מרץ 2019

הנדון: אפיביר תמיסה לשתיה
Epivir Oral Solution

רופא/ה נכבד/ה
רוקח/ת נכבד/ה,

חברת גלקסוסמיתקליין ישראל בע"מ (GSK) מבקשת להודיע על עדכון העלונים לרופא ולצרכן של התכשיר: **Epivir Oral Solution**.
העדכונים בעלונים כללו שינוי במשטר המינון של התכשיר ושינויים רבים אחרים. על כן אנו ממליצים לקרוא את העלונים בעיון מתחילתם ועד סופם.

בהודעה זו כלולים השינויים המהותיים בעלונים לרופא ולצרכן. בעלונים ישנם שינויים נוספים.

מרכיבים פעילים וחוזקם:

Lamivudine – 10 mg/ml

התוויה הרשומה לתכשיר בישראל:

Epivir is indicated as part of antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infected adults and children.

עדכונים מהותיים נעשו בסעיפים הבאים בעלון לרופא :

2. Qualitative and Quantitative Composition

Each ml of oral solution contains 10 mg of lamivudine.

Excipient(s) with known effect:

Each 15 ml dose contains :
3 g sucrose (20% w/v).
~~Excipients:~~

~~Sucrose 20% (3 g/15 ml)~~
Methyl parahydroxybenzoate
Propyl parahydroxybenzoate
Each 15 ml dose contains 300 mg propylene glycol.
Each 15 ml dose contains 44.1 mg sodium.~~Sodium citrate~~

For the full list of excipients, see section 6.1.

4.2 Posology and method of administration

The therapy should be initiated by a physician experienced in the management of HIV infection.

Epivir may be administered with or without food.

Epivir is also available as a tablet formulation~~.~~ for patients who weigh at least 14 kg (see section 4.4).

For patients who are unable to swallow tablets, the tablet(s) may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately (see section 5.2).

Adults~~ and~~, adolescents and children (weighing at least ~~30~~25 kg):

The recommended dose of Epivir is 300 mg daily. This may be administered as either 150 mg (15 ml) twice daily or 300 mg (30 ml) once daily (see section 4.4).

~~Patients changing to the once daily regimen should take 150 mg (15 ml) twice a day and switch to 300 mg (30 ml) once a day the following morning. Where an evening once daily regimen is preferred, 150 mg (15 ml) of~~

~~Epivir should be taken on the first morning only, followed by 300 mg (30 ml) in the evening. When changing back to a twice daily regimen, patients should complete the days treatment and start 150 mg (15 ml) twice a day the following morning.~~

Children

~~*From three months up to 30*~~ *(weighing less than 25 kg):*

Children from one year of age: The recommended dose is ~~4~~ 5 mg/kg twice ~~daily~~up to daily, or 10 mg/kg once daily up to a maximum total daily dose of 300 mg ~~daily~~(30 ml) (see sections 4.4 and 4.5).

Children from three months to one year of age: The recommended dose is 5 mg/kg twice daily. If a twice daily regimen is not feasible, a once daily regimen (10 mg/kg/day) could be considered. It should be taken into account that data for the once daily regimen are very limited in this population (see sections 4.4, 5.1 and 5.2).

Children less than three months of age: ~~the~~The limited data available are insufficient to propose specific dosage recommendations (see section 5.2).

Patients changing from the twice daily dosing regimen to the once daily dosing regimen should take the recommended once daily dose (as described above) approximately 12 hours after the last twice daily dose, and then continue to take the recommended once daily dose (as described above) approximately every 24 hours. When changing back to a twice daily regimen, patients should take the recommended twice daily dose approximately 24 hours after the last once daily dose.

Special populations:

Older people: No specific data are available; however, special care is advised in this age group due to age-associated changes such as the decrease in renal function and alteration of haematological parameters.

Renal impairment: Lamivudine concentrations are increased in patients with moderate - severe renal impairment due to decreased clearance. The dose should therefore be adjusted (see tables).

Dosing recommendations – Adults ~~and~~, adolescents and children (weighing at least ~~30~~25 kg~~:~~):

Creatinine clearance (ml/min)	**First dose**	**Maintenance dose**
≥50	300 mg (30 ml) or 150 mg (15 ml)	300 mg (30 ml) once daily 150 mg (15 ml) twice daily
30 to<50	150 mg (15 ml)	150 mg (15 ml) once daily
15 to <30	150 mg (15 ml)	100 mg (10 ml) once daily
5 to <15	150 mg (15 ml)	50 mg (5 ml) once daily
<5	50 mg (5 ml)	25 mg (2.5 ml) once daily

There are no data available on the use of lamivudine in children with renal impairment. Based on the assumption that creatinine clearance and lamivudine clearance are correlated similarly in children as in adults it is recommended that the dosage in children with renal impairment be reduced according to their creatinine clearance by the same proportion as in adults.

Dosing recommendations – Children ~~from~~aged at least 3 months ~~up to 30~~and weighing less than 25 kg:

Creatinine clearance (ml/min)	**First dose**	**Maintenance dose**
≥50	8 mg/kg or 4 mg/kg	8 mg/kg once daily 4 mg/kg twice daily
30 to<50	4 mg/kg	4 mg/kg once daily
15 to <30	4 mg/kg	2.6 mg/kg once daily
5 to <15	4 mg/kg	1.3 mg/kg once daily
<5	1.3 mg/kg	0.7 mg/kg once daily

Hepatic impairment: Data obtained in patients with moderate to severe hepatic impairment shows that lamivudine pharmacokinetics are not significantly affected by hepatic dysfunction. Based on these data, no dose adjustment is necessary in patients with moderate or severe hepatic impairment unless accompanied by renal impairment.

4.4 Special warnings and precautions for use

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Mitochondrial dysfunction following exposure in utero: Nucleoside and nucleotide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine.~~have been demonstrated *in vitro* and *in vivo* to cause a variable degree of mitochondrial damage.~~ There have been reports of mitochondrial dysfunction in HIV-negative infants exposed *in utero* and/or post-natally to nucleoside analogues~~.~~; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse ~~events~~reactions reported are haematological disorders (anaemia, neutropenia~~),~~) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events ~~are~~have often been transitory. ~~Some late~~Late-onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether ~~the~~such neurological disorders are transient or permanent is currently unknown. ~~Any~~These findings should be considered for any child exposed *in utero* to nucleoside and nucleotide analogues, ~~even HIV-negative children, should have~~ who presents with severe clinical ~~and laboratory follow-up and should be fully investigated for possible mitochondrial dysfunction in case~~findings of ~~relevant signs or symptoms~~unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

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:

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Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterium infections, and *Pneumocystis jirovecii~~carinii~~* pneumonia (often referred to as PCP). 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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Paediatric population: In a study performed in paediatric patients (see section 5.1 ARROW study), lower rates of virologic suppression and more frequent viral resistance were reported in children receiving the oral solution of Epivir as compared to those receiving the tablet formulation.

Whenever possible in children, an all-tablet regimen should preferably be used. Epivir oral solution given concomitantly with sorbitol-containing medicines should be used only when an all-tablet regimen cannot be used and the benefits of treatment outweigh possible risks including lower virological suppression. Consider more frequent monitoring of HIV-1 viral load when Epivir is used with chronically-administered, sorbitol-containing medicines [e.g. Ziagen oral solution]. Although not studied, the same effect would be expected with other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol (see section 4.5)).

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4.5 Interaction with other medicinal products and other forms of interaction

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Coadministration of sorbitol solution (3.2 g, 10.2 g, 13.4 g) with a single 300 mg dose of lamivudine oral solution resulted in dose-dependent decreases of 14%, 32%, and 36% in lamivudine exposure (AUC_{∞}) and 28%, 52%, and 55% in the C_{max} of lamivudine in adults. When possible, avoid chronic coadministration of Epivir with medicinal products containing sorbitol or other osmotic acting poly-alcohols or monosaccharide alcohols (e.g. xylitol, mannitol, lactitol, maltitol). Consider more frequent monitoring of HIV-1 viral load when chronic coadministration cannot be avoided (see section 4.4).

4.8 Undesirable effects

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Metabolism and nutrition disorders

Very rare: Lactic acidosis

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Weight and levels of blood lipids and glucose may increase during antiretroviral therapy (see section 4.4)

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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 (see section 4.4).

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עדכונים מהותיים נעשו בסעיפים הבאים בעלון לצרכן :

2. לפני שימוש בתרופה

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אין להשתמש בתרופות הבאות יחד עם אפיביר:

- **תרופות (לרוב נוזליות) שמכילות סורביטול וסוכרים כוהליים אחרים (כגון: קסיליטול, מניטול, לקטיטול או מלטיטול), במידה ונלקחות באופן קבוע.**

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מידע חשוב על חלק מה~~רכיבים~~מרכיבים של אפיביר

אם אתה סוכרתי, אנא שים לב שכל מנה (150 מ"ג = 15 מ"ל) מכילה 3 ג' סוכר.

אפיביר מכילה סוכרוז. אם נאמר לך על ידי הרופא שלך שיש לך אי-סבילות לסוכרים מסוימים, פנה לרופא שלך לפני נטילת אפיביר. סוכרוז עלול להזיק לשיניים.

~~תכשיר רפואי זה מכיל כ-3 מ"ג נתרן ל-1 מ"ל. מטופלים הנמצאים על דיאטת נתרן צריכים לקחת זאת בחשבון.~~

אפיביר מכילה גם חומרים משמרים (*פאראהידרוקסיבנזואטים*) העלולים לגרום לתגובות אלרגיות (תיתכן תגובה מאוחרת).

תרופה זו מכילה 300 מ"ג פרופילן גליקול בכל 15 מ"ל תרופה.

תרופה זו מכילה פחות מ- 1 מילימול נתרן (23 מ"ג) למ"ל, כך שבמהותה היא נטולת נתרן.

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3. כיצד תשתמש בתרופה?

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המינון ואופן הטיפול יקבעו על ידי הרופא בלבד. המינון המקובל בדרך כלל הוא:

מבוגרים, מתבגרים וילדים השוקלים לפחות ~~30~~ 25 ק"ג:

המינון המקובל בדרך כלל של אפיביר ~~הוא~~ הינו 30 מ"ל ליום (300 מ"ג) שילקח ~~פעם ביום או~~כ- 15 מ"ל (150 מ"ג) פעמיים ביום ~~בשעות קבועות~~,(בהפרשים של כ-12 שעות בין כל מנה) או כ-30 מ"ל (300 מ"ג) פעם ביום..

ילדים ~~בגילאי~~ מגיל 3 חודשים ~~ועד 30~~השוקלים פחות מ-25 ק"ג

המינון תלוי במשקל הגוף של הילד.

המינון המקובל בדרך כלל של אפיביר ~~הוא~~ הינו ~~4~~-5 מ"ג / ק"ג פעמיים ביום (בהפרשים של כ-12 שעות בין כל מנה) או 10 מ"ג/ק"ג פעם ביום עד למינון מירבי יומי של 300 מ"ג ליום. ~~תן לילדך כל מנה בשעה קבועה, בהפרשים של כ-12 שעות בין כל מנה.~~

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4. תופעות לוואי

במהלך הטיפול ל- HIV יכולה להיות עליה במשקל וברמות השומנים והסוכר בדם. זה קשור חלקית לבריאות ולאורך החיים, ובמקרה של שומנים בדם לפעמים לתרופות ה-HIV עצמן. הרופא שלך יבדוק שינויים אלה.

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מקרא לעדכונים המסומנים :

מידע שהוסר – מסומן בקו אדום חוצה ~~XXX~~

תוספת – כתב **כחול**

תוספת החמרה - כתב **כחול** – מסומן בצהוב מרקר

העלונים לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://www.old.health.gov.il/units/pharmacy/trufot/index.asp?safa=h וניתן לקבלם מודפסים על-ידי פניה לחברת גלקסוסמיתקליין רח' בזל 25 פתח תקוה בטלפון: 03-9297100.

בברכה,
טניה רשקובן
רוקחת ממונה