מרץ 2019

הנדון: זיאגן טבליות טבליות מצופות
Ziagen Film Coated Tablets

רופא/ה נכבד/ה
רוקח/ת נכבד/ה,

חברת גלקסוסמיתקליין ישראל בע"מ (GSK) מבקשת להודיע על עדכון העלונים לרופא ולצרכן של התכשיר: **Ziagen tablets**.
העדכונים בעלונים כללו שינוי במשטר המינון של התכשיר ושינויים רבים אחרים בסעיפי הבטיחות בעלון. בין היתר נעשתה גם הרמוניזציה של הטקסט בסעיף ההתוויה בעלון לרופא של הטבליות לזה של התמיסה לשתייה. 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:

Abacavir (as sulfate) - 300 mg

התוויה הרשומה לתכשיר בישראל:

Ziagen is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infected.

עדכונים מהותיים נעשו בסעיפים הבאים בעלון לרופא :

4.1 Indication

Ziagen is indicated in antiretroviral combination therapy for the treatment of Human Immunodeficiency Virus (HIV) infection.

The demonstration of the benefit of Ziagen is mainly based on results of studies performed with a twice daily regimen, in treatment-naïve adult patients on combination therapy (see section 5.1).

Before initiating treatment with abacavir, screening for carriage of the HLA-B*5701 allele should be performed in any HIV-infected patient, irrespective of racial origin~~. Screening is also recommended prior to re-initiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir (see "Management after an interruption of Ziagen therapy")~~. (see section 4.4). Abacavir should not be used in patients known to carry the HLA-B*5701 allele~~, unless no other therapeutic option is available in these patients, based on the treatment history and resistance testing (see section 4.4 and 4.8).~~

4.2 Posology and method of administration

Ziagen should be prescribed by physicians experienced in the management of HIV infection.

Ziagen can be taken with or without food.

To ensure administration of the entire dose, the tablet(s) should ideally be swallowed without crushing.

Ziagen is also available as an oral solution for use in children over three months of age and weighing less than 14 kg and for those patients for whom the tablets are inappropriate.

Alternatively, 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 ~~(over 12 years of age):~~ and children (weighing at least 25 kg):

The recommended dose of Ziagen is 600 mg daily. This may be administered as either 300 mg (one tablet) twice daily or 600 mg (two tablets) once daily (see sections 4.4 and 5.1).

~~Patients changing to the once daily regimen should take 300 mg twice a day and switch to 600 mg once a day the following morning. Where an evening once daily regimen is preferred, 300 mg of Ziagen should be~~

~~taken on the first morning only, followed by 600 mg in the evening. When changing back to a twice daily regimen, patients should complete the day's treatment and start 300 mg twice a day the following morning.~~

Children (~~under 12 years of age~~weighing less than 25 kg):

Dosing according to weight bands is recommended for Ziagen tablets. ~~This dosing regimen for paediatric patients weighing 14-30 kg is based primarily on pharmacokinetic modelling. A pharmacokinetic overexposure of abacavir can occur since accurate dosing can not be achieved with this formulation. Therefore close safety monitoring is warranted in these patients.~~

~~*Children weighing* at least 30 *kg*: the adult dosage of 300 mg twice daily should be taken.~~

~~Children weighing > 21~~ ~~*kg* to < 30 kg:~~ *Children weighing ≥ 20 kg to < 25 kg*: The recommended dose is 450 mg daily. This may be administered as either one 150 mg (one half of a ~~Ziagen~~ tablet) taken in the morning and 300 mg (one whole tablet) taken in the evening~~.~~
, or 450 mg (one and a half tablets) taken once daily.

Children weighing 14 to ~~21 kg~~< *20 kg*: The recommended dose is 300 mg daily. This may be administered as either 150 mg (one half of a ~~Ziagen~~ tablet) twice daily or 300 mg (one whole tablet) once daily.

Children less than three months~~: the~~ of age: The clinical experience in children aged less than three months is limited and 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

Renal impairment~~: no~~
No dosage adjustment of Ziagen is necessary in patients with renal dysfunction. However, Ziagen is not recommended for patients with end-stage renal disease (see section 5.2).

Hepatic impairment~~: abacavir~~
Abacavir is primarily metabolised by the liver. No definitive dose recommendation can be made in patients with mild hepatic impairment~~.~~ (Child-Pugh score 5-6). In patients with moderate or severe hepatic impairment, no clinical data are available, therefore the use of abacavir is not recommended unless judged necessary. If abacavir is used in patients with mild ~~or moderate~~ hepatic impairment, then close monitoring is required, ~~and if feasible,~~including monitoring of abacavir plasma levels ~~is recommended~~if feasible (see ~~section~~sections 4.4 and 5.2). ~~Abacavir is contraindicated in patients with severe hepatic impairment (see section 4.3 and 4.4).~~

Elderly~~: no~~
No pharmacokinetic data are currently available in patients over 65 years of age.

4.3 Contraindications

Hypersensitivity to ~~the active substance~~abacavir or to any of the excipients listed in section 6.1. ~~See BOXED INFORMATION ON HYPERSENSITIVITY REACTIONS in~~See sections 4.4~~.~~ and 4.8.

~~Severe hepatic impairment.~~

4.4 Special warnings and precautions for use

Hypersensitivity reactions (see also section 4.8)

Abacavir is associated with a risk for hypersensitivity reactions (HSR) (see section4.8) characterised by fever and/or rash with other symptoms indicating multi-organ involvement. HSRs have been observed with abacavir, some of which have been life-threatening, and in rare cases fatal, when not managed appropriately.

The risk for abacavir HSR to occur is high for patients who test positive for the HLA-B*5701 allele. However, abacavir HSRs have been reported at a lower frequency in patients who do not carry this allele.

Therefore the following should be adhered to:

- HLA-B*5701 status must always be documented prior to initiating therapy.
- Ziagen should never be initiated in patients with a positive HLA-B*5701 status, nor in patients with a negative HLA-B*5701 status who had a suspected abacavir HSR on a previous abacavir-containing regimen. (e.g. Kivexa, Trizivir, Triumeq)
- **Ziagen must be stopped without delay**, even in the absence of the HLA-B*5701 allele, if an HSR is suspected. Delay in stopping treatment with Ziagen after the onset of hypersensitivity may result in a life-threatening reaction.
- After stopping treatment with Ziagen for reasons of a suspected HSR, **Ziagen or any other medicinal product containing abacavir** (e.g. Kivexa, Trizivir, Triumeq) **must never be re-initiated**.
- Restarting abacavir containing products following a suspected abacavir HSR can result in a prompt return of symptoms within hours. This recurrence is usually more severe than on initial presentation, and may include life-threatening hypotension and death.
- In order to avoid restarting abacavir, patients who have experienced a suspected HSR should be instructed to dispose of their remaining Ziagen tablets

Clinical description of abacavir HSR

Abacavir HSR has been well characterised through clinical studies and during post marketing follow-up. Symptoms usually appeared within the first six weeks (median time to onset 11 days) of initiation of treatment with abacavir, **although these reactions may occur at any time during therapy.**

Almost all HSR to abacavir include fever and/or rash . Other signs and symptoms that have been observed as part of abacavir HSR are described in detail in section 4.8 (Description of selected adverse reactions), including respiratory and gastrointestinal symptoms. Importantly, such symptoms **may lead to misdiagnosis of HSR as respiratory disease (pneumonia, bronchitis, pharyngitis), or gastroenteritis.**

The symptoms related to HSR worsen with continued therapy and can be life-threatening. These symptoms usually resolve upon discontinuation of abacavir.

Rarely, patients who have stopped abacavir for reasons other than symptoms of HSR have also experienced life-threatening reactions within hours of re- initiating abacavir therapy (see Section 4.8 Description of selected adverse reactions). Restarting abacavir in such patients must be done in a setting where medical assistance is readily available.

Mitochondrial dysfunction following exposure in utero

Nucleoside and nucleotide analogues ~~have been demonstrated *in vitro* and *in vivo*~~ may impact mitochondrial function to ~~cause~~ a variable degree~~ of mitochondrial damage.~~, which is most pronounced with stavudine, didanosine and zidovudine. 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 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 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 of relevant signs or symptoms.~~findings of 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.

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Liver disease

The safety and efficacy of Ziagen has not been established in patients with significant underlying liver disorders. Ziagen is ~~contraindicated~~ not recommended in patients with moderate or severe hepatic impairment (see ~~section~~sections 4.~~3~~2 and 5.2).
Patients with pre-existing liver dysfunction, including chronic active hepatitis, have an increased frequency of liver function abnormalities during combination antiretroviral therapy, 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.
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Immune Reactivation Syndrome
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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.
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~~4~~.8 Undesirable effects

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Metabolism and nutrition disorders
Common: anorexia
Very rare: lactic acidosis

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~~*Cases*~~Description of ~~*lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly*~~Selected Adverse Reactions

Abacavir hypersensitivity reactions
The signs and ~~hepatic steatosis,~~symptoms of this HSR are listed below. These have been identified either from clinical studies or post marketing surveillance. Those reported ~~with the use of nucleoside analogues (see section 4.4).~~**in at least 10%** of patients with a hypersensitivity reaction are in bold text.

~~Combination antiretroviral therapy has been associated with redistribution of body fat (lipodystrophy) in HIV patients including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).~~

~~Combination antiretroviral therapy has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia (see section 4.4).~~

Almost all patients developing hypersensitivity reactions will have fever and/or rash (usually maculopapular or urticarial) as part of the syndrome, however reactions have occurred without rash or fever. Other key symptoms include gastrointestinal, respiratory or constitutional symptoms such as lethargy and malaise.

Skin	**Rash** (usually maculopapular or urticarial)
Gastrointestinal tract	**Nausea, vomiting, diarrhoea, abdominal pain**, mouth ulceration
Respiratory tract	**Dyspnoea, cough**, sore throat, adult respiratory distress syndrome, respiratory failure

Miscellaneous	**Fever, lethargy, malaise**, oedema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis
Neurological/Psychiatry	**Headache**, paraesthesia
Haematological	Lymphopenia
Liver/pancreas	**Elevated liver function tests,** hepatitis, hepatic failure
Musculoskeletal	**Myalgia**, rarely myolysis, arthralgia, elevated creatine phosphokinase
Urology	Elevated creatinine, renal failure

Symptoms related to this HSR worsen with continued therapy and can be life- threatening and in rare instance, have been fatal.

Restarting abacavir following an abacavir HSR results in a prompt return of symptoms within hours. This recurrence of the HSR is usually more severe than on initial presentation, and may include life-threatening hypotension and death. Similar reactions have also occurred infrequently after restarting abacavir in patients who had only one of the key symptoms of hypersensitivity (see above) prior to stopping abacavir; and on very rare occasions have also been seen in patients who have restarted therapy with no preceding symptoms of a HSR (i.e., patients previously considered to be abacavir tolerant).

Metabolic parameters

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

Immune reactivation syndrome

In HIV-infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (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 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).

עדכונים מהותיים נעשו בסעיפים הבאים בעלון לצרכן :

2. לפני שימוש בתרופה

אין להשתמש בתרופה אם:

- אתה **רגיש** (אלרגי) לאבקויר (או לכל תרופה אחרת המכילה אבקויר כגון **טריזיויר, טריומק** או **קיווקסה**) או לכל אחד מה~~כ~~יביםמרכיבים הנוספים אשר מכילה התרופה (מפורט בסעיף 6).

קרא בעיון את כל המידע על תגובות רגישות יתר בסעיף 4.

- ~~יש לך **מחלת כבד חמורה**~~

בדוק עם הרופא שלך אם אתה חושב ~~שאחד מאלה~~ שזה חל עליך.

אזהרות מיוחדות הנוגעות לשימוש בתרופה

אנשים מסוימים הלוקחים זיאגן ל- HIV הינם בסיכון מוגבר לתופעות לוואי חמורות. עליך לשים לב במיוחד לסיכונים הנוספים:

- אם יש לך **מחלת כבד מתונה או חמורה**
- אם סבלת בעבר **ממחלת כבד**, כולל ~~צהבת~~דלקת כבד מסוג B או C
- אם הנך **במשקל עודף** משמעותי (במיוחד אם את אישה)
- ~~אם אתה **סוכרתי** ומשתמש באינסולין~~
- אם יש לך **מחלת כליה חמורה.**

פנה לרופא שלך אם אחד מאלה ~~מתיחס אליך~~ חל עליך. יתכן ותזדקק לבדיקות נוספות, כולל בדיקות דם, בזמן שאתה לוקח את התרופה שלך. **ראה סעיף 4 למידע נוסף.**

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3. כיצד תשתמש בתרופה?

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המינון המקובל בדרך כלל **הוא:**

מבוגרים ומתבגרים **וילדים** ~~**מעל לגיל 12 שנים**~~**השוקלים לפחות 25 ק"ג**

המינון המקובל של זיאגן הוא 600 מ"ג ביום. ניתן לקחת כטבליה אחת של 300 מ"ג פעמיים ביום או שתי טבליות של 300 מ"ג פעם אחת ביום.

ילדים מגיל שנה השוקלים פחות מ- 25 ק"ג

~~**ילדים בגיל 3 חודשים עד 12 שנים**~~

המינון הניתן תלוי במשקל הגוף של ילדך. המינון המקובל הוא:

- ~~ילדים השוקלים לפחות 30 ק"ג צריכים לקחת את המינון למבוגרים של טבליה אחת פעמיים ביום.~~
- ילדים השוקלים ~~יותר מ-21~~לפחות 20 ק"ג ופחות מ-~~30~~ 25 ק"ג: המינון המקובל של זיאגן הינו 450 מ"ג ליום. הניתן כ- 150 מ"ג (חצי טבליה ~~(1/2) של זיאגן~~) בבוקר ו- 300 מ"ג (טבליה אחת שלמה) בערב~~.~~או 450 מ"ג (טבליה וחצי) פעם אחת ביום כפי שהומלץ ע"י הרופא שלך.

ילדים השוקלים לפחות 14 ק"ג ~~עד~~ ופחות מ-20 ~~21~~ ק"ג: המינון המקובל של זיאגן הינו 300 מ"ג ליום. הניתן כ- 150 מ"ג (חצי טבליה ~~(1/2) של זיאגן~~) פעמיים ביום או 300 מ"ג (טבליה אחת שלמה) פעם ביום כפי שהומלץ ע"י הרופא שלך.

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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