary for an overview of the post-authorisation development plan.* |

| **Important potential risk: Medication errors including treatment non-compliance** | |
|---|---|
| Evidence for linking the risk to the medicine | In clinical studies, medication errors were uncommon; those that occurred had minimal clinical impact on subjects. There is potential for detection of some, but not all administration or dosing errors from the clinical studies and would likewise be the same in clinical practice as it is difficult to readily determine if an incorrect injectable dose has been administered. Overall, the potential risk to subjects due to medication errors is considered to be low, as the efficacy of the CAB+RPV regimen has not been affected in most cases observed in the clinical studies to date.<br><br>Human factor studies were conducted using commercially representative medicinal product kits including representative drug product vials, to-be-marketed delivery devices and packaging, and to-be-marketed labelling including instructions for use for the initiation and continuation doses of the combination drug regimen (CAB+RPV) under simulated use conditions with the objective to provide evidence that the user requirements have been adequately met. The conclusions from the human factor studies were used to create and refine the instructions for use.<br><br>The risk of non-compliance and treatment discontinuation without prompt introduction of an appropriate new regimen is theoretical and could not be assessed in clinical trials. |
| Risk factors and risk groups | The CAB+RPV regimen will initially be novel to Healthcare Professionals. The treatment has either two or three stages for dosing, if an optional oral lead-in dosing is used, or direct initiation of injection dose(s), followed by different continuation injection doses corresponding to the Q4W and Q8W regimens, intramuscular initiation dose, and intramuscular continuation dose, with both CAB and RPV being administered as separate injections. There is a risk of administering an incomplete regimen, potentially resulting in sub-optimal therapeutic levels. Inadvertent partial intravenous administration resulting in a higher than expected peak exposure initially could occur if an injection were accidentally administered into a vein in the early phases followed by a decline in drug levels in later phases also resulting in sub-optimal therapeutic levels. Treatment with CAB+RPV LA should not be initiated in patients who are not suitably suppressed, or those who may not be adherent to the regimen as this could potentially result in sub-optimal therapeutic levels. |

| **Important potential risk: Medication errors including treatment non-compliance** | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures:**<br>• SmPC section 4.2, 4.4<br>• PL section 2 & 3<br>• Administered by healthcare professionals.<br>• Different packaging colours and logo for each phase of treatment.<br><br>**Additional risk minimisation measures**: None |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>**Study short name:** Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients initiating an ARV regimen of CAB+RPV LA in Collaboration with EuroSIDA<br><br>*See section II.C of this summary for an overview of the post-authorisation development plan.* |

| **Missing information: Use in Pregnancy** | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures:**<br>• SmPC section 4.6.<br>• PL section 2<br>• This is a prescription only medicine.<br>• Prescribed by physicians experienced in the treatment of HIV<br><br>**Additional risk minimisation measures:** None |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br><br>**Study short name:** Antiretroviral Pregnancy Registry (APR)<br><br>**Study short name:** European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)<br><br>*See section II.C of this summary for an overview of the post-authorisation development plan.* |

## II.C Post-authorisation development plan

### II.C.1 Studies which are conditions of the marketing authorisation

### Study short name: Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients initiating an ARV regimen of CAB+RPV LA in Collaboration with EuroSIDA

Purpose of the study: ViiV Healthcare proposes a five-year DUS to be conducted in a real-world context. This prospective observational cohort study will aim to better understand the patient population receiving CAB LA and/or RPV LA containing regimens in routine clinical practice, usage patterns, adherence, and post marketing clinical effectiveness of these regimens and monitor for resistance among virologic failures for whom data on resistance testing are available. All patients who discontinue the regimen for any reason, will be followed for 24 months after discontinuation. During this 24-month follow up period, the study will collect data on the ARV regimen in the patients who switches to subsequent to CAB+RPV LA discontinuation, patient virological outcomes and data on resistance, where tested for and as available

The proposed study will be conducted through collaboration with EuroSIDA, a well-established, prospective observational cohort study of more than 22,000 patients followed in over 100 hospitals in 31 European countries, Israel and Argentina. A detailed study protocol, once approved, will be implemented by the EuroSIDA coordinating centre.

The study will evaluate the effectiveness of routine risk minimization measures for the safety concern of medication errors and assess the use of CAB LA and/or RPV LA containing injection regimens according to the SmPC recommendations by addressing the specific study objectives as outlined below. Following the initiation of any ARV regimen containing CAB LA and/or RPV LA among HIV infected patients, the study will aim to assess usage patterns, durability, discontinuation, and virological outcomes among persons first exposure to CAB LA and /or RPV LA containing regimens. The specific aims are to:

1. Describe CAB LA and/or RPV LA containing regimens usage patterns
    - Descriptive analysis of patient population by baseline demographic and clinical characteristics
    - Monitor for use of oral lead-in
    - Comparison of treatment groups*
        a. CAB LA monotherapy
        b. CAB LA use in combination with ARVs other than RPV LA
        c. RPV LA monotherapy
        d. RPV LA use in combination with ARVs other than CAB LA
        e. CAB+RPV LA containing regimens used in combination

    * Note that depending on numbers within these 5 treatment groups, groups may be combined.

2. Assess adherence, durability and discontinuation for persons starting one of the regimens a-e above;

- Proportion of patients discontinuing the regimens of interest and lost to follow-up will be assessed.
- Reasons for discontinuation will be assessed.
- Non-adherence to dosing schedule will be assessed by
    a. Estimating the number of patients that missed one or more consecutive injections without taking daily oral bridging therapy or any other oral ARV regimen while not on CAB LA and/or RPV LA containing regimens and average number of injections missed during a 12-month period
    a. Estimating the number of patients who received the injections seven or more days later than their scheduled injection visit and average duration of delayed injections

3. Assess the clinical effectiveness (i.e. proportion of patients experiencing virologic failure) among HIV patients who initiate CAB+RPV LA regimen and had suppressed viral load at regimen initiation (VL <50 copies/mL without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class )
    - Estimate the proportion of patients with virologic failure, during the first 6 months after initiation of CAB+RPV LA
    - Estimate the proportion of patients with virologic failure, 6, 12 and 24 months after initiation of CAB+RPV LA
4. Monitor for resistance and next treatment response among individuals who switched off CAB LA and/or RPV LA containing regimens a-e, where viral load data are available and resistance testing has been done as part of routine clinical practice
    - Describe the ARV regimen patients are switched to after discontinuation of CAB LA and/or RPV LA containing regimens
    - Monitor for resistance during the 24 months following the switch
    - Describe virologic outcomes at 24 months after discontinuation of CAB LA and/or RPV LA containing regimens

### Study short name: COMBINE-2 for Cabotegravir + Rilpivirine LA Regimen: A Prospective Cohort Study to Monitor Effectiveness, Adherence and Resistance

Purpose of the study: The study will aim to gather data from 1000 patients to assess clinical effectiveness, adherence, durability and discontinuations after initiating CAB+RPV LA regimen. The study will also monitor for resistance and response to subsequent ARV regimen among patients who switched off CAB+RPV LA regimen.

The study population will include HIV positive patients over the age of 18 years, from NEAT ID Network clinical sites who are prescribed CAB+RPV LA regimen. As per label, adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class will be eligible for inclusion.

### II.C.2 Other studies in post-authorisation development plan

## Study short name: A prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients initiating cabotegravir containing antiretroviral regimen.

Purpose of the study: Uncommon cases of DILI with oral CAB were observed during the clinical trials program for CAB and RPV. During Phase III studies although hepatotoxicity was observed at higher rates with CAB LA compared to the oral comparator ART therapy, the difference was largely driven by acute viral hepatitis which occurred more frequently in subjects receiving CAB LA. Hepatotoxicity has been reported in a limited number of patients receiving CAB with or without known pre-existing hepatic disease. Healthcare professional should monitor liver chemistries and discontinue treatment with CAB if hepatotoxicity is suspected.

ViiV Healthcare proposes a five-year post authorization safety study (PASS) to be conducted in a real-world context. This prospective observational cohort study will monitor for hepatotoxicity and discontinuation of the regimen due to liver- related adverse events following initiation of CAB based ARV regimen.

This safety study will be conducted through collaboration with EuroSIDA, a well-established, prospective observational cohort study of more than 22,000 patients followed in over 100 hospitals in 31 European countries, Israel and Argentina. A detailed study protocol, once approved, will be implemented by the EuroSIDA coordinating centre.

Following the initiation of any ARV regimen containing CAB LA among HIV infected patients, the study will aim to:

1. characterise the rates and risks of hepatotoxicity by:
    - estimating the incidence of alanine aminotransferase (ALT) elevations and risk factors for elevations
    - estimating the incidence of cases of combined ALT and total bilirubin elevations and risk factors for elevations
2. Estimate the number of patients discontinuing CAB based ARV regimen due to any reason and specifically discontinuations due to liver related adverse events

## Study short name: European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)

Purpose of the study: Data from the EPPICC will assess maternal outcomes (pregnancy outcomes, abortions, still births and maternal viral load) and foetal outcomes (still births) following CAB use during pregnancy. The exposure to CAB relative to all gestation period including conception will be captured in this study, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures.

## Study short name: Antiretroviral Pregnancy Registry (APR)

Purpose of the study: The APR is an international registry that monitors prenatal exposures to antiretroviral drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration cohort. The APR is a ViiV Healthcare-sponsored study

involving the collaborative effort of multiple companies. Data from the APR will assess maternal (pregnancy outcomes, abortions, still births and maternal viral load) and foetal outcomes (still births) following CAB use during pregnancy. Exposure to CAB relative to all gestation period and conception will be captured in the registry, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures.

# Summary of risk management plan for Vocabria Prolonged-release suspension for injection (cabotegravir)

This is a summary of the risk management plan (RMP) for Vocabria prolonged-release suspension for injection. The RMP details important risks of Vocabria prolonged-release suspension for injection, how these risks can be minimised, and how more information will be obtained about Vocabria prolonged-release suspension for injection's risks and uncertainties (missing information).

Vocabria prolonged-release suspension for injection's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Vocabria prolonged-release suspension for injection should be used.

This summary of the RMP for Vocabria prolonged-release suspension for injection should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Vocabria prolonged-release suspension for injection's RMP.

## I. The medicine and what it is used for

Vocabria prolonged-release suspension for injection is authorised, in combination with rilpivirine injection, for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies /mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class (see SmPC for the full indication). It contains cabotegravir as the active substance and it is given by intramuscular injection.

Further information about the evaluation of Vocabria prolonged-release suspension for injection's benefits can be found in Vocabria prolonged-release suspension for injection's EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage:

https://www.ema.europa.eu/en/documents/rmp-summary/vocabria-epar-risk-management-plan-summary_en.pdf

## II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Vocabria prolonged-release suspension for injection, together with measures to minimise such risks and the proposed studies for learning more about Vocabria prolonged-release suspension for injection's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Vocabria prolonged-release suspension for injection is not yet available, it is listed under 'missing information' below.

## II.A List of important risks and missing information

Important risks of Vocabria prolonged-release suspension for injection are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Vocabria prolonged-release suspension for injection. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

| **List of important risks and missing information** | |
|---|---|
| Important identified risks | Hepatotoxicity |
| Important potential risks | Medication errors including treatment non-compliance |
| Missing information | Use in Pregnancy |

## II.B Summary of important risks

| **Important identified risk: Hepatotoxicity** | |
|---|---|
| Evidence for linking the risk to the medicine | Clinical trials have shown that transient elevations of liver enzymes (transaminitis) can potentially occur with a CAB-containing regimen for a variety of reasons; these events are uncommon. Clinical study data from the development programme with CAB provide the evidence for this risk. |
| Risk factors and risk groups | None identified, as reports have been received involving a limited number of subjects receiving cabotegravir in clinical studies, with or without known pre-existing hepatic disease. |
| Risk minimisation measures | **Routine risk minimisation measures***:*<br>• SmPC section 4.4, 4.8<br>• PL section 2 & 4<br>• Recommendation for liver chemistry monitoring are included in SmPC section 4.4<br>• This is a prescription only medicine.<br>• Prescribed by physicians experienced in the treatment of HIV<br><br>**Additional risk minimisation measures***:* None |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities***:*<br>**Study short name:** A prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients initiating cabotegravir containing antiretroviral regimen<br>*See section II.C of this summary for an overview of the post-authorisation development plan.* |

| **Important potential risk: Medication errors including treatment non-compliance** | |
|---|---|
| Evidence for linking the risk to the medicine | In clinical studies, medication errors were uncommon; those that occurred had minimal clinical impact on subjects. There is potential for detection of some, but not all administration or dosing errors from the clinical studies and would likewise be the same in clinical practice as it is difficult to readily determine if an incorrect injectable dose has been administered. Overall, the potential risk to subjects due to medication errors is considered to be low, as the efficacy of the CAB+RPV regimen has not been affected in most cases observed in the clinical studies to date.<br><br>Human factor studies were conducted using commercially representative medicinal product kits including representative drug product vials, to-be-marketed delivery devices and packaging, and to-be-marketed labelling including instructions for use for the initiation and continuation doses of the combination drug regimen (CAB+RPV) under simulated use conditions with the objective to provide evidence that the user requirements have been adequately met. The conclusions from the human factor studies were used to create and refine the instructions for use.<br><br>The risk of non-compliance and treatment discontinuation without prompt introduction of an appropriate new regimen is theoretical and could not be assessed in clinical trials. |
| Risk factors and risk groups | The CAB+RPV regimen will initially be novel to Healthcare Professionals. The treatment has either two or three stages for dosing; if an optional oral lead-in dosing is used, or direct initiation of injection dose(s), followed by different continuation injection doses corresponding to the Q4W and Q8W regimens, intramuscular initiation dose, and intramuscular continuation dose, with both CAB and RPV being administered as separate injections. There is a risk of administering an incomplete regimen, potentially resulting in sub-optimal therapeutic levels. Inadvertent partial intravenous administration resulting in a higher than expected peak exposure initially could occur if an injection were accidentally administered into a vein in the early phases followed by a decline in drug levels in later phases, also resulting in sub-optimal therapeutic levels. Treatment with CAB+RPV LA should not be initiated in patients who are not suitably suppressed, or those who may not be adherent to the regimen as this could potentially result in sub-optimal therapeutic levels. |

| **Important potential risk: Medication errors including treatment non-compliance** | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures:**<br>• SmPC section 4.2, 4.4<br>• PL section 2 & 3<br>• Administered by Healthcare Professionals.<br>• Different packaging colours and logo for each phase of treatment.<br><br>**Additional risk minimisation measures:** None |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>**Study short name:** Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients initiating an ARV regimen of CAB+RPV LA in Collaboration with EuroSIDA<br>*See section II.C of this summary for an overview of the post-authorisation development plan.* |

| **Missing information: Use in Pregnancy** | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures:**<br>• SmPC section 4.6.<br>• PL section 2<br>• This is a prescription only medicine.<br>• Prescribed by physicians experienced in the treatment of HIV.<br><br>**Additional risk minimisation measures**: None |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>**Study short name:** Antiretroviral Pregnancy Registry (APR)<br>**Study short name:** European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)<br>*See section II.C of this summary for an overview of the post-authorisation development plan.* |

## II.C Post-authorisation development plan

### II.C.1 Studies which are conditions of the marketing authorisation

### Study short name: Drug Utilization, Adherence, Effectiveness and Resistance: A Prospective Observational Cohort Study in Patients initiating an ARV regimen of CAB+RPV LA in Collaboration with EuroSIDA

Purpose of the study: ViiV Healthcare proposes a five-year DUS to be conducted in a real-world context. This prospective observational cohort study will aim to better understand the patient population receiving CAB LA and/or RPV LA containing regimens in routine clinical practice, usage patterns, adherence, and post marketing clinical effectiveness of these regimens and monitor for resistance among virologic failures for whom data on resistance testing are available. All patients who discontinue the regimen for any reason, will be followed for 24 months after discontinuation. During this 24-month follow up period, the study will collect data on the ARV regimen in the patients who switches to subsequent to CAB+RPV LA discontinuation, patient virological outcomes and data on resistance, where tested for and as available.

The proposed study will be conducted through collaboration with EuroSIDA, a well-established, prospective observational cohort study of more than 22,000 patients followed in over 100 hospitals in 31 European countries, Israel and Argentina. A detailed study protocol, once approved, will be implemented by the EuroSIDA coordinating centre.

The study will evaluate the effectiveness of routine risk minimization measures for the safety concern of medication errors and assess the use of CAB LA and/or RPV LA containing injection regimens according to the SmPC recommendations by addressing the specific study objectives as outlined below. Following the initiation of any ARV regimen containing CAB LA and/or RPV LA among HIV infected patients, the study will aim to assess usage patterns, durability, discontinuation, and virological outcomes among persons first exposure to CAB LA and /or RPV LA containing regimens. The specific aims are to:

1. Describe CAB LA and/or RPV LA containing regimens usage patterns
    - Descriptive analysis of patient population by baseline demographic and clinical characteristics
    - Monitor for use of oral lead-in
    - Comparison of treatment groups*
        a. CAB LA monotherapy
        b. CAB LA use in combination with ARVs other than RPV LA
        c. RPV LA monotherapy
        d. RPV LA use in combination with ARVs other than CAB LA
        e. CAB+RPV LA containing regimens used in combination

    * Note that depending on numbers within these 5 treatment groups, groups may be combined.

2. Assess adherence, durability and discontinuation for persons starting one of the regimens a-e above;

- Proportion of patients discontinuing the regimens of interest and lost to follow-up will be assessed.
- Reasons for discontinuation will be assessed.
- Non-adherence to dosing schedule will be assessed by
    a. Estimating the number of patients that missed one or more consecutive injections without taking daily oral bridging therapy or any other oral ARV regimen while not on CAB LA and/or RPV LA containing regimens and average number of injections missed during a 12-month period
    b. Estimating the number of patients who received the injections seven or more days later than their scheduled injection visit and average duration of delayed injections

3. Assess the clinical effectiveness (i.e. proportion of patients experiencing virologic failure) among HIV patients who initiate CAB+RPV LA regimen and had suppressed viral load at regimen initiation (VL <50 copies/mL without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class)
    - Estimate the proportion of patients with virologic failure, during the first 6 months after initiation of CAB+RPV LA
    - Estimate the proportion of patients with virologic failure, 6, 12 and 24 months after initiation of CAB+RPV LA
4. Monitor for resistance and next treatment response among individuals who switched off CAB LA and/or RPV LA containing regimens a-e, where viral load data are available and resistance testing has been done as part of routine clinical practice
    - Describe the ARV regimen patients are switched to after discontinuation of CAB LA and/or RPV LA containing regimens
    - Monitor for resistance during the 24 months following the switch
    - Describe virologic outcomes at 24 months after discontinuation of CAB LA and/or RPV LA containing regimens

### Study short name: COMBINE-2 for Cabotegravir + Rilpivirine LA Regimen: A Prospective Cohort Study to Monitor Effectiveness, Adherence and Resistance

Purpose of the study: The study will aim to gather data from 1000 patients to assess clinical effectiveness, adherence, durability and discontinuations after initiating CAB+RPV LA regimen. The study will also monitor for resistance and response to subsequent ARV regimen among patients who switched off CAB+RPV LA regimen.

The study population will include HIV positive patients over the age of 18 years, from NEAT ID Network clinical sites who are prescribed CAB+RPV LA regimen. As per label, adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class will be eligible for inclusion.

### II.C.2 Other studies in post-authorisation development plan

## Study short name: A prospective observational cohort study to monitor for hepatotoxicity and regimen discontinuation due to liver related adverse events among patients initiating cabotegravir containing antiretroviral regimen.

Purpose of the study: Uncommon cases of DILI with oral CAB were observed during the clinical trials program for CAB and RPV. During Phase III studies although hepatotoxicity was observed at higher rates with CAB LA compared to the oral comparator ART therapy, the difference was largely driven by acute viral hepatitis which occurred more frequently in subjects receiving CAB LA. Hepatotoxicity has been reported in a limited number of patients receiving CAB with or without known pre-existing hepatic disease. Healthcare professional should monitor liver chemistries and discontinue treatment with CAB if hepatotoxicity is suspected.

ViiV Healthcare proposes a five-year post authorization safety study (PASS) to be conducted in a real-world context. This prospective observational cohort study will monitor for hepatotoxicity and discontinuation of the regimen due to liver- related adverse events following initiation of CAB based ARV regimen.

This safety study will be conducted through collaboration with EuroSIDA, a well-established, prospective observational cohort study of more than 22,000 patients followed in over 100 hospitals in 31 European countries, Israel and Argentina. A detailed study protocol, once approved, will be implemented by the EuroSIDA coordinating centre.

Following the initiation of any ARV regimen containing CAB LA among HIV infected patients, the study will aim to:

1. characterise the rates and risks of hepatotoxicity by:
    - estimating the incidence of alanine aminotransferase (ALT) elevations and risk factors for elevations
    - estimating the incidence of cases of combined ALT and total bilirubin elevations and risk factors for elevations
2. Estimate the number of patients discontinuing CAB based ARV regimen due to any reason and specifically discontinuations due to liver related adverse events

## Study short name: European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)

Purpose of the study: Data from the EPPICC will assess maternal outcomes (pregnancy outcomes, abortions, still births and maternal viral load) and foetal outcomes (still births) following CAB use during pregnancy. The exposure to CAB relative to all gestation period including conception will be captured in this study, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures.

## Study short name: Antiretroviral Pregnancy Registry (APR)

Purpose of Study: The APR is an international registry that monitors prenatal exposures to antiretroviral drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration cohort. The APR is a ViiV Healthcare-sponsored study

involving the collaborative effort of multiple companies. Data from the APR will assess maternal (pregnancy outcomes, abortions, still births and maternal viral load) and foetal outcomes (still births) following CAB use during pregnancy. Exposure to CAB relative to all gestation period and conception will be captured in the registry, thus enabling assessment of pre-conception exposures along with first, second and third trimester exposures.