אוקטובר 2022

רופא/ה נכבד/ה,

רוקח/ת נכבד/ה,

<u>הנדון:</u>
Rekambys®
רקמביס™

חברת יאנסן ישראל (J-C Health Care Ltd.) מבקשת להודיעכם כי העלונים לרופא ולצרכן של התכשיר שבנדון התעדכנו בספטמבר 2022.

פרטי העדכון העיקריים מופיעים בהמשך *(טקסט שנוסף מסומן באדום, טקסט שהושמט מסומן כטקסט* ~~כחול עם קו חוצה~~*, טקסט המהווה החמרה מודגש ברקע צהוב)*,אך קיימים עדכונים נוספים.

ההתוויות המאושרות לתכשיר בישראל:

REKAMBYS is indicated, in combination with cabotegravir 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

מרכיב פעיל: Rilpivirine 300mg/ 1 ml

העלון המעודכן נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://israeldrugs.health.gov.il/#!/byDrug.

כמו כן, מצורף לפרסום זה וניתן לקבל העתק מודפס שלו באמצעות פנייה לבעל הרישום:

ג'י-סי הלת'קר בע"מ - יאנסן ישראל , קיבוץ שפיים, 6099000, טל': 09-9591111.

בברכה,
ויקטוריה גוטלויבר-הדדי
רוקחת ממונה
ג'י-סי הלת'קר בע"מ

העדכונים העיקריים בעלון לרופא הינם:

4. CLINICAL PARTICULARS

4.2 Posology and Method of administration

Method of administration

For intramuscular use.

Care should be taken to avoid inadvertent injection of REKAMBYS into a blood vessel. The suspension should be injected slowly (see section 4.4).

Prior to administration, the REKAMBYS vial should be brought to room temperature.

4.4 Special warnings and precautions for use

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. ..

Post-injection reactions

Accidental intravenous administration may result in AEs due to temporarily high plasma concentrations. In clinical studies, serious post-injection reactions were reported within minutes after the injection of rilpivirine. These events included symptoms such as dyspnoea, bronchospasm, agitation, abdominal cramping, rash/urticaria, dizziness, flushing, sweating, oral numbness, changes in blood pressure, and pain (e.g., back and chest). These events were very rare and began to resolve within minutes after the injection. Some of the patients received symptomatic treatment, at the discretion of the treating physician.

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4.8 Undesirable effects

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Table 6: Tabulated summary of adverse reactions

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5. Pyrexia includes the following grouped MedDRA preferred terms: pyrexia, feeling hot, body temperature increased. The majority of pyrexia events were reported within one week of injections.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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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 ~~analysis~~ analyses

Multivariable analyses of pooled ~~phase~~ Phase 3 studies (ATLAS through 96 weeks, FLAIR through 124 weeks, ATLAS-2M through 152 weeks)~~, including data from1039 HIV-infected adults with no prior exposure to rilpivirine plus cabotegravir~~, examined the influence of various factors on the risk of CVF.~~the following covariates: baseline viral and participants characteristics, dosing regimen (Q4W or Q8W), and post-baseline plasma drug concentrations on CVF using regression modeling with a covariate selection procedure.~~ 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. ~~Through Week 48 in these studies, 13/1039 (1.25%) participants had CVF while receiving rilpivirine plus cabotegravir.~~ 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 ~~Four covariates were significantly associated (P < 0.05 for each adjusted odds ratio) with increased risk of CVF:~~ rilpivirine ~~resistance associated~~ mutations (~~RAMs) at baseline identified by proviral DNA genotypic assay~~, incidence rate ratio IRR=21.65, p<0.0001), HIV-1 subtype A6/A1~~ (associated with integrase L74I polymorphism), rilpivirine trough concentration 4 weeks following initial injection dose, BMI of at least 30 kg/m^2 (associated with cabotegravir pharmacokinetics).~~ 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 ~~covariates~~ variables including Q4W or Q8W dosing, female gender, or CAB/INSTI resistance mutations ~~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~~ A combinationof 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/m^2 (Table 11).

Table 11 Week 48 Outcomes by Presence of Key Baseline Factors of rilpivirine resistance associated mutations, HIV-1 Subtype A6/A1[1] and BMI ≥ 30 kg/m^2

Baseline Factors (number)	Virologic Successes[2]	Confirmed Virologic Failure (%)[3]
0	844/970 (87.0) ~~694/732 (94.8)~~	4/970 (0.4)~~3/732 (0.41)~~
1	343/404 (84.9)~~261/272 (96.0)~~	8/404 (2.0)[4]~~1/272 (0.37)~~[4]
≥ 2	44/57 (77.2)~~25/35 (71.4)~~	11/57 (19.3)[5]~~9/35 (25.7)~~[5]
TOTAL (95% Confidence Interval)	1231/1431 (86/0) (84.1%, 87.8%)~~980/1039 (94.3) (92.74%, 95.65%)~~	23/1431 (1.6)[6] (1.0%, 2.4%)~~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 at Week 48 for ATLAS, at Week 124 for FLAIR, at Week 152 for ATLAS-2M.

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%
PPV 26%; NPV 99.6%; sensitivity 69%; specificity 97.5%.

5 Analysis dataset with all non-missing covariates for baseline factors (out of a total of 1651 individuals).

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.

6. PHARMACEUTICAL PARTICULARS

6.4 Special precautions for storage

Prior to administration, the vial should be brought to room temperature (not to exceed 25°C). The vial may remain in the carton at room temperature for up to 6 hours. If not used after 6 hours, it must be discarded (refer to section 6.3).

העדכונים העיקריים בעלון לצרכן הינם:

- **<u>לפני השימוש בתרופה</u>**

תגובה לזריקות: תסמינים של תגובה לאחר הזרקה הופיעו בתוך דקות אצל חלק מהאנשים לאחר קבלת זריקת רילפיווירין. מרבית התסמינים נעלמו בתוך כמה דקות לאחר ההזרקה. תסמינים של תגובה לאחר ההזרקה יכולים לכלול: קשיי נשימה, התכווציות בבטן, פריחה, הזעה, נימול בפה, תחושת חרדה, תחושת חמימות, תחושת סחרחורת או תחושה שאתה עומד להתעלף, שינויים בלחץ הדם וכאב (לדוגמא כאבי גב וכאבים בחזה). ספר לרופא אם הופיעו אצלך תסמינים אלה לאחר קבלת זריקות.

- **<u>תופעות לוואי</u>**

תופעות לוואי שדווחו עם השימוש ברקמביס יחד עם זריקת קבוטגרוויר

תופעות לוואי שכיחות מאוד (מופיעות לפחות במשתמש אחד מתוך 10) :

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6 תגובות במקום ההזרקה - בדרך כלל בדרגה קלה עד בינונית ותדירותן יורדת עם הזמן.
התסמינים עשויים לכלול:

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- שכיחים: ...תחושת חמימות או חבורות (שעשויות לכלול שינוי צבע או הצטברות של דם מתחת לעור)
- לא שכיחים: ... תחושת חום/חום, שעלולים להתרחש תוך שבוע אחרי ההזרקה