ינואר 2022

רופא/ה נכבד/ה
רוקח/ת נכבד/ה

הנדון: <u>סטגלטרו 5 מ"ג/ STEGLATRO 5MG</u>
<u>סטגלטרו 15 מ"ג/ STEGLATRO 15MG</u>

Dosage Form: Film Coated Tablets
Composition: Ertugliflozin 5mg / Ertugliflozin 15mg

חברת מרק שארפ ודוהם (ישראל-1996) בע"מ, (MSD ישראל) מבקשת ליידע על עדכון העלונים לרופא ולצרכן של Steglatro.

להלן לשון ההתוויה המאושרת לתכשיר:
Steglatro is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an
adjunct to diet and exercise to improve glycaemic control:
• as monotherapy in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.
• in addition to other medicinal products for the treatment of diabetes.

למידע מלא ולהוראות מתן מפורטות, יש לעיין בעלון לרופא המאושר על ידי משרד הבריאות.

<u>עדכונים מהותיים בעלון לרופא:</u>

טקסט מהותי שהתווסף מודגש בקו תחתון.
טקסט מהותי שהוסר מסומן בקו מחיקה.

4.4 Special warnings and precautions for use
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<u>Diabetic ketoacidosis</u>
Rare cases of DKA, including life-threatening and fatal cases, have been reported in clinical trials and post-marketing in patients treated with sodium glucose co-transporter-2 (SGLT2) inhibitors, ~~and cases have been reported in clinical trials with~~<u>including</u> ertugliflozin.
...
<u>Lower limb amputations</u>
~~In an ongoing clinical study of ertugliflozin added to existing therapy in type 2 diabetes patients with a history of established cardiovascular disease, an approximately 1.2-1.6-fold increase in cases of lower limb amputation (primarily of the toe) has been observed in patients treated with ertugliflozin.~~ <u>In a long-term cardiovascular outcomes study VERTIS CV (eValuation of ERTugliflozin efflcacy and Safety, CardioVascular), a study in patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease, non-traumatic lower limb amputations (primarily of the toe) were reported with an incidence of 2.0% (0.57 subjects with event per 100 patient years), 2.1% (0.60 subjects with event per 100 patient years) and 1.6% (0.47 subjects with event per 100 patient years) for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo groups. The event rates of lower limb amputations were 0.75 and 0.96 versus 0.74 events per 100 patient years for ertugliflozin 5 mg and ertugliflozin 15 mg versus placebo, respectively.</u> An increase in cases of lower limb amputation (primarily of the toe) has ~~also~~ been observed in long-term clinical studies <u>in type 2 diabetes mellitus</u> with ~~another~~ SGLT2 inhibitor<u>s</u>. ~~As an underlying mechanism has not been established, risk factors, apart from general risk factors, for amputation are~~<u>It is not</u> ~~un~~known <u>whether this constitutes a class effect. It is important to counsel patients with diabetes on routine preventative foot care</u>.

~~Before initiating ertugliflozin, consider factors in the patient history that may increase the risk for amputation. As precautionary measures, consideration should be given to carefully monitoring patients with a higher risk for amputation events and counselling patients about the importance of routine preventative foot care and maintaining adequate hydration. Consideration may also be given to stopping treatment with ertugliflozin in patients who develop events which may precede amputation such as lower-extremity skin ulcer, infection, osteomyelitis or gangrene.~~

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Urinary tract infections

Urinary glucose excretion may be associated with an increased risk of urinary tract infections (see section 4.8). ~~The incidence of urinary tract infections was not notably different in the ertugliflozin 5 mg and 15 mg groups (4.0% and 4.1%) and the placebo group (3.9%). Most of the events were mild or moderate and no serious case was reported.~~

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4.8 Undesirable effects

Summary of the safety profile

The safety and tolerability of ertugliflozin were assessed in 7 placebo- or active comparator-controlled studies with a total of 3,409 patients with type 2 diabetes mellitus treated with ertugliflozin 5 mg or 15 mg. In addition, the safety and tolerability of ertugliflozin in patients with type 2 diabetes and established atherosclerotic cardiovascular disease were assessed in VERTIS CV (see section 5.1) with a total of 5,493 patients treated with ertugliflozin 5 mg or 15 mg and a mean duration of exposure of 2.9 years.

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Table 1: Adverse reactions from placebo- and active comparator-controlled clinical trials and post-marketing experience

System Organ Class Frequency	**Adverse Reaction**
Infections and infestations	
… Very common …	… Urinary tract infections[†] …

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Description of selected adverse reactions

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Hypoglycaemia

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In the VERTIS CV sub-studies, when ertugliflozin was added to insulin with or without metformin, the incidences of documented hypoglycaemia were 39.4%, 38.9% and 37.5% for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively. When ertugliflozin was added to a sulphonylurea, the incidences of hypoglycaemia were 7.3%, 9.3% and 4.2% for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively. When ertugliflozin was added to metformin and a sulphonylurea, the incidences of hypoglycaemia were 20.0%, 26.5% and 14.5% for ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively.

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Diabetic ketoacidosis

In VERTIS CV, ketoacidosis was identified in 19 (0.3%) ertugliflozin-treated patients and in 2 (0.1%) placebo-treated patients. Across ~~the clinical program~~7 other Phase 3 clinical trials in the ertugliflozin development program, ketoacidosis was identified in 3 ~~of 3,409~~ (0.1%) ertugliflozin-treated patients and 0.0% of comparator-treated patients (see section 4.4).

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Urinary tract infections

In VERTIS CV, urinary tract infections occurred in 12.2%, 12.0% and 10.2% of patients treated with ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively.

The incidences of serious urinary tract infections were 0.9%, 0.4%, and 0.8% with ertugliflozin 5 mg, ertugliflozin 15 mg and placebo, respectively.

Across 7 other Phase 3 clinical trials in the ertugliflozin development program, the incidences of urinary tract infections were 4.0% and 4.1% for ertugliflozin 5 mg and 15 mg groups and 3.9% for placebo. Most of the events were mild or moderate, and no serious cases were reported.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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Ertugliflozin as add-on combination therapy with insulin (with or without metformin)
In an 18-week randomised, double-blind, multi-centre, placebo-controlled, glycaemic sub-study of VERTIS CV, a total of 1,065 patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease with inadequate glycaemic control (HbA1c between 7% and 10.5%) with background therapy of insulin ≥20 units/day (59% patients were also on metformin ≥1,500 mg/day) were randomised to ertugliflozin 5 mg, ertugliflozin 15 mg or placebo once daily (see Table 8).

Table 8: Results at Week 18 from an add-on study of Steglatro in combination with insulin (with or without metformin) in patients with type 2 diabetes mellitus*

	Steglatro 5 mg	**Steglatro 15 mg**	**Placebo**
HbA1c (%)	**N = 348**	**N = 370**	**N = 347**
Baseline (mean)	8.4	8.4	8.4
Change from baseline (LS mean†)	-0.8	-0.8	-0.2
Difference from placebo (LS mean†, 95% CI)	-0.6‡ (-0.7, -0.4)	-0.6‡ (-0.8, -0.5)	
Patients [N (%)] with HbA1c <7%	72 (20.7) §	78 (21.1) §	37 (10.7)
Body Weight (kg)	**N = 348**	**N = 370**	**N = 347**
Baseline (mean)	93.8	92.1	93.3
Change from baseline (LS mean†)	-1.9	-2.1	-0.2
Difference from placebo (LS mean†, 95% CI)	-1.6‡ (-2.1, -1.1)	-1.9‡ (-2.4, -1.4)	

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.
† Least squares means adjusted for time, insulin stratum, baseline eGFR, and the interaction of time by treatment.
‡ p< 0.001 compared to placebo.
§ p< 0.001 compared to placebo (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).

Ertugliflozin as add-on combination therapy with metformin and sulphonylurea
In an 18-week randomised, double-blind, multi-centre, placebo-controlled, glycaemic sub-study of VERTIS CV, a total of 330 patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease with inadequate glycaemic control (HbA1c between 7% and 10.5%) with background therapy of metformin ≥1,500 mg/day and a sulphonylurea were randomised to ertugliflozin 5 mg, ertugliflozin 15 mg or placebo once daily (see Table 9).

Table 9: Results at Week 18 from an add-on study of Steglatro in combination with metformin and a sulphonylurea in patients with type 2 diabetes mellitus*

	Steglatro 5 mg	Steglatro 15 mg	Placebo
HbA1c (%)	**N = 100**	**N = 113**	**N = 117**
Baseline (mean)	8.4	8.3	8.3
Change from baseline (LS mean†)	-0.9	-1.0	-0.2
Difference from placebo (LS mean†, 95% CI)	-0.7‡ (-0.9, -0.4)	-0.8‡ (-1.0, -0.5)	
Patients [N (%)] with HbA1c <7%	37 (37.0)§	37 (32.7)§	15 (12.8)
Body Weight (kg)	**N = 100**	**N = 113**	**N = 117**
Baseline (mean)	92.1	92.9	90.5
Change from baseline (LS mean†)	-2.0	-2.4	-0.5
Difference from placebo (LS mean†, 95% CI)	-1.6‡ (-2.3, -0.8)	-1.9‡ (-2.6, -1.2)	

* N includes all randomised, treated patients who had at least one measurement of the outcome variable.
† Least squares means adjusted for time, baseline eGFR, and the interaction of time by treatment.
‡ p< 0.001 compared to placebo.
§ p< 0.001 compared to placebo (based on adjusted odds ratio comparisons from a logistic regression model using multiple imputation for missing data values).

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עדכונים מהותיים בעלון לצרכן:

טקסט מהותי שהתווסף מודגש בקו תחתון.
טקסט מהותי שהוסר מסומן בקו מחיקה.

אזהרות מיוחדות הנוגעות לשימוש בתרופה

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- ~~הייתה לך קטיעת גפיים תחתונות.~~

חשוב לבדוק את כפות הרגליים באופן קבוע ולהישמע לכל עצה אחרת הניתנת על ידי אנשי מקצוע רפואיים בנוגע לטיפול נאות בכף הרגל. ~~ומתן מספק של לחות, הניתנת על ידי איש מקצוע רפואי. עליך להודיע לרופא שלך מיד אם אתה מבחין בפצעים או שינויי צבע כלשהם, או אם אתה חווה כל סוג של רגישות או כאב ברגליים. כמה מחקרים מצביעים על כך שלקיחת ארטוגליפלוזין תרמה לעלייה במקרים של קטיעת גפיים תחתונות (בעיקר של הבוהן).~~

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תופעות לוואי

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פנה לרופא בהקדם האפשרי אם אתה שם לב לתסמינים הבאים:

דלקת בדרכי השתן (תופעת לוואי שכיחה מאוד, שעלולה להופיע ביותר ממשתמש 1 מתוך 10)
הסימנים לדלקת בדרכי השתן הם:
- תחושת צריבה בעת מתן שתן
- שתן שנראה עכור
- כאב באגן או באמצע הגב (כאשר הכליות נגועות)

למרות שזה נדיר, אם יש לך חום או רואים דם בשתן, ספר לרופא מיד.

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העלון לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום, חברת MSD, בטלפון 09-9533333.
STEGLATRO 5mg/ STEGLATRO 15mg מופצת ע"י חברת נובולוג בע"מ.

בברכה,
מיכל סרפר
רוקחת ממונה
MSD ישראל

References:
Israeli PC & PPI revised on January 2022