REKAMBYS

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
II/0022	Extension of indication to include, in combination with cabotegravir injection, the treatment of adolescents (at least 12 years of age and weighing at least 35 kg) for Rekambys, based on interim results from study 208580. This is an ongoing Phase 1/Phase 2 multicentre, open-label, non-comparative	12/12/2024	13/01/2025	SmPC, Labelling and PL	Please refer to Scientific Discussion 'Rekambys-H-C-005060-II-0022'

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	study evaluating the safety, acceptability, tolerability, and pharmacokinetic of oral and long-acting injectable cabotegravir and long-acting injectable rilpivirine in virologically suppressed HIV-infected adolescents 12 to <18 years of age and weighing at least 35 kg who are receiving stable combination antiretroviral therapy consisting of 2 or more drugs from 2 or more classes of antiretroviral drugs. Consequently, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.2 of the RMP has also been adopted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.4. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUSA/10901 /202403	Periodic Safety Update EU Single assessment - rilpivirine (for intramuscular use)	03/10/2024	n/a		PRAC Recommendation - maintenance
II/0020	Update of section 4.2 of the SmPC in order to update administration instructions to mitigate product leakage related to the correct use of the vial adapter, based on Human Factor studies. The Package Leaflet (Instructions for Use) is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	11/04/2024	13/01/2025	SmPC and PL	SmPC new text - Section 4.2 REKAMBYS should be administered by a healthcare professional. For instructions on administration, see "Instructions for Use" in the package leaflet. These instructions should be carefully followed when preparing the suspension for injection to avoid leakage.

	data				For more information, please refer to the Summary of Product Characteristics.
PSUSA/10901 /202303	Periodic Safety Update EU Single assessment - rilpivirine (for intramuscular use)	26/10/2023	n/a		PRAC Recommendation - maintenance
II/0019	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	28/09/2023	n/a		
IB/0017	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	07/06/2023	24/10/2023	SmPC and PL	
PSUSA/10901 /202209	Periodic Safety Update EU Single assessment - rilpivirine (for intramuscular use)	14/04/2023	n/a		PRAC Recommendation - maintenance
IB/0014	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/11/2022	24/10/2023	SmPC and PL	
PSUSA/10901 /202203	Periodic Safety Update EU Single assessment - rilpivirine (for intramuscular use)	27/10/2022	n/a		PRAC Recommendation - maintenance
IAIN/0015	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	24/10/2022	n/a		
II/0012	Update of sections 4.2 and 5.1 of the SmPC in order to describe data regarding oral bridging using other	15/09/2022	28/10/2022	SmPC and PL	Section 4.2. Missed every 1 month injection (Oral Dosing to Replace Up

	suppressive regimens than oral bridging with cabotegravir and rilpivirine based on studies 201584 (FLAIR), 207966 (ATLAS-2M), 200056 (LATTE 2) and 201585 (ATLAS). In addition, the MAH is also taking this opportunity to introduce editorial changes in the SmPC and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				to 2 Consecutive Monthly Injections) […] Limited data is available on oral bridging with other fully suppressive antiretroviral therapy (ART) (mainly INI-based), see section 5.1. Missed every 2 months injection (Oral Dosing to Replace 1 Every 2 Months Injection) […] Limited data is available on oral bridging with other fully suppressive antiretroviral therapy (ART) (mainly INI-based), see section 5.1. Section 5.1. Oral bridging with other ART In a retrospective analysis of pooled data from 3 clinical studies (FLAIR, ATLAS-2M, and LATTE-2/study 200056), 29 subjects were included who received oral bridging for a median duration of 59 days (25th and 75th percentile 53-135) with ART other than rilpivirine plus cabotegravir (alternative oral bridging) during treatment with REKAMBYS plus cabotegravir long-acting (LA) intramuscular (IM) injections. The median age of subjects was 32 years, 14% were female, 31% were non-white, 97% received an integrase inhibitor (INI)-based regimen for alternative oral bridging, 41% received an NNRTI as part of their alternative oral bridging regimen (including rilpivirine in 11/12 cases) and 62% received an NRTI. Three subjects withdrew during oral bridging or shortly following oral bridging for non-safety reasons. The majority (≥96%) of subjects maintained virologic suppression (plasma HIV-1 RNA <50 c/mL). During bridging with alternative oral bridging and during the period following alternative oral bridging (up to 2 REKAMBYS plus cabotegravir injections following oral bridging), no cases of CVF (confirmed plasma

					HIV-1 RNA ≥200 c/mL) were observed. For more information, please refer to the Summary of Product Characteristics.
II/0008	Update of sections 4.4 and 5.1 of the SmPC in order to update efficacy and safety information based on week 96 results from the clinical study 207966 (ATLAS-2M). This is an open-label, randomized, Phase IIIb trial to demonstrate non-inferior antiviral activity and safety of CAB + RPV Q8W compared with CAB + RPV Q4W. Supporting Cabotegravir (CAB) Long-acting Injectable (LA) + Rilpivirine (RPV) LA every 2 months (Q8W) dosing regimen for the treatment of HIV-1 infection. 1is recommended for approval C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/09/2022	28/10/2022	SmPC	Section 4.4. Baseline factors associated with virological failure Available data suggest that virologic failure occurs more often when these patients are treated according to the every 2 month dosing schedule as compared to the monthly dosing regimen. Section 5.1. Every 2 months dosing Patients virologically suppressed (stable on prior ART for at least 6 months) The efficacy results at Week 96 are consistent with the results of the primary endpoint at Week 48. Rilpivirine plus cabotegravir injections administered every 2 months is non-inferior to rilpivirine and cabotegravir administered every month. The proportion of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 96 in rilpivirine plus cabotegravir every 2 months dosing (n=522) and rilpivirine plus cabotegravir monthly dosing (n=523) was 2.1% and 1.1% respectively (adjusted treatment difference between rilpivirine plus cabotegravir every 2 months dosing and monthly dosing [1.0; 95% CI: -0.6, 2.5]). The proportion of subjects having plasma HIV-1 RNA <50 c/mL at Week 96 in rilpivirine plus cabotegravir every 2 months dosing and rilpivirine plus cabotegravir monthly dosing was 91% and

					90.2% respectively (adjusted treatment difference between rilpivirine plus cabotegravir every 2 months dosing and monthly dosing [0.8; 95% CI: -2.8, 4.3]). The efficacy results at Week 152 are consistent with the results of the primary endpoint at Week 48 and at Week 96. Rilpivirine plus cabotegravir injections administered every 2 months is non-inferior to rilpivirine and cabotegravir administered every month. In an ITT analysis, the proportion of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 152 in rilpivirine plus cabotegravir every 2 months dosing (n=522) and rilpivirine plus cabotegravir monthly dosing (n=523) was 2.7% and 1.0% respectively (adjusted treatment difference between rilpivirine plus cabotegravir every 2 months dosing and monthly dosing [1.7; 95% CI: 0.1, 3.3]). In an ITT analysis, the proportion of subjects having plasma HIV-1 RNA <50 c/mL at Week 152 in rilpivirine plus cabotegravir every 2 months dosing and rilpivirine plus cabotegravir monthly dosing was 87% and 86% respectively (adjusted treatment difference between rilpivirine plus cabotegravir every 2 months dosing and monthly dosing [1.5; 95% CI: -2.6, 5.6]). Post-hoc analyses Multivariable analyses of pooled Phase 3 studies (ATLAS through 96 weeks, FLAIR through 124 weeks, ATLAS-2M through 152 weeks) examined the influence of various factors on the risk of CVF. The baseline factors analysis (BFA) examined baseline viral and participants characteristics and dosing regimen; and the multivariable analysis (MVA) included the baseline factors and incorporated post-baseline predicted plasma drug concentrations on CVF using regression modelling with a variable selection procedure. Following a total of 4291

					person-years, the unadjusted CVF incidence rate was 0.54 per 100 person-years; 23 CVFs were reported (1.4% of 1651 individuals in these studies). The BFA demonstrated rilpivirine resistance mutations (incidence rate ratio IRR=21.65, p<0.0001), HIV-1 subtype A6/A1 (IRR=12.87, p<0.0001), and body mass index IRR=1.09 per 1 unit increase, p=0.04; IRR=3.97 of ≥30 kg/m2, p=0.01) were associated with CVF. Other variables including Q4W or Q8W dosing, female gender, or CAB/INSTI resistance mutations had no significant association with CVF. A combination of at least 2 of the following key baseline factors was associated with an increased risk of CVF: rilpivirine resistance associated mutations, HIV-1 subtype A6/A1, or BMI ≥ 30 kg/m2 (Table 12). In patients with at least two of these risk factors, the proportion of subjects who had a CVF was higher than observed in patients with none or one risk factor, with CVF identified in 6/24 patients [25.0%, 95% CI (9.8%, 46.7%)] treated with the every 2 months dosing regimen and 5/33 patients [15.2%, 95% CI (5.1%, 31.9%)] treated with the monthly dosing regimen. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10901 /202109	Periodic Safety Update EU Single assessment - rilpivirine (for intramuscular use)	07/04/2022	n/a		PRAC Recommendation - maintenance
II/0010	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/01/2022	28/10/2022	SmPC and PL	

II/0006	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/12/2021	28/10/2022	SmPC and PL	To change section 6.3 of the Summary of Product Characteristics from 2 years to 3 years.
IB/0007	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	04/11/2021	28/10/2022	SmPC	
II/0004	Update of section 4.2 (to change posology recommendations) and sections 4.8, 5.1 and 5.2 of the SmPC (to update safety and efficacy information) based on week 124 results from the FLAIR study. This is a Phase III, randomized, open-label study to evaluate the efficacy, safety and tolerability of the combined treatment Cabotegravir and Rilpivirine. The Package Leaflet has been updated accordingly. Editorial changes and corrections have been carried out throughout the PI. The RMP version 3.1 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/09/2021	19/10/2021	SmPC and PL	SmPC new text 4.2 Posology and method of administration […] REKAMBYS may be initiated with oral lead-in or without (direct to injection). The healthcare professional and patient may decide to use rilpivirine tablets as an oral lead-in prior to the initiation of REKAMBYS injections to assess tolerability (see Table 1), or proceed directly to REKAMBYS therapy (see Tables 2 and 3, for monthly and every 2 months dosing recommendations, respectively). […] 4.8 Undesirable effects […] The overall safety profile at Week 96 and Week 124 in the FLAIR study was consistent with that observed at Week 48, with no new safety findings identified. In the extension phase of the FLAIR study, initiating the rilpivirine plus cabotegravir injection regimen without oral lead-in (direct to injection) was not associated with any new safety concerns related to omitting the oral lead-in phase. […] 5.1 Pharmacodynamic properties […]

					Week 124 FLAIR Direct to Injection versus Oral Lead-In In the FLAIR study, an evaluation of safety and efficacy was performed at Week 124 for patients electing to switch at Week 100 from abacavir/dolutegravir/lamivudine to rilpivirine plus cabotegravir in the Extension Phase., Subjects were given the option to switch with or without an oral lead-in phase, creating an oral lead-in group and a direct to injection group. At Week 124, the proportion of subjects having plasma HIV-1 RNA ≥ 50 c/mL was 1/121 (0.8%) and 1/111 (0.9%) for the oral lead-in and direct to injection groups, respectively. The rates of virologic suppression (HIV-1 RNA < 50 c/mL) were similar in both the oral lead-in group (113/121 [93.4%]) and direct to injection group (110/111 [99.1%]). For more information, please refer to the Summary of Product Characteristics.
IA/0009/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure A.7 - Administrative change - Deletion of manufacturing sites B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	15/10/2021	n/a		
PSUSA/10901 /202103	Periodic Safety Update EU Single assessment - rilpivirine (for intramuscular use)	30/09/2021	n/a		PRAC Recommendation - maintenance

N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/06/2021	19/10/2021	PL	
IB/0002	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	18/04/2021	n/a		
IAIN/0001	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	27/01/2021	n/a		