Version 13th October 2021

Recommendations for Therapeutic Drug Monitoring of CABOTEGRAVIR and RILPIVIRINE during long-acting injectable administration of Vocabria®/Rekambys® every 2 months in HIV-infected patients

ANRS-MIE - AC43 Pharmacologic and Resistance groups

This document will be updated regularly according to available data from the literature and the evolution of therapeutic management.

Discussion concerning the follow-up and pharmacological management of HIV-infected patients treated with the combination Cabotegravir/Rilpivirine administered intramuscularly every 2 months (long-acting) outside the clinical research protocol.

Therapeutic Drug Monitoring (TDM) of antiretroviral drugs (ARV) is officially recommended in France in a certain number of indications, because of a significant inter-individual pharmacokinetic variability and pharmacokinetic-pharmacodynamic relationships (virological efficacy and/or toxicity) established for most ARVs (1).

In the context of the upcoming availability of the long-acting injectable combination of cabotegravir and rilpivirine, we propose the following modalities for the implementation of TDM for these two compounds.

1. Level of evidence

These recommendations are based on:

- **pharmacokinetic data from phase 3 trials** (Flair and Atlas pooled data) at week 48 reporting significant inter-individual variability in trough plasma concentrations (Cmin) of cabotegravir and rilpivirine with values below the respective geometric mean for patients with virologic failure (2).

- **results of the multivariate analysis of virologic failures in the phase 3 Flair and Atlas trials** (3) identifying trough plasma rilpivirine concentration at S8 (i.e., 4 weeks after the initiation injection) as a risk factor for virologic failure. The analysis reported that the presence of at least two of the risk factors at initiation among the A1/A6 viral subtype, the presence of archived rilpivirine resistance mutations, or a BMI ≥30 kg/m2 was associated with a higher risk of failure (25.7%). A lower trough cabotegravir plasma concentration at S8 (i.e. 4 weeks after the initiation injection) was also associated with a higher BMI (4). However, although related to virological failure, trough cabotegravir concentration was no longer predictive in the multivariate analysis but should remain a point of vigilance in the real-life setting. Indeed, recent data from the Flair trial at week 124 reported a new virologic failure between S96 and S124 in a patient presenting two of the identified risk factors: viral subtype A6 and a rilpivirine Cmin below 32 ng/mL (i.e 24.6 ng/mL) and a cabotegravir Cmin below 1,120 ng/mL (i.e 1005 ng/mL).

For information, a recent French study conducted in 3 university hospitals in Paris reported a prevalence of 10.1% of A6/A1 viral subtype OR resistant to rilpivirine (i.e with 1 of the 2 virological risk factors for failure) and a prevalence < 0.5% of A6/A1 viral subtype AND resistant to rilpivirine (i.e with the 2 virological risk factors for failure) (5).

- **the French transparency commission, recommending pharmacological monitoring, particularly in obese subjects** (6) :

"Caution is further recommended in the presence of archived resistance to rilpivirine, BMI ≥ 30 kg/m2, or HIV-1 subtype A6/A1, factors associated with the risk of virological failure in studies. In addition, the

trough plasma concentration of rilpivirine at 4 weeks after the initiation injection was associated with the risk of failure, so performing therapeutic drug monitoringof the 2 molecules is worth discussing especially in obese patients."

2. Indications and modalities of TDM

The sample is collected on a gel-free lithium heparinate tube (or EDTA, which is compatible with samples collected for plasma HIV-1 RNA), as currently recommended for the TDM of ARV:

- **At week 4 (W4) after initiation of oral treatment**, corresponding to the end of the lead-in phase, after the last oral dose, in the residual period (T>20h).
- **At week 8 (W8), i.e. 4 weeks after the first intra-muscular (IM) injection**, before the new administration
- in the following indications:
    - in case of **missed or delayed injection(s)**, and before resuming the treatment as defined in the Summary of Products Characteristics (SPCs)
    - in case of **occurrence of adverse events**
    - in case of **virological failure**
    - in case of **pregnancy** occurring during treatment*
    - in case of **drug-drug interaction** that may significantly alter the exposure of cabotegravir and/or rilpivirine (**see list below)
    - along with viral load monitoring in patients with a **BMI ≥ 30 kg/m2 and/or A1/A6 viral subtype.**

TDM should be performed preferentially either prior to the next injection or before re-starting treatment as recommended in the SPCs for missed injections (specify the estimated time of interruption) (7,8).

*In case of pregnancy occurring during treatment, monitoring plasma of concentrations is recommended whether the treatment is maintained (documentation and follow-up with bodyweight changes) or stopped (monitoring of the decrease in plasma concentrations, given the long elimination half-life of the two compounds). The frequency of the pharmacological follow-up will be determined on a case-by-case basis according to the context and discussed in a multidisciplinary staff.

3. TDM interprétation

To date, no specific target value are officially validated for maintenance treatment and IM administration.

To date, TDM is therefore proposed in accordance with the expected values published in the respective SPCs, with **an alert threshold corresponding to the 1st quartile of trough plasma concentrations** presented in the multivariate analysis of failures (3, 7-8).

In case of a Cmin below this threshold, close virological monitoring is recommended along with a new pharmacological control after checking the absence of other factors associated with virological failure (viral sub-type, resistance profile, BMI).

Cabotegravir and Rilpivirine trough plasma concentrations after oral administration and long-acting IM administration every two months

Geometric mean [5th ; 95th percentiles]†

	W4* End of oral lead-in period	**W8**** 4 weeks after the 1st IM injection	**W48** At steady-state	**Alert threshold‡**
Cabotegravir, (ng/mL)	4,600 [2,800 ; 7,500]	1,500 [650 ; 2,900]	1,600 [800 ; 3,000]	**< 1,120**
Rilpivirine (ng/mL)	79.4 [31.8 ; 177]	42.0 [21.8; 78.9]	65.6 [36.9; 113]	**< 32**

*W4 : End of oral lead-in period, i.e after the last oral dose; **W8 : 4 weeks after the 1st IM injection ; †individual post-hoc estimates from the population pharmacokinetic model of pooled data from the Flair/Atlas/Atlas-2M phase 3 trials (7,8); ‡value corresponding to the 1st quartile of Cmin at W8 of the pooled data analysis of the phase 3 trials (3).

For information, the protein binding adjusted inhibitory concentration 90% or IC90-ap is 166 ng/mL for cabotegravir and 12 ng/mL for rilpivirine, respectively.

**** List of contraindicated and not recommended drug-drug interactions with cabotegravir and/or rilpivirine for intramuscular administration :**

- contraindicated because of significant decrease in cabotegravir and rilpivirine plasma exposure: dexamethasone (except in single dose), carbamazepine, St. John's wort, phenytoïn, phenobarbital, oxcarbazepine, rifabutin, rifampicin, rifapentin.

- not recommended as expected increase in rilpivirine plasma exposure : clarithromycin, erythromycin

- rilpivirine should be used with caution if co-administered with drugs with a known risk of torsade de pointes

- other drugs to be used with caution due to moderate inductive and/or inhibitory effect which may significantly modulate cabotegravir and/or rilpivirine plasma exposures (non-exhaustive list) (9) : artemisinin, betamethasone, bexarotene, bosentan, clobazam, enzalutamide, fluconazole, ginkgo biloba, griseofulvin, ifosfamide, modafinil, paclitaxel, primidone, vinblastine.

* List of **additional drug-drug interactions** only contraindicated or not recommended with cabotegravir and/or rilpivirine during the **oral "lead-in" phase or when oral therapy is resumed**: proton pump inhibitors (omeprazole/esomeprazole, lansoprazole, pantoprazole, rabeprazole)

Respect **the staggered dosing** as recommended in SPCs with antacids and all specialities containing di- or trivalents (Al, Ca, Mg, Iron …), anti-H2 (famotidine, ranitidine) et le liraglutide.

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