Gilead Sciences Israel Ltd.
4 HaHarash Street, Hod Hasharon
Tel: 972-8802050

פברואר 2019

הודעה על עדכון עלונים:

Viread film coated tablets

(tenofovir disoproxil (as fumarate) 245 mg)

רופאים ורוקחים נכבדים,

חברת גיליאד סיאנסז ישראל בע"מ מבקשת להודיעכם על עדכון בעלון לרופא ולצרכן של התכשירים בנדון מאוקטובר 2018.

ההתוויה הרשומה לתכשיר בישראל:

HIV-1 infection
Viread is indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults and paediatric patients 12 years of age and older.
The choice of Viread to treat antiretroviral experienced patients with HIV-1 infection should be based on individual viral resistance testing and/or treatment history of patients.

Hepatitis B infection
Viread 245 mg film-coated tablets are indicated for the treatment of chronic hepatitis B in adults with:

- compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis (see section 5.1).
- decompensated liver disease (see sections 4.4, 4.8 and 5.1).

השינויים מסומנים בעלון המצורף כאשר הטקסט המודגש באדום הוסף לעלון ואילו הטקסט המחוק ~~בקו חוצה~~ נגרע ממנו. הסימונים בצהוב הינם החמרות במידע הבטיחותי.

העדכונים המשמעותיים ביותר מופיעים במכתב זה, קיימים עדכונים מינוריים נוספים.

העלונים לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות.

כמו כן ,ניתן לקבלם מודפסים על ידי פנייה לבעל הרישום:

גיליאד סיאנסז ישראל בע"מ, רחוב החרש 4 ,ת.ד. 6090, פארק העסקים הוד השרון 4524075, ישראל

בברכה,

מריה חורגין

רוקחת ממונה

גיליאד סיאנסז ישראל בע"מ

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עדכונים בעלון לרופא:

4.4 Special warnings and precautions for use

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Use with certain hepatitis C virus antiviral agents

Co-administration of tenofovir disoproxil ~~fumarate~~ with ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir has been shown to increase plasma concentrations of tenofovir, especially when used together with an HIV regimen containing tenofovir disoproxil ~~fumarate~~ and a pharmacokinetic enhancer (ritonavir or cobicistat). The safety of tenofovir disoproxil ~~fumarate~~ in the setting of ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir and a pharmacokinetic enhancer has not been established. The potential risks and benefits associated with co-administration of ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir with tenofovir disoproxil ~~fumarate~~ given in conjunction with a boosted HIV protease inhibitor (e.g. atazanavir or darunavir) should be considered, particularly in patients at increased risk of renal dysfunction. Patients receiving ledipasvir/sofosbuvir, sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir concomitantly with tenofovir disoproxil ~~fumarate~~ and a boosted HIV protease inhibitor should be monitored for adverse reactions related to tenofovir disoproxil ~~fumarate~~.

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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; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

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Medicinal product by therapeutic areas (dose in mg)	Effects on drug levels Mean percent change in AUC, C_{max}, C_{min}	Recommendation concerning co-administration with 245 mg tenofovir disoproxil
Sofosbuvir/Velpatasvir/ Voxilaprevir (400 mg/100 mg/ 100 mg+100 mg q.d.)[3] +~~Efavirenz~~ Darunavir (800 mg q.d.) + Ritonavir (100 mg q.d.) + Emtricitabine/Tenofovir disoproxil ~~fumarate~~ (~~600 mg/~~ (200 mg/~~300~~245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↓ ~~19~~30% C_{min}: N/A GS-331007[2]: AUC: ↔ C_{max}: ~~↓23~~↔ ~~Efavirenz~~ C_{min}: N/A Velpatasvir: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Voxilaprevir: AUC: ↑ 143% C_{max}:↑ 72% C_{min}: ↑ 300% Darunavir: AUC: ↔ C_{max}: ↔ C_{min}: ↓ 34% Ritonavir: AUC: ↑ 45% C_{max}: ↑ 60% C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ~~↔~~↑ 39% C_{max}: ↑ ~~25~~48% C_{min}: ~~↔~~↑ 47%	~~No dose adjustment is required.~~ Increased plasma concentrations of tenofovir resulting from co-administration of tenofovir disoproxil, sofosbuvir/velpatasvir/voxilaprevir and darunavir/ritonavir may increase adverse reactions related to tenofovir disoproxil, including renal disorders. The safety of tenofovir disoproxil when used with sofosbuvir/velpatasvir/voxilaprevir and a pharmacokinetic enhancer (e.g. ritonavir or cobicistat) has not been established. The combination should be used with caution with frequent renal monitoring (see section 4.4).

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Sofosbuvir (400 mg q.d.) + Efavirenz/Emtricitabine/Tenofovir disoproxil (600 mg/200 mg/245 mg q.d.)	Sofosbuvir: AUC: ↔ C_{max}: ↓ 19% GS-331007[2]: AUC: ↔ C_{max}: ↓ 23% Efavirenz: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Emtricitabine: AUC: ↔ C_{max}: ↔ C_{min}: ↔ Tenofovir: AUC: ↔ C_{max}: ↑ 25% C_{min}: ↔	No dose adjustment is required.

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4.6 Fertility, pregnancy and lactation

Pregnancy

A ~~moderate~~large amount of data on pregnant women (~~between 300~~more than 1,000 pregnancy outcomes) indicate no malformations or foetal/neonatal toxicity associated with tenofovir disoproxil ~~fumarate~~. Animal studies do not indicate reproductive toxicity (see section 5.3). The use of tenofovir disoproxil ~~fumarate~~ may be considered during pregnancy, if necessary.

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4.8 Undesirable effects

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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; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see section 4.4).

עדכונים בעלון לצרכן

2. לפני השימוש בויראד

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תרופות אחרות וויראד

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- **כמו כן חשוב לספר לרופא אם אתה לוקח** לדיפסביר\ סופוסבוביר, סופוסבוביר\ ולפטסביר או סופוסבוביר\ ולפטסביר\ווקסילפרביר לטיפול בדלקת הפטיטיס C.