AstraZeneca

25 לאוקטובר 2020

רופא/ה נכבד/ה
רוקח/ת נכבד/ה שלום רב,

<u>פרסום עדכון בעלון התכשיר :</u>

<u>Onglyza 5 mg film-coated tablets</u>
<u>Onglyza 2.5 mg film-coated tablets</u>

הרכב:

Onglyza 2.5 mg film-coated tablets: Each tablet contains 2.5 mg saxagliptin (as hydrochloride).

Onglyza 5 mg film-coated tablets: Each tablet contains 5 mg saxagliptin (as hydrochloride)

Excipient(s) with known effect: Each tablet contains 99 mg lactose (as monohydrate) .

Onglyza contains less than 1 mmol sodium (23 mg) per dose, i.e. is essentially 'sodium-free.'

התוויה:

Monotherapy:
Onglyza is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus.
Onglyza should not be used in patients with ESRD

Combination therapy:
Add-on combination:
Onglyza is indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin, a thiazolidinedione (TZD), or a sulfonylurea (SU), when the single agent alone, with diet and exercise, does not provide adequate glycemic control.

Initial combination:
Onglyza is indicated for use as initial combination therapy with metformin, as an adjunct to diet and exercise, to improve glycemic control in patients with type 2 diabetes mellitus when dual saxagliptin and metformin therapy is appropriate.

Onglyza should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.
In combination with insulin (with or without metformin), when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.

חברת אסטרהזניקה ישראל מבקשת להודיע על עדכון עלון בהתאם להוראות משרד הבריאות בתאריך **אוקטובר 2020.**

העדכון העיקרי בעלון לרופא הוא:

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients <u>listed in section 6.1</u> or history of <u>a</u> serious hypersensitivity reaction, including anaphylactic reaction, anaphylactic shock, and angioedema ~~or exfoliative skin conditions~~, to any dipeptidyl peptidase 4 DPP4 inhibitor (see sections 4.4 and 4.8).

~~Do not take Onglyza if you are pregnant or breastfeeding.~~

4.4 Special warnings and precautions for use

Use with medicinal products known to cause hypoglycaemia

Sulphonylureas and insulin are known to cause hypoglycaemia. Therefore, a lower dose of sulphonylurea or insulin may be required to reduce the risk of hypoglycaemia when used in combination with Onglyza.

Hypersensitivity reactions Onglyza must ~~should~~ not be used in patients who have had any serious hypersensitivity reaction to a dipeptidyl peptidase 4 (DPP4) inhibitor- (see section 4.3)~~.~~

During postmarketing experience, including spontaneous reports and clinical trials, the following adverse reactions have been reported with the use of saxagliptin: serious hypersensitivity reactions, including anaphylactic reaction, anaphylactic shock and~~,~~ angioedema ~~and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with ONGLYZA, with some reports occurring after the first dose.~~

If a serious hypersensitivity reaction to saxagliptin is suspected, ~~discontinue~~ Onglyza should be discontinued, assess for other potential causes for the event, and institute alternative treatment for diabetes (see section~~s 4.3 and~~ 4.8).

~~Elderly patients~~

~~Of the 16,492 patients randomized in the SAVOR trial, 8561 (51.9%) patients were 65 years and over and 2330 (14.1%) were 75 years and over. The number of subjects treated with ONGLYZA in the SAVOR study that were 65 years and over was 4290 and the number of subjects that were 75 years and over was 1169.~~

~~Of the total number of subjects (N=4148) in six, double-blind, controlled clinical safety and efficacy studies of ONGLYZA, 634 (15.3%) patients were 65 years and over, of which 59 (1.4%) patients were 75 years and over.[~~

~~No overall differences in safety or effectiveness were observed between subjects 65 years and over, 75 years and over, and younger subjects.~~

~~While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.~~

~~Saxagliptin and its active metabolite are eliminated in part by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function~~

Skin disorders

Ulcerative and necrotic skin lesions have been reported in extremities of monkeys in non-clinical toxicology studies (see section 5.3). ~~Although~~ skin lesions were not observed at an increased incidence in clinical trials, ~~there is limited experience in patients with diabetic skin complications~~. Postmarketing reports of rash have been described in the DPP4 inhibitor class. Rash is also noted as an adverse reaction~~event (AE)~~ for Onglyza (see section 4.8). Therefore, in keeping with routine care of the diabetic patient, monitoring for skin disorders, such as blistering, ulceration or rash, is recommended.

Bullous pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalisation have been reported with DPP4 inhibitor use, including saxagliptin. In reported cases, patients typically responded to topical or systemic immunosuppressive treatment and discontinuation of the DPP4 inhibitor. If a patient develops blisters or erosions while receiving saxagliptin and bullous pemphigoid is suspected, this medicinal product should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment (see section 4.8).

Cardiac failure

Experience in NYHA class III-IV is still limited. In the SAVOR trial a smalln increase in the rate of for hospitalization for heart failure was observed in the saxagliptin treated patients compared to placebo, although a causal relationship has not been established (see section 5.1). Additional analysis did not indicate a differential effect among NYHA classes. Caution is warranted if Onglyza is used in patients who have known risk factors for hospitalization for heart failure, such as a history of heart failure or moderate to severe renal impairment. Patients should be advised of the characteristic symptoms of heart failure, and to immediately report such symptoms.

Arthralgia
Joint pain, which may be severe, has been reported in postmarketing reports for DPP4 inhibitors (see section 4.8). Patients experienced relief of symptoms after discontinuation of the medication and some experienced recurrence of symptoms with reintroduction of the same or another DPP4 inhibitor. Onset of symptoms following initiation of drug therapy may be rapid or may occur after longer periods of treatment. If a patient presents with severe joint pain, continuation of drug therapy should be individually assessed.

Immunocompromised patients Immunocompromised patients, such as patients who have undergone organ transplantation or patients diagnosed with human immunodeficiency syndrome, have not been studied in the Onglyza clinical program. Therefore, the efficacy and safety profile of saxagliptin in these patients has not been established.

Use with potent CYP 3A4 inducers Using CYP3A4 inducers like carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampicin may reduce the glycaemic lowering effect of Onglyza (see section 4.5).

Lactose

The tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Clinical data described below suggest that the risk for clinically meaningful interactions with co-administered medicinal products is low.

The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5).

In *in vitro* studies, saxagliptin and its major metabolite neither inhibited CYP1A2, 2A6, 2B6 , the co-administration 2C9, 2C19, 2D6, 2E1, or 3A4, nor induced CYP1A2, 2B6, 2C9, or 3A4. In studies conducted in healthy subjects, neither the pharmacokinetics of saxagliptin and CYP3A4/5 inducers, other than rifampicin (such as carbamazepine, dexamethasone, phenobarbital and phenytoin) have not been studied and may result in decreased plasma concentration of saxagliptin and increased concentration of its major metaboliteits major metabolite, were meaningfully altered by metformin, glibenclamide, pioglitazone, digoxin, simvastatin, omeprazole, antacids or famotidine. In addition, Glycaemic control should be carefully assessed when saxagliptin did not meaningfully alter the pharmacokinetics of metformin, glibenclamide, pioglitazone, digoxin, simvastatin, diltiazem or ketoconazole or an estrogen/progestin combined oral contraceptive is used concomitantly with potent CYP3A4/5 inducer

Concomitant administration of saxagliptin with the moderate inhibitor of CYP3A4/5 diltiazem, increased the Cmax and AUC of saxagliptin by 63% and 2.1-fold, respectively, and the corresponding values for the active metabolite were decreased by 44% and 34%, respectively.

Concomitant administration of saxagliptin with the potent inhibitor of CYP3A4/5 ketoconazole,

increased the Cmax and AUC of saxagliptin by 62% and 2.5-fold, respectively, and the corresponding values for the active metabolite were decreased by 95% and 88%, respectively.

Concomitant administration of saxagliptin with the potent CYP3A4/5 inducer rifampicin, reduced Cmax and AUC of saxagliptin by 53% and 76%, respectively. The exposure of the active metabolite and the plasma DPP4 activity inhibition over a dose interval were not influenced by rifampicin (see section 4.4).

In *in vitro* studies, saxagliptin and its major metabolite neither inhibited CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4, nor induced CYP1A2, 2B6, 2C9, or 3A4. In studies conducted in~~The co-administration of saxagliptin and CYP3A4/5 inducers, other than rifampicin (such as~~

healthy subjects, neither the pharmacokinetics of saxagliptin nor its major metabolite, were meaningfully altered by metformin, glibenclamide, pioglitazone, digoxin, simvastatin, omeprazole, antacids or famotidine. In addition, saxagliptin did not meaningfully alter the pharmacokinetics of metformin, glibenclamide, pioglitazone, digoxin, simvastatin, the active components of a combined oral contraceptive (ethinyl estradiol and norgestimate), diltiazem or ketoconazole.
~~carbamazepine, dexamethasone, phenobarbital and phenytoin) have not been studied and may result in decreased plasma concentration of saxagliptin and increased concentration of its major metabolite. Glycaemic control should be carefully assessed when saxagliptin is used concomitantly with a potent CYP3A4 inducer.~~

The effects of smoking, diet, herbal products, and alcohol use on the pharmacokinetics of saxagliptin have not been specifically studied.

4.7 Effects on ability to drive and use machines

Onglyza may have a negligible influence on the ability to drive and use machines.

~~No studies on the effects on the ability to drive and use machines have been performed. However,~~ when driving or using machines, it should be taken into account that dizziness has been reported in studies with saxagliptin. In
addition, patients should be alerted to the risk of hypoglycaemia when Onglyza is used in combination with other antidiabetic medicinal products known to cause hypoglycaemia (e.g. insulin, sulphonylureas).

4.8 Undesirable effects

Table 1 Frequency of adverse reactions by system organ class from clinical trials and postmarketing experience

System organ class Adverse Reaction	Frequency of adverse reactions by treatment regimen			
	Saxagliptin monotherapy	**Saxagliptin with metformin[1]**	**Saxagliptin with a sulphonylurea (glibenclamide)**	**Saxagliptin with a thiazolidinedione**
Infections and infestations				
Upper respiratory infection	Common	Common	Common	Common
Urinary tract infection	Common	Common	Common	Common
Gastroenteritis	Common	Common	Common	Common
Sinusitis	Common	Common	Common	Common

Nasopharyngitis		Common[2]		
Immune system disorders				
Hypersensitivity reactions†‡	Uncommon	Uncommon	Uncommon	Uncommon
Anaphylactic reactions including anaphylactic shock†‡	Rare	Rare	Rare	Rare
Metabolism and nutrition disorders				
Hypoglycaemia			Very common[3]	
Dyslipidemia			Uncommon	
Hypertri-Glyceridemia			Uncommon	
Nervous system disorders				
Dizziness	Common			
Headache	Common	Common	Common	Common
Gastrointestinal disorders				
Abdominal pain†	Common	Common	Common	Common
Diarrhoea[4]	Common	Common	Common	Common
Dyspepsia		Common		
Gastritis		Common		
Nausea†	Common	Common	Common	Common
Vomiting	Common	Common	Common	Common
Pancreatitis†	Uncommon	Uncommon	Uncommon	Uncommon
Constipation†	Not Known	Not Known	Not Known	Not Known
Skin and subcutaneous tissue disorders				
Rash†	Common	Common	Common	
Dermatitis†	Uncommon	Uncommon	Uncommon	Uncommon
Pruritus†	Uncommon	Uncommon	Uncommon	Uncommon
Urticaria†	Uncommon	Uncommon	Uncommon	Uncommon
Angioedema†‡	Rare	Rare	Rare	Rare
Bullous pemhigoid†	Not known	Not known	Not known	Not known
Musculo-skeletal and connective tissue disorders				
Arthralgia		Uncommon		
Myalgia[5]		Common		
Reproductive system and breast disorders				
Erectile dysfunction		Uncommon		
General disorders and administration site conditions				
Fatigue	Common		Uncommon	
Oedema peripheral				Common

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clinical ~~safety and~~ efficacy and safety

In randomised, controlled, double-blind clinical trials (including developmental and postmarketing experience), over 17,000 patients with type 2 diabetes have been treated with saxagliptin.

Glycaemiccontrol

A total of 4,148 patients with type 2 diabetes, including 3,021 patients treated with, saxagliptin were randomised in 6 double-blind, controlled clinical safety and efficacy studies conducted to evaluate the effects of saxagliptin on glycaemic control~~. In these studies 634 patients were 65 years and older, while 59 patients were 75 years and older~~. Treatment with saxagliptin 5 mg once daily produced clinically relevant and statistically significant improvements in haemoglobin A1c (HbA1c), fasting plasma glucose (FPG) and postprandial glucose (PPG) compared to placebo in monotherapy, in combination with metformin (initial or add-on therapy), in combination with a sulphonylurea, and in combination with a thiazolidinedione (see Table 2). There was also no apparent change in body weight associated with saxagliptin. Reductions in HbA1c were seen across subgroups including gender, age, race, and baseline body mass index (BMI) and higher baseline HbA1c was associated with a greater adjusted mean change from baseline with saxagliptin.

~~*Controlled long-term study extension*~~
~~Patients who completed all visits during the initial 24-week study period without need for hyperglycaemia rescue therapy were eligible to enter a controlled long-term study extension. Patients who received saxagliptin plus metformin in the initial 24-week study period maintained the same dose of saxagliptin in the long-term extension. Treatment with saxagliptin 5 mg plus metformin was associated with a greater reduction in HbA1c than in the placebo plus metformin group, and this effect was sustained up to Week 102. The HbA1c change for saxagliptin 5 mg plus metformin compared to placebo plus metformin was − 0.7% at Week 102.~~

Saxagliptin in combination with metformin as initial therapy

Cardiovascular safety

In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction (SAVOR) Trial, the effect of ONGLYZA study (saxagliptin) on the occurrence of major cardiovascular disease (CVD) events SAVOR was assessed A cv outcome trial in 16,492 adult patients with type 2 diabetes who had either HbA1c ≥6.5% and <12% (12959 with established CVD or CV disease, 3533 with multiple risk factors for vascular disease, including patients with moderate or severe renal impairment. Patients ≥40 years of age, diagnosed with type 2 diabetes and with A1C ≥6.5%, and with either established CVD or multiple CV risk factors only) who were enrolled.

Patients were randomly assigned randomised to saxagliptin (n=8280) or placebo (n=8212) or saxagliptin (5 mg or 2.5 mg for patients with moderate or severe renal insufficiency) once daily (n=8280). Randomization added to the saxagliptin saxagliptinr egional standards of care for HbA1c and placebo groups was stratified by CV risk factors with 3533 patients (21.4%) with CV risk only and 12,959 patients (78.6%) with established CVD and by renal impairment including 13,916 subjects (84.4%) with normal renal function to mild impairment, 2240 subjects (13.6%) with moderate impairment, and 336 subjects (2.0%) with severe renal impairment. Patients with established CVD were defined by a history of ischemic heart disease, peripheral vascular disease, or ischemic stroke. Patients with CV risk factors only had age as a CV risk factor (men ≥55 years and women ≥60 years) plus at least one additional risk factor of dyslipidemia, hypertension, or current cigarette smoking.

The demographics and baseline characteristics of subjects were balanced between the saxagliptin and placebo groups. The study population was 67% male and 33% female with a mean age at randomization of included those ≥ 65 years. Of the 16,492 patients randomized, n=8561 (52%) patients were 65 years) and over and 2330 (14%) were ≥75 years and over. ≥(n=2330), with normal or mild renal impairment (n=13,916) as well as moderate (n=2240) or severe (n=336) renal impairment.

All study subjects had a mean duration of T2DM of 12 years (median = 10.3) and a mean A1C level of 8.0% (median = 7.6%). Overall, 25% of subjects had baseline A1C levels <7%. Subjects were followed for a mean duration of 2 (median = 2.0) years. Concomitant medication use was similar for the two treatment groups. Overall, the use of diabetes medications was consistent with local treatment practice and the saxagliptin clinical program (metformin 69%, insulin 41%, sulfonylureas 40%, and TZDs 6%). The use of CVD medications was also consistent with local treatment practice (ACE inhibitors or ARBs 79%, statins 78%, aspirin 75%, beta blockers 62%, and nonaspirin antiplatelet medications 24%). Approximately 6% of subjects were treated with diet and exercise only at baseline. Concomitant medications were managed throughout the trial to local guideline targets for glycemic control and CV risk reduction in order to minimize differences between the two treatment groups, particularly for glycemic control.

The primary safety (noninferiority) and efficacy (superiority) endpoint was a composite endpoint consisting of the time-tofirst occurrence of any of the following major adverse CV events (MACE): CV death, nonfatal myocardial infarction, or nonfatal ischemic stroke.

The after a mean follow up of 2 years, the trial met its primary safety objective of this trial was to establish that the upper bound of the 2-sided 95% CI for the estimated risk ratio comparing the incidence of the composite endpoint of CV death, non-fatal MI or non-fatal ischemic stroke observed with demonstrating saxagliptin to that observed does not increase the cardiovascular risk in the placebo group was <1.3 patients

The primary efficacy objective was to determine, as a superiority assessment, whether treatment with saxagliptin, compared with type 2 diabetes compared to placebo when added to current background therapy, resulted in no a significant reduction in the primary benefit was observed for MACE endpoint. or

The first secondary efficacy endpoint was a composite endpoint consisting of the time-to-first occurrence of MACE plus hospitalization for heart failure, hospitalization for unstable angina

pectoris, or hospitalization for coronary revascularization (MACE plus). The next secondary efficacy endpoint was to determine whether treatment with saxagliptin compared with placebo when added to current background therapy in subjects with T2DM would result in a reduction of all-cause mortality.

The cardiovascular safety of saxagliptin was evaluated in the SAVOR trial which established that saxagliptin did not increase the CV risk (CV death, nonfatal myocardial infarction, or nonfatal ischemic stroke) in patients with T2DM compared to placebo when added to current background therapy (HR 1.00; 95% CI: 0.89, 1.12; P<0.001 for noninferiority).

The primary efficacy endpoint did not demonstrate a statistically significant difference in major adverse coronary events for saxagliptin compared to placebo when added to current background therapy in patients with T2DM.

Table 3: Primary and Secondary Clinical Endpoints by Treatment Group in the SAVOR Study *

Endpoint	TRADEMARK (N=8280)		Placebo (N=8212)		Hazard Ratio (95% CI)†
	Subjects with events n (%)	Event rate per 100 patient-yrs	Subjects with events n (%)	Event rate per 100 patient-yrs	
Primary composite endpoint: MACE	613 (7.4)	3.76	609 (7.4)	3.77	1.00 (0.89, 1.12)‡,§
Secondary composite endpoint: MACE plus	1059 (12.8)	6.72	1034 (12.6)	6.60	1.02 (0.94, 1.11)¶
All-cause mortality	420 (5.1)	2.50	378 (4.6)	2.26	1.11 (0.96, 1.27)¶

* Intent-to-treat population

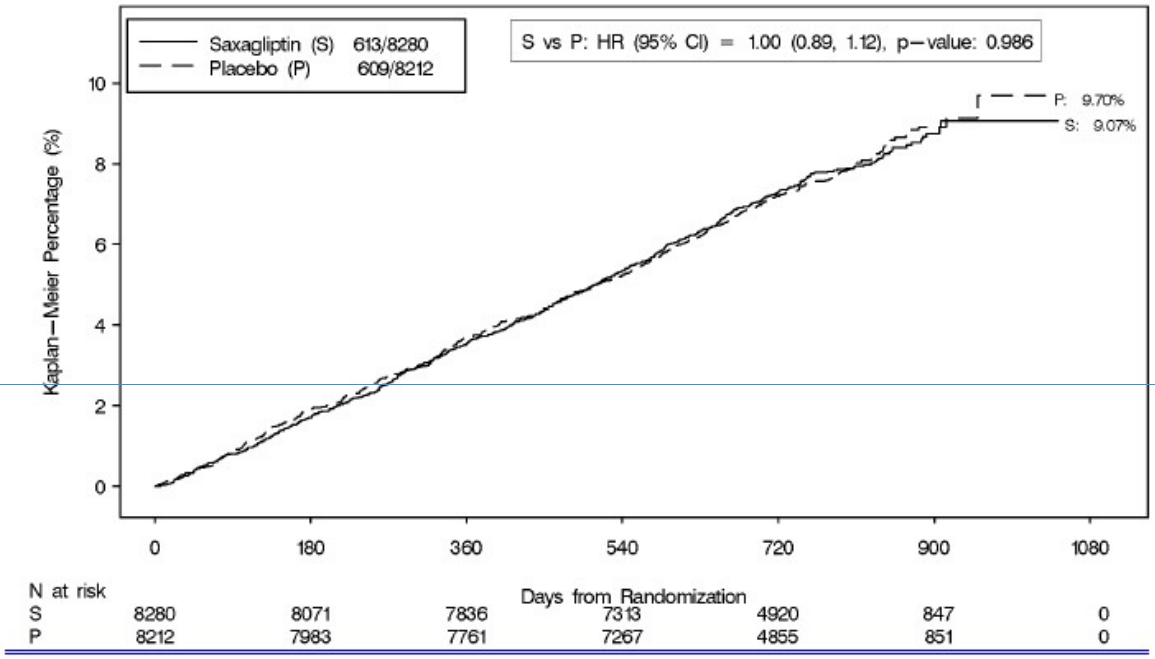
† Hazard ratio adjusted for baseline renal function category and baseline CVD risk category.

‡ P-value <0.001 for noninferiority (based on HR <1.3) compared to placebo.

§ P-value = 0.99 for superiority (based on HR <1.0) compared to placebo.

¶ Significance not tested.

Figure 1 : Cumulative percent of time to first CV event for primary composite endpoint *



* Intent-to-treat population

Endpoint	Saxagliptin (N=8280)		Placebo (N=8212)		Hazard Ratio (95% CI)†
	Subjects with events n (%)	Event rate per 100 patient-yrs	Subjects with events n (%)	Event rate per 100 patient-yrs	
Primary composite endpoint: MACE	613 (7.4)	3.76	609 (7.4)	3.77	1.00 (0.89, 1.12)‡,§,#
Secondary composite endpoint: MACE plus	1059 (12.8)	6.72	1034 (12.6)	6.60	1.02 (0.94, 1.11)¶
All-cause mortality	420 (5.1)	2.50	378 (4.6)	2.26	1.11 (0.96, 1.27)¶

* Intent-to-treat population
† Hazard ratio adjusted for baseline renal function category and baseline CVD risk category.
‡ p-value <0.001 for noninferiority (based on HR <1.3) compared to placebo.
§ p-value = 0.99 for superiority (based on HR <1.0) compared to placebo.

Events accumulated consistently over time, and the event rates for ONGLYZA and placebo did not diverge notably over time.
¶ Significance not tested.

One component of the secondary composite endpoint, hospitalization for heart failure, occurred at a greater rate in the saxagliptin group (3.5%) compared with the placebo group (2.8%), with nominal statistical significance (~~ie, without adjustment for testing of multiple endpoints)~~ favouring placebo [HR = 1.27; (95% CI 1.07, 1.51); P = 0.007]. Clinically relevant factors predictive of increased relative risk with saxagliptin treatment could not be definitively identified. Subjects at higher risk for hospitalization for heart failure, irrespective of treatment assignment, could be identified by known risk factors for heart failure such as baseline history of heart failure or impaired renal function. However, subjects on saxagliptin with a history of heart failure or impaired renal function at baseline were not at an increased risk relative to placebo for the primary or secondary composite endpoints or all-cause mortality.

~~No increased risk for the primary~~ Another secondary endpoint ~~was observed between saxagliptin and placebo in any~~ all-cause mortality, occurred at a rate of ~~the following subgroups: CVD, multiple risk factors for CVD, mild, moderate, or severe renal impairment, age, gender, race, region, duration of type 2 diabetes, history of heart failure, baseline A1C, albumin/creatinine ratio, baseline antidiabetic medication, or baseline use of statins, aspirin, ACE inhibitors, ARBs, beta-blockers, or antiplatelet medications~~.

~~Despite active management of concomitant antidiabetic therapy in both study arms, mean A1C levels were lower~~ 5.1% in the saxagliptin group ~~compared to~~ and 4.6% in the placebo group ~~at Year 1 (7.6% versus 7.9%, difference of -0.35% [~~(see Table 4). CV deaths were balanced across the treatment groups. There was a numerical imbalance in non-CV death, with more events on saxagliptin (1.8%) than placebo (1.4%) [HR = 1.27; ([95% CI: ~~-0.38, -0.31]) and at Year 2 (7.6% versus 7.9%,~~ 1.00, 1.62); P = 0.051]. ~~difference of -0.30% [95% CI: -0.34, -0.26]). The proportions of subjects with A1C <7% in the~~ A1C was lower with saxagliptin ~~group~~ compared to ~~the placebo group were 38% versus 27% at Year 1 and 38%~~ in an exploratory analysis. Paediatric population ~~versus 29% at Year 2.~~

~~Compared~~ The European Medicines Agency has deferred the obligation to ~~placebo, saxagliptin resulted~~ submit the results of studies with Onglyza in ~~less need for the initiation of new~~ one or ~~increases~~ more subsets of the paediatric population in the treatment of type 2 diabetes mellitus (see section 4.2 for information on paediatric use)

Elderly ~~current oral diabetes medications or insulin. The improvements~~ population

In the SAVOR study subgroups over 65 and over 75 years of age, efficacy and safety were consistent with the overall study population.

GENERATION was a 52-week glycaemic control study in ~~A1C and~~ 720 elderly patients, the mean age was 72.6 years; 433 subjects (60.1%) were < 75 years of age, and 287 subjects (39.9%) were ≥ 75 years of age. Primary endpoint was the proportion of patients reaching HbA1c < 7% without confirmed or severe hypoglycaemia. There appeared to be no difference in percentage responders: 37.9% (saxagliptin) and 38.2% (glimepiride) achieved the primary endpoint. A lower proportion of patients in the saxagliptin group (44.7%) compared to the glimepiride group (54.7%) achieved an HbA1c target of 7.0%. A lower proportion of patients in the saxagliptin group (1.1%) compared to the glimepiride group (15.3%) experienced a confirmed or severe hypoglycaemic event.

~~subjects reaching A1C targets among saxagliptin-treated subjects were observed despite lower rates of upward adjustments in diabetes medications or initiation of new diabetes medications or insulin compared with placebo.~~

העדכון העיקרי בעלון לצרכן הוא:

2. לפני השימוש בתרופה

אזהרות מיוחדות הנוגעות בשימוש באונגלייזה

- פציעות עוריות הינן סיבוך שכיח בחולי סוכרת. פריחה הינה תופעה שנראתה בעקבות שימוש באונגלייזה (ראה סעיף 4 – תופעות לוואי) ותרופות אנטי סוכרתיות אחרות באותה קבוצה תרפויטית. עליך לעקוב אחר הוראות הרופא לגבי הטיפול בעור וטיפול ברגליים הניתנות על ידי הרופא או האחות. צור קשה עם הרופא במידה ואתה נתקל בשלפוחיות בעור, יתכן וזה סימן למצב הנקרא בולוס פומפיגואיד. יתכן והרופא ינחה אותך להפסיק לטול אונגלייזה .

נהיגה ושימוש במכונות

~~השימוש בתרופה זו עלול לגרום לסחרחורת.~~ אם הינך חש בסחרחורת בעת נטילת האונגלייזה, אין לנהוג ברכב, אין להפעיל מכונות מסוכנות או לבצע כל פעילות המחייבת עירנות. היפוגליקמיה עלולה להשפיע על היכולת שלך לנהוג ולהפעיל מכונות מסוכנות. קיים סיכון להיפוגליקמיה כשנוטלים אונגלייזה עם תכשירים הידועים כגורמים להיפוגליקמיה כמו אינסולין וסולפונילאוריאה.

מידע חשוב על חלק מהמרכיבים של התרופה

הטבליות מכילות לקטוז) סוכר החלב) . אם נאמר לך על-ידי הרופא שיש לך אי סבילות לסוכרים מסוימים, היוועץ ברופא לפני נטילת תרופה זו.

טבליות אונגלייזה 2.5 מ"ג וטבליות אונגלייזה 5 מ"ג: כל טבליה מכילה 99 מ"ג לקטוז מונוהידראט.

תכולת הנתרן בתרופה הינה פחותה מ- 23 מ"ג לטבליה. כך שלמעשה התרופה נחשבת כנטולת נתרן.

4. תופעות לוואי

יש להפסיק את השימוש באונגלייזה ולפנות מיידית לרופא אם הינך מרגיש את התופעות הבאות שנובעות מרמת סוכר נמוכה בדם

- **תופעות שכיחות מאד (משפיעות על יותר מחולה 1 מתוך 10):**
- רעד ,
- הזעה ,
- חרדה ,
- טשטוש ראייה ,
- ~~דופק מהיר ,~~
- עקצוץ בשפתיים ,
- חיוורון ,
- שינוי במצב הרוח ,
- ערפול או בלבול (היפוגליקמיה) ,
- ~~כאב ראש,~~
- ~~רעב.~~

יש להפסיק לטול אונגלייזה ולצור קשר מיידית עם הרופא אם הנך מבחין בתופעת הלוואי החמורה הבאה:

- כאב בטן חמור ומתמשך שיכול להקרין לגב, כמו גם בחילות והקאות, זה יכול להיות סימן של דלקת בלבלב (פנקראטיטיס) .

יש לפנות לרופא במידה והנך סובל מתופעת הלוואי הבאה

- כאב פרקים חמור

<u>תופעות לוואי אפשריות בנטילת אונגלייזה עם מטפורמין :</u>

תופעות לוואי שכיחות (תופעות שמופיעות ב 1 עד 10 משתמשים מתוך 100):

- סינוסיטיס עם תחושת כאב ומלאות מאחורי הלחיים והעיניים ,

<u>תופעות לוואי אפשריות בנטילת אונגלייזה עם סולפונילאוריאה :</u>

תופעות לוואי שכיחות (תופעות שמופיעות ב 1 עד 10 משתמשים מתוך 100) :

- סינוסיטיס עם תחושת כאב ומלאות מאחורי הלחיים והעיניים ,

<u>תופעות לוואי אפשריות בנטילת אונגלייזה יחד עם תיאזולידינדיון :</u>

תופעות לוואי שכיחות (תופעות שמופיעות ב 1 עד 10 משתמשים מתוך 100) :

- סינוסיטיס עם תחושת כאב ומלאות מאחורי הלחיים והעיניים ,

תופעות לוואי אפשריות בנטילת אונגלייזה בלבד או בשילוב תרופתי אחר:

תופעות לוואי ששכיחותן אינה ידועה (תופעות ששכיחותן טרם נקבעה)

- עצירות
- שלפוחיות בעור (בולוס פמפיגואיד)

תוספות לעלון מסומנות בצבע וקו תחתון וטקסט שנמחק מסומן בצבע ובקו חוצה.
העלונים מפורסמים במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום.
בכבוד רב,

קארין קנבל דובסון
רוקחת ממונה
אסטרהזניקה (ישראל) בע"מ

אסטרהזניקה (ישראל) בע"מ, ת.ד 1455, הוד השרון 4524075
טלפון 09-7406528 פקס 09-7406527