ספטמבר 2022

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

הנדון:

Film-coated tablets Eucreas 50/500mg, 50/850mg, 50/1000mg,

יוקריאס 500/50מ"ג, 850/50מ"ג, 1000/50מ"ג, טבליות מצופות

התכשיר שבנדון רשום בישראל להתוויות הבאות:

Eucreas is indicated in the treatment of type 2 diabetes mellitus:

- Eucreas is indicated in the treatment of adult patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets.

- Eucreas is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled with metformin and a sulphonylurea.

- Eucreas is indicated in triple combination therapy with insulin as an adjunct to diet and exercise to improve glycaemic control in adult patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control.

המרכיב הפעיל: Vildagliptin 50mg
Metformin Hydrochloride 500mg/ 850mg/ 1000mg

ברצוננו להודיעכם על עדכונים בעלון לרופא ובעלון לצרכן של התכשיר שבנדון.

העדכונים מפורטים להלן (קו תחתי משמעו תוספת טקסט, ~~קו חוצה~~ משמעו מחיקת טקסט, החמרות מודגשות בצהוב):

עדכונים בעלון לרופא:

4.8 Undesirable effects

Summary of the safety profile

Safety data were obtained from a total of 6 197 patients exposed to vildagliptin/metformin in randomised placebo-controlled trials. Of these patients, 3 698 patients received vildagliptin/metformin and 2 499 patients received placebo/metformin.

There have been no therapeutic clinical trials conducted with Eucreas. However, bioequivalence of Eucreas with co-administered vildagliptin and metformin has been demonstrated (see section 5.2). ~~The data presented here relate to the co-administration of vildagliptin and metformin, where vildagliptin has been added to metformin. There have been no studies of metformin added to vildagliptin.~~

~~Summary of the safety profile~~

The majority of adverse reactions were mild and transient, not requiring treatment discontinuations. No association was found between adverse reactions and age, ethnicity, duration of exposure or daily dose. Vildagliptin use is associated with the risk of development of pancreatitis. Lactic acidosis has been reported following the use of metformin, especially in patients with underlying renal impairment (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions reported in patients who received vildagliptin in double-blind ~~studies~~clinical trials as monotherapy and add-on therapies are listed below by system organ class and absolute frequency. ~~Adverse reactions listed in Table 5 are based on information available from the metformin Summary of Product Characteristics available in the EU.~~ Frequencies are defined as very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse reactions reported in patients who received vildagliptin and metformin (as mono-components or as fixed dose combination), or in combination with other anti-diabetic treatments, in clinical trials and in post-marketing experience

System organ class - adverse reaction	**Frequency**
Infections and infestations	
Upper respiratory tract infection	Common
Nasopharyngitis	Common

Metabolism and nutrition disorders	
Hypoglycaemia	Uncommon
Loss of appetite	Uncommon
Decrease of vitamin B12 absorption and lactic acidosis	Very rare*
Nervous system disorders	
Dizziness	Common
Headache	Common
Tremor	Common
Metallic taste	Uncommon
Gastrointestinal disorders	
Vomiting	Common
Diarrhoea	Common
Nausea	Common
Gastro-oesophageal reflux disease	Common
Flatulence	Common
Constipation	Common
Abdominal pain including upper	Common
Pancreatitis	Uncommon
Hepatobiliary disorders	
Hepatitis	Uncommon
Skin and subcutaneous tissue disorders	
Hyperhidrosis	Common
Pruritis	Common
Rash	Common
Dermatitis	Common
Erythema	Uncommon
Urticaria	Uncommon
Exfoliative and bullous skin lesions, including bullous pemphigoid	Not known†
Cutaneous vasculitis	Not known
Musculoskeletal and connective tissue disorders	
Arthralgia	Common
Myalgia	Uncommon

General disorders and administration site conditions	
Asthenia	Common
Fatigue	Uncommon
Chills	Uncommon
Oedema peripheral	Uncommon
Investigations	
Abnormal liver function tests	Uncommon

* Adverse reactions reported in patients who received metformin as monotherapy and that were not observed in patients who received vildalgiptin+metformin fixed dose combination. Refer to summary of product characteristics for metformin for additional information.
Based on post-marketing experience.

~~**Table 1 Adverse reactions reported in patients who received vildagliptin 100 mg daily as add-on therapy to metformin compared to placebo plus metformin in double-blind studies (N=208)**~~

~~**Metabolism and nutrition disorders**~~
~~Common Hypoglycaemia~~
~~**Nervous system disorders**~~
~~Common Tremor~~
~~Common Headache~~
~~Common Dizziness~~
~~Uncommon Fatigue~~
~~**Gastrointestinal disorders**~~
~~Common Nausea~~

~~*Description of selected adverse reactions*~~
~~In controlled clinical trials with the combination of vildagliptin 100 mg daily plus metformin, no withdrawal due to adverse reactions was reported in either the vildagliptin 100 mg daily plus metformin or the placebo plus metformin treatment groups.~~

~~In clinical trials, the incidence of hypoglycaemia was common in patients receiving vildagliptin in combination with metformin (1%) and uncommon in patients receiving placebo + metformin (0.4%). No severe hypoglycaemic events were reported in the vildagliptin arms.~~

~~In clinical trials, weight did not change from baseline when vildagliptin 100 mg daily was added to metformin (+0.2 kg and -1.0 kg for vildagliptin and placebo, respectively).~~

~~Clinical trials of up to more than 2 years' duration did not show any additional safety signals or unforeseen risks when vildagliptin was added on to metformin.~~

Combination with a sulphonylurea

Table 2 Adverse reactions reported in patients who received vildagliptin 50 mg twice daily in combination with metformin and a sulphonylurea (N=157)

Metabolism and nutritional disorders	
Common	Hypoglycemia
Nervous system disorders	
Common	Dizziness, tremor
Skin and subcutaneous tissue disorders	
Common	Hyperhidrosis
General disorder and administration site conditions	
Common	Asthenia

group.

The incidence of hypoglycemia was common in both treatment groups (5.1% for the vildagliptin + metformin + glimepiride group versus 1.9% for the placebo + metformin + glimepiride group). One severe hypoglycaemic event was reported in the vildagliptin group.

At the end of the study, effect on mean body weight was neutral (+0.6 kg in the vildagliptin group and -0.1 kg in the placebo group).

Combination with insulin

Table 3 Adverse reactions reported in patients who received vildagliptin 100 mg daily in combination with insulin (with or without metformin) in double-blind studies (N=371)

Metabolism and nutrition disorders	
Common	Decreased blood glucose
Nervous system disorders	
Common	Headache, chills
Gastrointestinal disorders	
Common	Nausea, gastro-oesophageal reflux disease
Uncommon	Diarrhoea, flatulence

Description of selected adverse reactions

In controlled clinical trials using vildagliptin 50 mg twice daily in combination with insulin, with or without concomitant metformin, the overall incidence of withdrawals due to adverse reactions was 0.3% in the vildagliptin treatment group and there were no withdrawals in the placebo group.

The incidence of hypoglycemia was similar in both treatment groups (14.0% in the vildagliptin group vs 16.4% in the placebo group). Two patients reported severe hypoglycaemic events in the vildagliptin group, and 6 patients in the placebo group.

At the end of the study, effect on mean body weight was neutral (+0.6 kg change from baseline in the vildagliptin group and no weight change in the placebo group).

Additional information on the individual active substances of the fixed combination

Vildagliptin

Table 4 Adverse reactions reported in patients who received vildagliptin 100 mg daily as monotherapy in double-blind studies (N=1855)

Infections and infestations	
Very rare	Upper respiratory tract infection
Very rare	Nasopharyngitis
Metabolism and nutrition disorders	
Uncommon	Hypoglycaemia
Nervous system disorders	
Common	Dizziness
Uncommon	Headache
Vascular disorders	
Uncommon	Oedema peripheral
Gastrointestinal disorders	
Uncommon	Constipation
Musculoskeletal and connective tissue disorders	
Uncommon	Arthralgia

Description of selected adverse reactions

The overall incidence of withdrawals from controlled monotherapy trials due to adverse reactions was no greater for patients treated with vildagliptin at doses of 100 mg daily (0.3%) than for placebo (0.6%) or comparators (0.5%).

In comparative controlled monotherapy studies, hypoglycaemia was uncommon, reported in 0.4% (7 of 1,855) of patients treated with vildagliptin 100 mg daily compared to 0.2% (2 of 1,082) of patients in the groups treated with an active comparator or placebo, with no serious or severe events reported.

In clinical trials, weight did not change from baseline when vildagliptin 100 mg daily was administered as monotherapy (-0.3 kg and -1.3 kg for vildagliptin and placebo, respectively).

Clinical trials of up to 2 years' duration did not show any additional safety signals or unforeseen risks with vildagliptin monotherapy.

Metformin

Table 5 Adverse reactions for metformin component

Metabolism and nutrition disorders	
Very rare	Decrease of vitamin B_{12} absorption and lactic acidosis*
Nervous system disorders	
Common	Metallic taste
Gastrointestinal disorders	
Very common	Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite
Hepatobiliary disorders	
Very rare	Liver function test abnormalities or hepatitis**
Skin and subcutaneous tissue disorder	
Very rare	Skin reactions such as erythema, pruritus and urticaria

**A decrease in vitamin B12 absorption with decrease in serum levels has been very rarely observed in patients treated long-term with metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.*

***Isolated cases of liver function test abnormalities or hepatitis resolving upon metformin*

~~*discontinuation have been reported.*~~

~~Gastrointestinal adverse reactions occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 daily doses during or after meals. A slow increase in the dose may also improve gastrointestinal tolerability.~~

~~Post-marketing experience~~
~~Table 6 Post-marketing adverse reactions~~

~~Gastrointestinal disorders~~	
~~Not known~~	~~Pancreatitis~~
~~Hepatobiliary disorders~~	
~~Not known~~	~~Hepatitis (reversible upon discontinuation of the medicinal product)~~ ~~Abnormal liver function tests (reversible upon discontinuation of the medicinal product)~~
~~Musculoskeletal and connective tissue disorders~~	
~~Not known~~	~~Myalgia~~
~~Skin and subcutaneous tissue disorders~~	
~~Not known~~	~~Urticaria~~ ~~Exfoliative and bullous skin lesions, including bullous pemphigoid~~

Description of selected adverse reactions

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Hypoglycaemia
Hypoglycaemia was uncommon when vildagliptin (0.4%) was used as monotherapy in comparative controlled monotherapy studies with an active comparator or placebo (0.2%). No severe or serious events of hypoglycaemia were reported. When used as add-on to metformin, hypoglycaemia occurred in 1% of vildagliptin-treated patients and in 0.4% of placebo-treated patients. When pioglitazone was added, hypoglycaemia occurred in 0.6% of vildagliptin-treated patients and in 1.9% of placebo-treated patients. When sulphonylurea was added, hypoglycaemia occurred in 1.2% of vildagliptin treated patients and in 0.6% of placebo-treated patients. When sulphonylurea and metformin were added, hypoglycaemia occurred in 5.1% of vildagliptin-treated patients and in 1.9% of placebo-treated patients. In patients taking vildagliptin in combination with insulin, the incidence of hypoglycaemia was 14% for vildagliptin and 16% for placebo.

Metformin
Decrease of vitamin B12 absorption
A decrease in vitamin B12 absorption with decrease in serum levels has been observed very rarely in patients who have been treated with metformin over a long period. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.

Liver function
Isolated cases of liver function test abnormalities or hepatitis resolving upon metformin discontinuation have been reported.

עדכונים בעלון לצרכן:

4. תופעות לוואי

יש להפסיק לקחת יוקריאס ולפנות מיד לרופא אם יש לך אחד או יותר מהתסמינים הבאים

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- מחלת כבד (הפטיטיס) (לא שכיח: תופעות שמופיעות ב 1-10 משתמשים מתוך 1,000 ~~נדיר~~): התסמינים כוללים הצהבה של העור והעיניים, בחילה, חוסר תיאבון, שתן כהה, שעשויים להצביע על מחלת כבד (הפטיטיס).
- דלקת של הלבלב (פנקריאטיטיס) (לא שכיח: תופעות שמופיעות ב 1-10 משתמשים מתוך ~~שכיחות אינה ידועה~~): התסמינים כוללים כאב חמור ומתמשך באזור הבטן אשר עלול להקרין לגב כמו גם בחילות והקאות.

תופעות לוואי אחרות:

חולים מסוימים חוו את תופעות הלוואי הבאות בעת נטילת יוקריאס:

~~תופעות לוואי שכיחות מאוד (תופעות שמופיעות ביותר ממשתמש אחד מעשרה): בחילה; הקאה; שלשול; כאב בטן; חוסר תיאבון.~~

- תופעות לוואי שכיחות (תופעות שמופיעות ב 1-10 משתמשים מתוך 100): כאב גרון, נזלת, חום, פריחה מגרדת, הזעת יתר, כאבי פרקים, סחרחורת, כאב ראש, רעד בלתי נשלט,~~טעם מתכתי; רמת גלוקוז נמוכה בדם~~, עצירות, בחילה, הקאות, שלשול, הצטברות גזים במערכת העיכול, צרבת, כאבים בתוך ומסביב לקיבה (כאב בטני).
- תופעות לוואי שאינן שכיחות (תופעות שמופיעות ב 1-10 משתמשים מתוך 1,000)~~: כאב במפרקים~~; עייפות, חולשה, טעם מתכתי, רמת גלוקוז נמוכה, איבוד תיאבון, נפיחות של כפות הידיים, הקרסוליים או כפות הרגליים (בצקת), צמרמורות, דלקת בלבלב, כאבי שרירים.~~עצירות; נפיחות של כפות הידיים, הקרסוליים או כפות הרגליים (בצקת).~~

~~חולים מסוימים חוו את תופעות הלוואי הבאות בעת נטילת שילוב יוקריאס עם אינסולין:~~
~~תופעות לוואי שכיחות: כאבי ראש; צמרמורות; בחילה; רמת גלוקוז נמוכה בדם, צרבת.~~
~~תופעות לוואי שאינן שכיחות: שלשול; הצטברות גזים במערכת העיכול.~~

~~חולים מסוימים חוו את תופעות הלוואי הבאות בעת נטילת שילוב יוקריאס עם סולפונילאוראה:~~
~~תופעות לוואי שכיחות: סחרחורת; רעד; חולשה; רמת גלוקוז נמוכה בדם; הזעת יתר.~~

מאז שהתכשיר משווק, דווחו תופעות הלוואי הבאות:

שכיחות אינה ידועה (לא ניתן להעריך מהנתונים הקיימים): ~~פריחה מגרדת; דלקת בלבלב;~~ קילופים מקומיים של העור או שלפוחיות~~; כאבי שריריים.~~ דלקת של כלי דם (וסקוליטיס) שעשויה לגרום לפריחה בעור או לנקודות מורמות, שטוחות, אדומות עגולות מתחת לפני העור או לחבורות.

העלונים לרופא ולצרכן כוללים שינויי עריכה / שינויים נוספים שאינם החמרות.

מומלץ לקרוא בעיון את כל תוכן העלונים, נא לעדכן את המטופלים במידע הרלוונטי להם.

העלונים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על-ידי פניה לבעל הרישום.

בברכה,
סיון דוד
רוקחת ממונה
נוברטיס ישראל בע"מ