

רופא/ה, רוקח/ת נכבד/ה,



הנדון: טרובדה טבליות מצופות Truvada coated tablets

Emtricitabine 200 mg and Tenofovir Disoproxil (as Fumarate) 245 mg מרכיב פעיל:

התוויה המאושרת:

Truvada is indicated in combination with other anti-retroviral medicinal products for the treatment of HIV-1 infected adults over 18 years of age.

Truvada is indicated in combination with safer sex practices for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 infection in adults at high risk.

חברת גיליאד סיאנסז ישראל בע"מ מבקשת ליידע על החמרות בעלון לרופא ולצרכן שהוגשו למשרד הבריאות באוקטובר 2018.

העדכונים מופיעים <mark>כטקסט אדום, <mark>הסימונים בצהוב</mark> הינם החמרות במידע הבטיחותי. קו חוצה מסמן טקסט שנמחק.</mark>

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

העלון לרופא ולצרכן בפורמט החדש נשלחו למשרד הבריאות לצורך פרסומם במאגר התרופות שבאתר משרד הבריאות:

https://data.health.gov.il/drugs/index.html#/byDrug

2 כמו כן, ניתן לקבלם מודפסים על-ידי פניה לחברת גיליאד סיאנסז ישראל בע"מ: רחוב החרש 4, ניתן לקבלם מודפסים על-ידי פניה לחברת גיליאד סיאנסז ישראל העסקים הוד השרון 4524075, ישראל

בברכה,

מריה חורגין רוקחת ממונה גיליאד סיאנסז ישראל



עדכונים מהותיים בעלון לרופא:

4.4 Special warnings and precautions for use

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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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Co-administration of other medicinal products

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Use with ledipasvir and sofosbuvir-or, sofosbuvir and velpatasvir<u>-or</u> sofosbuvir, velpatasvir and velpatasvir or sofosbuvir, velpatasvir and velpatasvir or sofosbuvir, velpatasvir and velpatasvir or sofosbuvir.

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—when co-administered with 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 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.



4.5 Interaction with other medicinal products and other forms of interaction

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| $ \begin{array}{c ccccccccccccccccccccccccccccccccccc$ | | | |
|---|---------------------------------|---|--|
| $ \begin{array}{c} \text{therapeutic areas} \\ \text{Sofosbuvir/Velpa} \\ \text{tasvii/} \\ \text{Voxilaprevir} \\ (400 mg/100 mg$ | | | |
| Intervals if available (mechanism) Sofosbuvir/Velpa Sofosbuvir: Sofosbuvir: AUC: \leftrightarrow Cmax: $\frac{1}{2}$ | product by | Mean percent change in AUC, | co-administration with Truvada |
| $ \begin{array}{c ccccccccccccccccccccccccccccccccccc$ | therapeutic areas | C_{max} , C_{min} with 90% confidence | (emtricitabine 200 mg, tenofovir disoproxil |
| $ \begin{array}{llllllllllllllllllllllllllllllllllll$ | | intervals if available (mechanism) | fumarate 300 <u>245</u> mg) |
| $ \begin{array}{c c} \hline Voxilaprevir \\ (400 \ mg/100 \ mg/\\ 100 \ mg+100 \ mg/\\ 100 \ mg+100 \ mg/\\ q.d.) + \\ \hline Efavirenz/^3 + \\ Darunavir \\ (800 \ mg \ q.d.) + \\ Entricitabine/Te \\ nofovir \\ disoproxil \\ fumarate \\ (600 \ mg/200 \ mg/300245 \ mg \ q.d.) \\ \hline \\ Darunavir \\ AUC: \leftrightarrow \\ C_{max}: \leftrightarrow \\ C_{min}: \rightarrow \\ C_{min}: \rightarrow \\ C_{min}: \uparrow 300\% \\ \hline \\ Darunavir \\ AUC: \leftrightarrow \\ C_{min}: \uparrow 300\% \\ \hline \\ Darunavir \\ AUC: \leftrightarrow \\ C_{min}: \uparrow 300\% \\ \hline \\ Darunavir \\ AUC: \uparrow 143\% \\ C_{max}: \leftrightarrow \\ C_{min}: \uparrow 300\% \\ \hline \\ Darunavir \\ AUC: \leftrightarrow \\ C_{min}: \uparrow 300\% \\ \hline \\ Emtricitabine \\ AUC: \leftrightarrow \\ C_{min}: \rightarrow \\ C_{min}: \rightarrow \\ \hline \\ C_{min}: \uparrow 300\% \\ \hline \\ C_{min}: \rightarrow \\ \hline \\ C_{$ | Sofosbuvir/Velpa | Sofosbuvir: | No dose adjustment is required. Increased |
| $ \begin{array}{c ccccccccccccccccccccccccccccccccccc$ | tasvir/ | AUC: ↔ | plasma concentrations of tenofovir resulting |
| $ \begin{array}{c} \frac{100 \text{ mg} + 100 \text{ mg}}{\text{q.d.}) +} \\ \frac{\text{Efavirenz}^3 +}{\text{Efavirenz}^3 +} \\ \frac{\text{Darunavir}}{(800 \text{ mg q.d.}) +} \\ \frac{\text{Ritonavir}}{(100 \text{ mg q.d.}) +} \\ \frac{\text{Efavirenz} \\ \frac{\text{Efavirenz} \\ \frac{\text{C}_{max}}{\text{min}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Cmax} \cdot \downarrow 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Cmax} \cdot \downarrow 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Efavirenz} \\ \frac{\text{Efavirenz} \\ \frac{\text{C}_{min}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Cmax} \cdot \downarrow 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Efavirenz} \\ \frac{\text{C}_{min}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Efavirenz} \\ \frac{\text{C}_{min}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Composite}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Composite}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Composite}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Composite}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Composite}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Composite}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Composite}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Composite}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Composite}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Composite}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Composite}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Composite}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Composite}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Composite}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Composite}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Composite}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Composite}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Composite}}{\text{Composite}} + 23\% (\downarrow 30 \text{ to} \uparrow 16); \leftrightarrow}{\text{Composite}} \\ \frac{\text{Composite}}{\text{Composite}} + 23\% (\downarrow 30 $ | <u>Voxilaprevir</u> | $C_{\text{max}}: \downarrow \frac{19\% (\downarrow 40 \text{ to} \uparrow 10)30\%}{}$ | from co-administration of tenofovir |
| $\begin{array}{c} q.d.) + \\ \hline \textit{Efavirenz}^3 + \\ Darunavir \\ (800 \text{ mg q.d.}) + \\ \hline \textit{Ritonavir} \\ (100 \text{ mg q.d.}) + \\ \hline \textit{Emtricitabine/Te} \\ \textit{nofovir} \\ \textit{disoproxil} \\ \textit{fumarate} \\ (600 \text{ mg/}(200 \text{ mg}) \\ \textit{300245} \text{ mg q.d.}) \\ \hline \textit{Darunavir:} \\ AUC: \leftrightarrow \\ C_{max}: + 23\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 \text{ to} \uparrow 16); \leftrightarrow \\ C_{max}: + 3\% (\frac{1}{3}0 $ | (400 mg/100 mg/ | $\underline{C_{\min}}$: N/A | |
| $\begin{array}{lll} AUC: & \leftrightarrow \\ C_{max}: + 23\% (\downarrow \ 30 \ to \ \uparrow \ 16); \leftrightarrow \\ C_{max}: + 23\% (\downarrow \ 30 \ to \ \uparrow \ 16); \leftrightarrow \\ \hline (800 \ mg \ q.d.) + \\ Ritonavir \\ (100 \ mg \ q.d.) + \\ Ritonavir \\ (100 \ mg \ q.d.) + \\ Entricitabine/Te \\ nofovir \\ disoproxil \\ fumarate \\ (600 \ mg/(200 \ mg) \\ / 300245 \ mg \ q.d.) \\ \hline \\ Darunavir: \\ AUC: & \leftrightarrow \\ C_{min}: & \leftrightarrow \\ C_{min}: & 1300\% \\ \hline Darunavir: \\ AUC: & \leftrightarrow \\ C_{min}: & \rightarrow \\ C_{min}:$ | 100 mg+100 <u>mg</u> | GS 331007 ² · | sofosbuvir/velpatasvir/voxilaprevir and |
| $\begin{array}{c} \frac{\text{Estavirenz}^n}{\text{Darunavir}} \\ (800 \text{ mg q.d.}) + \\ \frac{\text{Eitonavir}}{(100 \text{ mg q.d.}) +} \\ \text{Emtricitabine/Te} \\ \text{nofovir} \\ \text{disoproxil} \\ \text{fumarate} \\ (600 \text{ mg/}(200 \text{ mg}) \\ \text{/}300245 \text{ mg q.d.}) \\ \\ \frac{\text{Darunavir}}{\text{AUC:}} + \frac{143\%}{\text{Cmin:}} + \frac{300\%}{\text{Cmin:}} + \frac{169\%}{\text{Cmin:}} + \frac{169\%}{\text{Cmin:}$ | | | darunavir/ritonavir may increase adverse |
| $ \begin{array}{c} \frac{Datula Nit}{S00 \ mg \ q.d.) +} \\ \frac{Ri00 \ mg \ q.d.) +}{Ritonavir} \\ \frac{100 \ mg \ q.d.) +}{100 \ mg \ q.d.) +} \\ Emtricitabine/Te \\ nof ovir \\ disoproxil \\ \frac{Datula Nit}{Substantia} \\ D$ | Efavirenz/3 + | | - |
| Ritonavir (100 mg q.d.) + Emtricitabine/Te nofovir disoproxil fumarate (600 mg/(200 mg /300245 mg q.d.)) Darunavir: AUC: \leftrightarrow Cmin: $+$ 300% Darunavir: AUC: $+$ Cmax: $+$ Cmin: $+$ 300% Darunavir: AUC: $+$ Cmax: $+$ Cmin: $+$ 45% Cmin: $+$ 40% Cmin: $+$ 45% Cmin: $+$ 45 | <u>Darunavir</u> | Cmax. \$ 2370 (\$ 30 to 10).\(\frac{1}{2}\) | |
| $ \begin{array}{c ccccccccccccccccccccccccccccccccccc$ | | EfavirenzC _{min} : N/A | |
| $ \begin{array}{c} \text{Tomic quart} \\ \text{Emtricitabine/Te} \\ \text{nofovir} \\ \text{disoproxil} \\ \text{fumarate} \\ \text{(600 mg/(200 mg)} \\ \text{(300245 mg q.d.)} \\ \end{array} $ $ \begin{array}{c} \text{Voxilaprevir:} \\ \text{AUC:} \uparrow 143\% \\ \text{C}_{\text{max}} \uparrow 72\% \\ \text{C}_{\text{min:}} \uparrow 300\% \\ \end{array} $ $ \begin{array}{c} \text{Darunavir:} \\ \text{AUC:} \leftrightarrow \\ \text{C}_{\text{max}} \leftrightarrow \\ \text{C}_{\text{min:}} \downarrow 34\% \\ \text{Ritonavir:} \\ \text{AUC:} \uparrow 45\% \\ \text{C}_{\text{max}} \uparrow 60\% \\ \text{C}_{\text{min:}} \leftrightarrow \\ \end{array} $ $ \begin{array}{c} \text{Emtricitabine:} \\ \text{AUC:} \leftrightarrow \\ \text{C}_{\text{min:}} \leftrightarrow \\ \end{array} $ $ \begin{array}{c} \text{Cobicistat) has not been established.} \\ \end{array} $ | | Valnataavin | |
| $\begin{array}{c} \text{Emitritation in Fe nofovir} \\ \text{disoproxil} \\ \text{fumarate} \\ \text{(600 mg/(200 mg)} \\ \text{(300245 mg q.d.)} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$ | | | |
| $\begin{array}{llllllllllllllllllllllllllllllllllll$ | | | cobicistat) has not been established. |
| Figurate (600 mg/(200 mg / 300245 mg q.d.) Voxilaprevir: $AUC: \uparrow 143\%$ $C_{max}: \uparrow 72\%$ $C_{min}: \downarrow 340\%$ Ritonavir: $AUC: \uparrow 45\%$ $C_{max}: \leftrightarrow$ $C_{max}: \leftrightarrow$ $C_{min}: \leftrightarrow$ Emtricitabine: $AUC: \leftrightarrow$ $C_{max}: \leftrightarrow$ $C_{min}: \leftrightarrow$ Tenofovir: $AUC: \uparrow 39\%$ $C_{max}: \uparrow 25\% (\uparrow 8 \text{ to } \uparrow 45)48\%$ | | | |
| $ \begin{array}{c} (600 \ \text{mg}/(200 \ \text{mg})/(300245 \ \text{mg q.d.}) \\ \hline /300245 \ \text{mg q.d.}) \\ \hline \\ & Darunavir: \\ \hline AUC: \leftrightarrow \\ \hline C_{max}: \uparrow 300\% \\ \hline \\ & C_{min}: \downarrow 34\% \\ \hline \\ & Ritonavir: \\ \hline AUC: \uparrow 45\% \\ \hline \\ & C_{max}: \uparrow 60\% \\ \hline \\ & C_{min}: \leftrightarrow \\ \hline \\ & Emtric itabine: \\ \hline & AUC: \leftrightarrow \\ \hline & C_{max}: \leftrightarrow \\ \hline & C_{min}: \leftrightarrow \\ \hline \\ & Tenofovir: \\ \hline & AUC: \uparrow 39\% \\ \hline & C_{max}: \uparrow 25\% (\uparrow \$ \ \text{to} \uparrow 45)48\% \\ \hline \end{array} $ | 1 1 | C _{min} . ↔ | |
| $ \begin{array}{c} \begin{subarray}{lll} subarra$ | | Voxilaprevir: | |
| $\begin{array}{c} C_{min}:\uparrow 300\% \\ \hline Darunavir: \\ AUC: \leftrightarrow \\ C_{max}: \leftrightarrow \\ \hline C_{min}: \downarrow 34\% \\ \hline Ritonavir: \\ AUC: \uparrow 45\% \\ \hline C_{max}: \uparrow 60\% \\ \hline C_{min}: \leftrightarrow \\ \hline C_{min}: \leftrightarrow \\ \hline C_{max}: \leftrightarrow \\ \hline C_{min}: \leftrightarrow \\ C_{min}: \leftrightarrow \\ \hline C_{min}: \leftrightarrow \\ C$ | | AUC: 143% | section 4.4). |
| $\begin{array}{c} C_{min}: \uparrow 300\% \\ \hline Darunavir: \\ \hline AUC: \leftrightarrow \\ \hline C_{max}: \leftrightarrow \\ \hline C_{min}: \downarrow 34\% \\ \hline Ritonavir: \\ \hline AUC: \uparrow 45\% \\ \hline C_{max}: \uparrow 60\% \\ \hline C_{min}: \leftrightarrow \\ \hline Emtricitabine: \\ \hline AUC: \leftrightarrow \\ \hline C_{min}: \leftrightarrow \\ \hline \hline C_{min}: \leftrightarrow \\ \hline \hline Tenofovir: \\ \hline \hline AUC: \leftrightarrow \\ \hline AUC: \uparrow 39\% \\ \hline C_{max}: \uparrow 25\% (\uparrow 8 \text{ to} \uparrow 45) 48\% \\ \hline \end{array}$ | $\frac{300245}{300}$ mg q.d.) | <u>C</u> _{max} :↑ 72% | |
| | | | |
| | | Darunavir | |
| $\begin{array}{c} \underline{C_{max}:\leftrightarrow}\\ \underline{C_{min}:\downarrow34\%}\\ \\ \underline{Ritonavir:}\\ \underline{AUC:\uparrow45\%}\\ \underline{C_{max}:\uparrow60\%}\\ \underline{C_{min}:\leftrightarrow}\\ \\ \underline{Emtricitabine:}\\ \underline{AUC:\leftrightarrow}\\ \underline{C_{max}:\leftrightarrow}\\ \underline{C_{max}:\leftrightarrow}\\ \underline{C_{min}:\leftrightarrow}\\ \\ \underline{Tenofovir:}\\ \underline{AUC:\leftrightarrow}\\ \underline{AUC:\uparrow39\%}\\ \underline{C_{max}:\uparrow25\%(\uparrow8\ to\uparrow45)48\%} \end{array}$ | | | |
| $\begin{array}{c} \underline{C_{min}:\downarrow 34\%} \\ \underline{Ritonavir:} \\ \underline{AUC:\uparrow 45\%} \\ \underline{C_{max}:\uparrow 60\%} \\ \underline{C_{min}:\leftrightarrow} \\ \\ \underline{Emtricitabine:} \\ \underline{AUC:\leftrightarrow} \\ \underline{C_{max}:\leftrightarrow} \\ \underline{C_{min}:\leftrightarrow} \\ \\ \underline{Tenofovir:} \\ \underline{AUC:\uparrow 39\%} \\ \underline{C_{max}:\uparrow 25\% (\uparrow \$ \text{ to} \uparrow 45)48\%} \\ \end{array}$ | | | |
| Ritonavir: AUC: ↑ 45% C_{max} : ↑ 60% C_{min} : ↔ Emtricitabine: AUC: ↔ C_{max} : ↔ C_{max} : ↔ C_{min} : ↔ Tenofovir: AUC: ↔ AUC: ↑ 39% C_{max} : ↑ 25% (↑ 8 to ↑ 45)48% | | | |
| $\overline{AUC: \uparrow 45\%}$ $\overline{C_{max}: \uparrow 60\%}$ $\overline{C_{min}: \leftrightarrow}$ Emtricitabine: $AUC: \leftrightarrow$ $\overline{C_{max}: \leftrightarrow}$ $\overline{C_{max}: \leftrightarrow}$ $\overline{C_{min}: \leftrightarrow}$ Tenofovir: $\overline{AUC: \leftrightarrow}$ $\overline{AUC: \uparrow 39\%}$ $\overline{C_{max}: \uparrow 25\% (\uparrow 8 \text{ to } \uparrow 45)48\%}$ | | | |
| $\begin{array}{c} \underline{C_{max}} : \uparrow 60\% \\ \underline{C_{min}} : \longleftrightarrow \\ \\ \underline{AUC} : \longleftrightarrow \\ \\ \underline{C_{max}} : \longleftrightarrow \\ \\ \underline{C_{max}} : \longleftrightarrow \\ \\ \underline{C_{max}} : \longleftrightarrow \\ \\ \underline{C_{min}} : \longleftrightarrow \\ \\ \underline{AUC} : \longleftrightarrow \\ \underline{AUC} : \uparrow 39\% \\ \underline{C_{max}} : \uparrow 25\% \ (\uparrow 8 \text{ to} \uparrow 45) \underline{48\%} \\ \end{array}$ | | Ritonavir: | |
| $\begin{array}{c} \underline{C_{min}} : \longleftrightarrow \\ \\ Emtricitabine: \\ AUC: \longleftrightarrow \\ \\ C_{max} : \longleftrightarrow \\ \\ C_{min} : \longleftrightarrow \\ \\ \\ Tenofovir: \\ \\ \underline{AUC: \longleftrightarrow} \\ \underline{AUC: \uparrow 39\%} \\ \\ \underline{C_{max}: \uparrow 25\% \ (\uparrow 8 \text{ to} \uparrow 45)48\%} \\ \end{array}$ | | <u>AUC: ↑ 45%</u> | |
| Emtricitabine: $AUC: \leftrightarrow \\ C_{max}: \leftrightarrow \\ C_{min}: \leftrightarrow \\ Tenofovir: \\ \frac{AUC: \leftrightarrow}{AUC: \uparrow 39\%} \\ C_{max}: \uparrow 25\% (\uparrow 8 \text{ to} \uparrow 45)48\%$ | | $\underline{C}_{\text{max}}$: $\uparrow 60\%$ | |
| $\begin{array}{c} AUC: \leftrightarrow \\ C_{max}: \leftrightarrow \\ C_{min}: \leftrightarrow \end{array}$ $\begin{array}{c} Tenofovir: \\ AUC: \leftrightarrow \\ AUC: \uparrow 39\% \\ C_{max}: \uparrow 25\% \ (\uparrow 8 \text{ to} \uparrow 45)48\% \end{array}$ | | $\underline{\mathbf{C}_{\min}} : \longleftrightarrow$ | |
| $\begin{array}{c} AUC: \leftrightarrow \\ C_{max}: \leftrightarrow \\ C_{min}: \leftrightarrow \end{array}$ $\begin{array}{c} Tenofovir: \\ AUC: \leftrightarrow \\ AUC: \uparrow 39\% \\ C_{max}: \uparrow 25\% \ (\uparrow 8 \text{ to} \uparrow 45)48\% \end{array}$ | | Emtricitabine: | 1 |
| $\begin{array}{c} C_{max} \colon \leftrightarrow \\ C_{min} \colon \leftrightarrow \end{array}$ $\begin{array}{c} Tenofovir \colon \\ AUC \colon \leftrightarrow \\ \underline{AUC} \colon \uparrow 39\% \\ C_{max} \colon \uparrow 25\% \ (\uparrow \ 8 \ to \ \uparrow \ 45) \underline{48\%} \end{array}$ | | | |
| $C_{min}: \leftrightarrow$ $Tenofovir:$ $AUC: \leftrightarrow$ $AUC: \uparrow 39\%$ $C_{max}: \uparrow 25\% (\uparrow 8 \text{ to } \uparrow 45)48\%$ | | | |
| Tenofovir: AUC: \leftrightarrow AUC: \uparrow 39% C_{max} : \uparrow 25% (\uparrow 8 to \uparrow 45)48% | | | |
| $\begin{array}{c} \text{AUC:} \leftrightarrow \\ \text{AUC:} \uparrow 39\% \\ \text{C}_{\text{max}} \uparrow 25\% (\uparrow 8 \text{ to} \uparrow 45)48\% \end{array}$ | | | |
| $\frac{AUC: \uparrow 39\%}{C_{max}: \uparrow \frac{25\%}{(\uparrow 8 \text{ to } \uparrow 45)48\%}}$ | | | 1 |
| C_{max} : $\uparrow 25\% (\uparrow 8 \text{ to } \uparrow 45)48\%$ | | | |
| | | | |
| $C_{\min} : \leftrightarrow \uparrow 47\%$ | | | |
| | | $C_{\min}: \longleftrightarrow \uparrow 47\%$ | |



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).

<u>עדכונים מהותיים בעלון לצרכן:</u>

2. לפני השימוש בתרופה בטרובדה

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חשוב גם שתספר לרופא אם הנך נוטל לדיפסוויר/סופוסבוביר, או סופוסבוביר/ולפטסביר או <u>סופוסבוביר/ולפטסביר/ווקסילפרביר</u> לטיפול בזיהום בדלקת כבד C.