**SUMMARY**

rilpivirine

# REKAMBYS 900 mg,

**prolonged-release suspension for injection**

Reassessment and MA amendments

**Original French opinion adopted by the Transparency Committee on 1 February 2023**

**The legally binding text is the original French opinion version**

## Key points

**Favourable opinion for maintenance of reimbursement** for the treatment of human immunodeficiency virus type 1 (HIV-1) infection, in combination with cabotegravir, only in adults who are virologically suppressed (viral load < 50 copies/mL) on a stable antiretroviral regimen for at least six months, with a CD4 count of more than 200 cells per $mm^3$ without present or past evidence of viral resistance to, and no prior virological failure with agents of the non-nucleoside reverse transcriptase inhibitors (NNRT) and integrase inhibitor (INI) class.

**Unfavourable opinion for reimbursement in other populations.**

## What therapeutic improvement?

No clinical added value in the therapeutic strategy.

## Role in the care pathway?

Treatment combinations with at least three highly active agents or two agents are recommended as first-line therapy. These include:

- triple therapy with two nucleoside reverse transcriptase inhibitors (NRTI) + a third agent (one integrase inhibitor [INI], one non-nucleoside reverse 1 transcriptase inhibitor [NNRTI] or one protease inhibitor [PI]);
- dual therapy with one INI + one NRTI (dolutegravir/lamivudine fixed-dose combination).

Once virological success is achieved (VL <50 copies/ml), whether after first-line treatment or following relay treatment, a change in antiretroviral treatment may be useful or necessary, under variable circumstances and with variable objectives.

Generally speaking, the aim is to tailor treatment in order to improve safety and/or ease of administration, while maintaining immunovirological efficacy.

**Role of the medicinal product in the care pathway**

**The new data submitted are not of a nature to modify the role of the medicinal product in the care pathway compared to the Committee's previous assessment, reiterated below:**

"When a switch strategy (treatment optimisation strategy) is envisaged in pretreated patients who are virologically suppressed (viral load < 50 copies/mL), considering the population included and the results of studies (FLAIR, ATLAS and ATLAS-2M) demonstrating the non-inferiority of a switch from conventional triple therapy to prolonged-release injectable dual therapy with cabotegravir + rilpivirine, the Committee considers that prolonged-release injectable dual therapy with VOCABRIA (cabotegravir) + REKAMBYS (rilpivirine) is a therapeutic option only in adults on a stable antiretroviral regimen for at least six months, with a CD4 count of more than 200 cells per $mm^3$ without present or past evidence of viral resistance to, and no prior virological failure with, agents of the NNRT and INI class.

On the basis of currently available data demonstrating a higher frequency of virological failure and resistance with the two-monthly administration regimen compared to monthly administration, particularly in the event of resistance to rilpivirine, the Committee recommends eliminating any risk of archived resistance mutation persistence, if necessary via proviral DNA genotypic assay before initiation of treatment.

The decision to introduce this prolonged-release injectable dual therapy should be taken by a physician experienced in the treatment of HIV. It should take into consideration the fact that perfect treatment compliance is essential, given the low genetic resistance barrier, particularly with respect to rilpivirine, but also the very long half-life of the two products, which is a source of particular concern. Plasma concentrations of cabotegravir and prolonged-release rilpivirine decrease slowly up to around one year, which can lead to infra-therapeutic serum concentrations and, consequently, the development of mutations in the event of missed doses or discontinuation of injections. Hence, the risk of selection (and potential transmission) of resistance to the two drug classes in the combination (INI and NNRT) in the event of treatment discontinuation without the immediate introduction of a suppressive regimen cannot be eliminated. Special warnings have been included in the SmPC concerning the need to carefully select patients and the risk of resistance in the event of any delay in initiating a fully suppressive antiretroviral regimen following treatment discontinuation.

It is therefore essential to inform patients about the importance of adherence to scheduled dosing visits to help maintain viral suppression and reduce the potential risk of the development of resistance.

This new strategy, aimed at simplifying treatment by avoiding the need for daily oral doses, could be of benefit in compliant patients seeking a long-acting treatment for whom daily oral treatment adversely affects their quality of life due to the psychological and emotional burden, as highlighted by patient associations. It could also be useful in patients who are incapable of taking oral treatment, such as those with swallowing difficulties. However, these advantages should be weighed up against the constraints related to its IM administration, which could represent an obstacle for some patients in practice and the impact of which on good long-term treatment compliance is a source of uncertainty at present: inconveniences related to the two IM injections at each administration (injection site reactions very common in clinical studies), need for the intervention of a healthcare professional to administer injections, and hospital visits every month or every two months compared to every six to 12 months currently if a community-hospital circuit cannot be put in place.

Hence, given the potential risk of resistance, this strategy does not appear to be very suitable for patients at risk of non-compliance, a population not assessed in clinical studies.

Moreover, caution is recommended in the presence of archived rilpivirine resistance, a BMI ≥ 30 kg/m² or HIV-1 subtype A6/A1, factors associated with a risk of virological failure in studies. In addition, residual rilpivirine concentrations four weeks after the initial injection have been associated with a risk of failure. Therefore the implementation of pharmacological monitoring of the two drugs should be discussed, particularly in obese patients."

## Special recommendations

Considering current data relative to the potential risk of congenital malformation in the event of treatment with dolutegravir at the moment of conception and during the first trimester of pregnancy, which cannot be eliminated for other drugs in the integrase inhibitor family, to which cabotegravir belongs, the Committee does not recommend cabotegravir + rilpivirine slow-release injectable dual therapy in women of childbearing potential.

When the prescription of this injectable dual therapy is desirable for a woman of childbearing potential, she should be informed about current data concerning the potential risk of neural tube defects (increase of 0.2% compared to triple therapy not including dolutegravir) and the need to use effective contraception. It may be prudent to perform a pregnancy test before initiation of cabotegravir.

In addition, prescribers should be informed about similarities with respect to the safety profile between dolutegravir and cabotegravir due to their structural analogy.

The Committee reiterates its wish for strengths appropriate for monthly administration to be made available: VOCABRIA 400 mg (cabotegravir) and REKAMBYS 600 mg (rilpivirine) prolonged-release suspensions for injection.

# Committee's conclusions

## Clinical Benefit

- HIV infection is a serious, life-threatening disease.
- The proprietary medicinal product REKAMBYS (rilpivirine) in combination with cabotegravir injection aims to prevent and/or correct the immune deficiency induced by HIV infection in adult patients who are virologically suppressed.
- The efficacy/adverse effects ratio of REKAMBYS (rilpivirine) in combination with cabotegravir injection remain high only in adults:
  - who are virologically suppressed (viral load <50 copies/mL) on a stable antiretroviral regimen for at least six months, and
  - with a CD4 count of more than 200 cells per $mm^3$, and
  - without present or past evidence of viral resistance to, and no prior virological failure with, agents of the NNRT and INI class.
- There are numerous therapeutic alternatives to these medicinal products (see section 05 of this opinion).
- It is a first-line treatment.

### Public health benefit

On the basis of currently available data, the previous assessment of the PHB is not modified: REKAMBYS (rilpivirine), in combination with cabotegravir injection, is unlikely to have an additional impact on public health.

**Consequently, the Committee deems that the clinical benefit of REKAMBYS (rilpivirine) 900 mg suspension for injection, in combination with cabotegravir injection, remains:**

- **substantial only in adults who are virologically suppressed (viral load < 50 copies/mL) on a stable antiretroviral regimen for at least six months, with a CD4 count of more than 200 cells per $mm^3$ without present or past evidence of viral resistance to, and no prior virological failure with, agents of the non-nucleoside reverse transcriptase inhibitors (NNRT) and integrase inhibitor (INI) class;**
- **insufficient to justify public funding in the other marketing authorisation populations.**

**The Committee issues a favourable opinion for maintenance of inclusion of in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the MA indication only in adults who are virologically suppressed (viral load < 50 copies/mL) on a stable antiretroviral regimen for at least six months, with a CD4 count of more than 200 cells per $mm^3$ without present or past evidence of viral resistance to, and no prior virological failure with, agents of the non-nucleoside reverse transcriptase inhibitor (NNRT) and integrase inhibitor (INI) class.**

**The Committee issues an unfavourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the other populations of the MA.**

## Recommended reimbursement rate: 100%

## Clinical Added Value

➔ **Adults who are virologically suppressed (viral load < 50 copies/mL) on a stable antiretroviral regimen for at least six months, with a CD4 count of more than 200 cells per mm3 without present or past evidence of viral resistance to, and no prior virological failure with, agents of the NNRT and INI class.**

The new data available is not of a nature to modify the previous assessment of the Committee, which considers that injectable dual therapy with a free combination of cabotegravir + rilpivirine provides no clinical added value (CAV V) in the management of HIV-1 in virologically suppressed patients compared to the available alternatives (oral triple therapies and dual therapies).