

2020 ספטמבר

רופא/ה נכבד/ה  
רוקח/ת נכבד/ה

ברצוננו להביא לידיעתכם את העדכונים בעלון לרופא ובעלון לצרכן של התכשיר:

**Eviplera**  
**(emtricitabine 200 mg, rilpivirine (as hydrochloride) 25 mg,**  
**tenofovir disoproxil (as fumarate) 245 mg)**

**המאשר להתוויה:**

EVIPLERA, a combination of two nucleoside analog HIV 1 reverse transcriptase inhibitors (emtricitabine and tenofovir disoproxil fumarate) and one non-nucleoside reverse transcriptase inhibitor (rilpivirine), is indicated for use as a complete regimen for the treatment of HIV-1 infection in adult patients with no antiretroviral treatment history and with HIV-1 RNA less than or equal to 100,000 copies/mL at the start of therapy, and in certain virologically-suppressed (HIV-1 RNA <50 copies/mL) adult patients on a stable antiretroviral regimen at start of therapy in order to replace their current antiretroviral treatment regimen (see below).

The following points should be considered when initiating therapy with EVIPLERA in adult patients with no antiretroviral treatment history:

- More rilpivirine-treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure (HIV-1 RNA  $\geq$  50 copies/mL) compared to rilpivirine-treated subjects with HIV-1 RNA less than or equal to 100,000 copies/mL [See Clinical Studies (14)].
- Regardless of HIV-1 RNA level at the start of therapy, more rilpivirine-treated subjects with CD4+ cell count less than 200 cells/mm<sup>3</sup> experienced virologic failure compared to rilpivirine-treated subjects with CD4+ cell count greater than or equal to 200 cells/mm<sup>3</sup> [See Clinical Studies (14)].
- The observed virologic failure rate in rilpivirine-treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz [See Microbiology (12.4)].
- More subjects treated with rilpivirine developed tenofovir and lamivudine/emtricitabine associated resistance compared to efavirenz [See Microbiology (12.4)].

השינויים המהותיים בעלון לרופא מופיעים בסעיפים הבאים:

#### 4.4 Special warnings and precautions for use

...

##### Co-administration of other medicinal products

Eviplera should not be administered concomitantly with other medicinal products containing emtricitabine, tenofovir disoproxil, **tenofovir alafenamide, or other cytidine analogues**, such as lamivudine (see section 4.5).

...

##### Renal impairment

...If serum phosphate is < 1.5 mg/dL (0.48 mmol/L) or CrCl is decreased to < 50 mL/min in any patient receiving Eviplera, renal function should be re-evaluated within one week, including measurements of blood glucose, blood potassium and urine glucose concentrations (see section 4.8, proximal tubulopathy). Since Eviplera is a combination product and the dosing interval of the individual components cannot be altered, treatment with Eviplera must be interrupted in patients with confirmed CrCl decreased to < 50 mL/min or decreases in serum phosphate to < 1.0 mg/dL (0.32 mmol/L). Interrupting treatment with Eviplera should also be considered in case of progressive decline of renal function when no other cause has been identified. Where discontinuation of therapy with one of the components of Eviplera is indicated or where dose modification is necessary, separate preparations of emtricitabine, rilpivirine hydrochloride and tenofovir disoproxil are available.

### Bone effects

A dual energy X ray absorptiometry (DXA) substudy for both the Phase III studies (C209 and C215) investigated the effect of rilpivirine as compared with control, overall and by background regimen on changes in whole body bone mineral density (BMD) and bone mineral content (BMC) at week 48 and week 96. DXA substudies showed that small but statistically significant decreases from baseline in whole body BMD and BMC were similar for rilpivirine and control at week 48 and week 96. There was no difference in the change from baseline in whole body BMD or BMC for rilpivirine compared with control, in the overall population or in those patients treated with a backbone regimen including tenofovir disoproxil.

... In other studies (prospective and cross-sectional), the most pronounced decreases in BMD were seen in patients treated with tenofovir disoproxil as part of a regimen containing a boosted protease inhibitor (PI). Alternative treatment regimens should be considered for patients with osteoporosis that are at a high risk for fractures.

...

### Patients with HIV and hepatitis B or C virus co-infection

Patients with chronic hepatitis B or C treated with antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse reactions.

...

Discontinuation of Eviplera therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis. Patients co-infected with HIV and HBV who discontinue Eviplera should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of hepatitis B therapy may be warranted. In patients with advanced liver disease or cirrhosis, treatment discontinuation is not recommended since post-treatment exacerbation of hepatitis may lead to hepatic decompensation.

### Liver disease

The safety and efficacy of Eviplera have not been established in patients with significant underlying liver disorders. The pharmacokinetics of emtricitabine has not been studied in patients with hepatic impairment...

Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy (CART) and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

### Weight and metabolic parameters

An increase in weight and in levels of blood lipids and glucose may occur during antiretroviral therapy. Such changes may in part be linked to disease control and life style. For lipids, there is in some cases evidence for a treatment effect, while for weight gain there is no strong evidence relating this to any particular treatment. For monitoring of blood lipids and glucose reference is made to established HIV treatment guidelines. Lipid disorders should be managed as clinically appropriate.

### Immune Reactivation Syndrome

In HIV infected patients with severe immune deficiency at the time of institution of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections, and *Pneumocystis jirovecii* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation;...

J-C Health Care Ltd.

Kibbutz Shefayim 6099000, ISRAEL  
tel +972-9-959-1111  
fax +972-9-958-3636



### Pregnancy

Lower exposures of rilpivirine were observed when rilpivirine 25 mg once daily was taken during pregnancy. In the Phase III studies (C209 and C215), lower rilpivirine exposure, similar to that seen during pregnancy, has been associated with an increased risk of virological failure, therefore viral load should be monitored closely (see sections 4.6, 5.1 and 5.2). Alternatively, switching to another antiretroviral regimen could be considered.

### **4.5 Interaction with other medicinal products and other forms of interaction**

Use of Eviplera should be avoided with concurrent or recent use of a nephrotoxic medicinal product. Some examples include, but are not limited to, aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, **vancomycin**, cidofovir or interleukin-2 (also called aldesleukin).

### **Table 1: Interactions between Eviplera or its individual component(s) and other medicinal products**

| Medicinal product by therapeutic areas                                                                                                                                | Effects on medicinal product levels.<br>Mean percent change in AUC, C <sub>max</sub> , C <sub>min</sub>                                                                   | Recommendation concerning co-administration with Eviplera                                                                                                                                                                                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Protease inhibitors (PIs) - boosted (with co-administration of low-dose ritonavir)</b>                                                                             |                                                                                                                                                                           |                                                                                                                                                                                                                                          |
| Atazanavir (300 mg once daily)/<br>Ritonavir (100 mg once daily)/<br>Tenofovir disoproxil (245 mg once daily)                                                         | Atazanavir:<br>AUC: ↓ 25%<br>C <sub>max</sub> : ↓ 28%<br>C <sub>min</sub> : ↓ 26%<br><br>Tenofovir:<br>AUC: ↑ 37%<br>C <sub>max</sub> : ↑ 34%<br>C <sub>min</sub> : ↑ 29% | Concomitant use of Eviplera with ritonavir-boosted PIs causes an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes).                                                                                     |
| Darunavir (800 mg once daily)/<br>Ritonavir (100 mg once daily)/<br>Rilpivirine <sup>1</sup>                                                                          | Darunavir:<br>AUC: ↔<br>C <sub>min</sub> : ↓ 11%<br>C <sub>max</sub> : ↔<br><br>Rilpivirine:<br>AUC: ↑ 130%<br>C <sub>min</sub> : ↑ 178%<br>C <sub>max</sub> : ↑ 79%      | No dose adjustment is required.                                                                                                                                                                                                          |
| Darunavir (300 mg once daily)/<br>Ritonavir (100 mg once daily)/<br>Tenofovir disoproxil (245 mg once daily)                                                          | Darunavir:<br>AUC: ↔<br>C <sub>min</sub> : ↔<br><br>Tenofovir:<br>AUC: ↑ 22%<br>C <sub>min</sub> : ↑ 37%<br>C <sub>max</sub> : ↑ 79%                                      |                                                                                                                                                                                                                                          |
| Lopinavir/Ritonavir/Emtricitabine                                                                                                                                     | Interaction not studied.                                                                                                                                                  |                                                                                                                                                                                                                                          |
| Lopinavir (400 mg twice daily)/<br>Ritonavir (100 mg twice daily)/<br>Rilpivirine <sup>1</sup> (soft capsule)                                                         | Lopinavir:<br>AUC: ↔<br>C <sub>min</sub> : ↓ 11%<br>C <sub>max</sub> : ↔<br><br>Rilpivirine:<br>AUC: ↑ 52%<br>C <sub>min</sub> : ↑ 74%<br>C <sub>max</sub> : ↑ 29%        |                                                                                                                                                                                                                                          |
| Lopinavir (400 mg twice daily)/<br>Ritonavir (100 mg twice daily)/<br>Tenofovir disoproxil (245 mg once daily)                                                        | Lopinavir/Ritonavir:<br>AUC: ↔<br>C <sub>max</sub> : ↔<br>C <sub>min</sub> : ↔<br><br>Tenofovir:<br>AUC: ↑ 32%<br>C <sub>max</sub> : ↔<br>C <sub>min</sub> : ↑ 51%        |                                                                                                                                                                                                                                          |
| Ledipasvir/Sofosbuvir (90 mg/400 mg once daily)/<br>Emtricitabine/Rilpivirine/<br>Tenofovir disoproxil (200 mg/25 mg/245 mg once daily)                               | Tenofovir:<br>AUC: ↑ 40%<br>C <sub>max</sub> : ↔<br>C <sub>min</sub> : ↑ 91%                                                                                              | No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4). |
| Sofosbuvir/Velpatasvir (400 mg/100 mg once daily)/<br>Emtricitabine/Rilpivirine/Tenofovir disoproxil (200 mg/25 mg/245 mg once daily)                                 | Tenofovir:<br>AUC: ↑ 40%<br>C <sub>max</sub> : ↑ 44%<br>C <sub>min</sub> : ↑ 84%                                                                                          |                                                                                                                                                                                                                                          |
| Sofosbuvir/Velpatasvir/<br>Voxilaprevir (400 mg/100 mg/100 mg + 100 mg once daily) <sup>5/</sup><br>Rilpivirine/Emtricitabine (25 mg/200 mg once daily) <sup>6/</sup> |                                                                                                                                                                           | No dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil, including renal disorders. Renal function should be closely monitored (see section 4.4). |

| Medicinal product by therapeutic areas                                                                                                                                                                              | Effects on medicinal product levels.<br>Mean percent change in AUC, C <sub>max</sub> , C <sub>min</sub>                                                                                                                                                                                                                                                                                          | Recommendation concerning co-administration with Eviplera                                                                                                                                                                                                                                                                                                              |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Rifabutin (300 mg once daily)/<br/>Rilpivirine<sup>3</sup></p> <p>Rifabutin (300 mg once daily)/<br/>Rilpivirine (25 mg once daily)</p> <p>Rifabutin (300 mg once daily)/<br/>Rilpivirine (50 mg once daily)</p> | <p>Rifabutin:<br/>AUC: ↔<br/>C<sub>min</sub>: ↔<br/>C<sub>max</sub>: ↔<br/>25-O-desacetyl-rifabutin:<br/>AUC: ↔<br/>C<sub>min</sub>: ↔<br/>C<sub>max</sub>: ↔<br/>Rilpivirine:<br/>AUC: ↓ 42%<br/>C<sub>min</sub>: ↓ 48%<br/>C<sub>max</sub>: ↓ 31%<br/>Rilpivirine:<br/>AUC: ↑ 16%*<br/>C<sub>min</sub>: ↔*<br/>C<sub>max</sub>: ↑ 43%*<br/>*compared to 25 mg once daily rilpivirine alone</p> |                                                                                                                                                                                                                                                                                                                                                                        |
| <p>Rifampicin (600 mg once daily)/<br/>Rilpivirine<sup>1</sup></p>                                                                                                                                                  | <p>Rifampicin:<br/>AUC: ↔<br/>C<sub>min</sub>: N/A<br/>C<sub>max</sub>: ↔</p> <p>25-desacetyl-rifampicin:<br/>AUC: ↓ 9%<br/>C<sub>min</sub>: N/A<br/>C<sub>max</sub>: ↔</p>                                                                                                                                                                                                                      | <p>Rilpivirine:<br/>AUC: ↓ 80%<br/>C<sub>min</sub>: ↓ 89%<br/>C<sub>max</sub>: ↓ 69%</p> <p>Eviplera must not be used in combination with rifampicin as co-administration is likely to cause significant decreases in rilpivirine plasma concentrations (induction of CYP3A enzymes). This may result in loss of therapeutic effect of Eviplera (see section 4.3).</p> |
| ...                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                        |

#### 4.6 Fertility, pregnancy and lactation

##### Women of childbearing potential / contraception in males and females

The use of Eviplera must be accompanied by the use of effective contraception.

##### Pregnancy

There are no adequate and well-controlled studies of Eviplera or its components in pregnant women. A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformative or foeto/neonatal toxicity of rilpivirine (see sections 4.4, 5.1 and 5.2). Lower exposures of rilpivirine were observed during pregnancy; therefore viral load should be monitored closely...

#### 4.8 Undesirable effects

...  
In virologically suppressed patients switching to Eviplera, the most frequently reported adverse reactions considered possibly or probably related to Eviplera were fatigue (3%), diarrhoea (3%), nausea (2%) and insomnia (2%) (48 week data from the Phase III study GS-US-264-0106).

##### Description of selected adverse reactions

###### *Renal impairment*

As Eviplera may cause renal damage, monitoring of renal function is recommended (see sections 4.4 and 4.8, *Summary of the safety profile*). Proximal renal tubulopathy generally resolved or improved after tenofovir disoproxil discontinuation. However, in some patients,

declines in CrCl did not completely resolve despite tenofovir disoproxil discontinuation. Patients at risk of renal impairment (such as patients with baseline renal risk factors, advanced HIV disease, or patients receiving concomitant nephrotoxic medications) are at increased risk of experiencing incomplete recovery of renal function despite tenofovir disoproxil discontinuation (see section 4.4).

#### Immune Reactivation Syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported;

#### Other special populations

##### HIV/HBV or HCV co-infected patients

The adverse reaction profile of emtricitabine, rilpivirine hydrochloride and tenofovir disoproxil in patients co-infected with HIV/HBV or HIV/HCV was similar to that observed in patients infected with HIV without co-infection. However, as would be expected in this patient population, elevations in AST and ALT occurred more frequently than in the general HIV infected population.

השינויים המהותיים בעלון לצרכ מופיעים בסעיפים הבאים:

#### 2. לפני השימוש בתרופה

אהרות מיוחדות הנוגעות לשימוש בתרופה:

ספר לרופא שלך באופן מידי והפסק נטילת אויפילרה אם הנך מפתח פריחה עורית המלווה בתסמינים הבאים: חום, שלפוחיות, אדמומיות בעיניים, ונפיחות של הפנים שלך, הפה או הגוף. ייתכן והמצב הזה עלול להפוך לחמור או מסכן חיים.

במהלך נטילת אויפילרה: בתקופה שהנך מתחיל ליטול אויפילרה, יש לעקוב אחר הופעת תסמינים הבאים: כל תסמין של דלקת או זיהום, בעיות בעצמות. אם הנך מבחין בכל אחד מהתסמינים האלה, יש לספר לרופא שלך באופן מידי.

#### אינטראקציות/תגובות בין תרופתיות

... תרופות אחרות המכלולות: טנופוביר דיסופרוקסיל, טנופוביר אלאפנאמיד

#### 4. תופעות לוואי

תופעות לוואי שכיחות מאוד (very common) – תופעות שמופיעות ביותר ממשתמש אחד מעשרה

... נדודי שינה, פריחה...

תופעות לוואי שכיחות (common) תופעות שמופיעות ב 10-1 משתמשים מתוך 100

... ירידה בהמוגלובין בדם (ספירה נמוכה של תאי דם אדומים)

במהלך טיפול בירוס ה-HIV, ייתכן ותתרחש עלייה במשקל וברמות של שומנים וסוכר בדם. אלה קשורים באופן חלקי בשיפור שחל בבריאות ובאורח החיים, ובמקרה של עלייה ברמות של שומנים בדם, הדבר קשור לעיתים לתרופות נגד וירוס ה-HIV עצמן. רופאך יבצע בדיקות לניטור שינויים אלו.

כלל השינויים מסומנים בעלונים המצורפים כאשר הטקסט המודגש באדום הוסף לעלון ואילו הטקסט המחוק הוסר. בנוסף, הטקסט המודגש בסימון צהוב מסמן החמרה. העלון לרופא והעלון לצרכן נשלחו לפרסום במלואם למאגר התרופות שבאתר משרד הבריאות.

כמו כן, ניתן לקבלם מודפסים בפניה אליהם לטלפון 09-9591111.

להלן העדכונים.

בברכה,  
אלינה ורמן, רוקחת ממונה