**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Komboglyze 2.5 mg/850 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5 mg of saxagliptin (as hydrochloride) and 850 mg of metformin hydrochloride.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Light brown to brown, biconvex, round, film-coated tablets, with "2.5/850" printed on one side and "4246" printed on the other side, in blue ink.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Komboglyze is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus inadequately controlled on their maximally tolerated dose of metformin alone or those already being treated with the combination of saxagliptin and metformin as separate tablets.

Komboglyze is also indicated in combination with insulin (ie, triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus when insulin and metformin alone do not provide adequate glycaemic control.

Komboglyze is also indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus when the maximally tolerated dose of both metformin and the sulphonylurea does not provide adequate glycaemic control.

### 4.2 Posology and method of administration

Posology
*For patients inadequately controlled on maximal tolerated dose of metformin monotherapy*
Patients not adequately controlled on metformin alone should receive a dose of Komboglyze equivalent to the total daily dose of saxagliptin 5 mg, dosed as 2.5 mg twice daily, plus the dose of metformin already being taken.

*For patients switching from separate tablets of saxagliptin and metformin*
Patients switching from separate tablets of saxagliptin and metformin should receive the doses of saxagliptin and metformin already being taken.

*For patients inadequately controlled on dual combination therapy of insulin and metformin, or, for patients controlled on triple combination therapy of insulin, and metformin plus saxagliptin as separate tablets.*
The dose of Komboglyze should provide saxagliptin 2.5 mg twice daily (5 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Komboglyze is used in combination

with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycaemia (see section 4.4).

*For patients inadequately controlled on dual combination therapy of a sulphonylurea and metformin, or for patients switching from triple combination therapy of saxagliptin, metformin and a sulphonylurea taken as separate tablets.*
The dose of Komboglyze should provide saxagliptin 2.5 mg twice daily (5 mg total daily dose), and a dose of metformin similar to the dose already being taken. When Komboglyze is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be required to reduce the risk of hypoglycaemia (see section 4.4).

*Special populations*
*Renal impairment*
No dose adjustment is recommended for patients with mild renal impairment. Komboglyze should not be used in patients with moderate to severe renal impairment (see sections 4.3, 4.4 and 5.2).

*Hepatic impairment*
Komboglyze should not be used in patients with hepatic impairment (see sections 4.3 and 5.2).

*Elderly (≥ 65 years)*
As metformin and saxagliptin are excreted by the kidney, Komboglyze should be used with caution in the elderly. Monitoring of renal function is necessary to prevent metformin-associated lactic acidosis, particularly in the elderly (see sections 4.3 and 4.4). Experience with saxagliptin in patients aged 75 years and older is very limited and caution should be exercised when treating this population (see sections 4.4 and 5.2).

*Paediatric population*
The safety and efficacy of Komboglyze in children from birth to < 18 years of age have not been established. No data are available.

Method of administration
Komboglyze should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin.

## 4.3 Contraindications

Komboglyze is contraindicated in patients with:

- hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1, or history of a serious hypersensitivity reaction, including anaphylactic reaction, anaphylactic shock, and angioedema, to any dipeptidyl peptidase 4 (DPP4) inhibitor (see sections 4.4 and 4.8);
- diabetic ketoacidosis, diabetic pre-coma;
- moderate and severe renal impairment (creatinine clearance < 60 ml/min) (see section 4.4);
- acute conditions with the potential to alter renal function such as:
  - dehydration,
  - severe infection,
  - shock;
- acute or chronic disease which may cause tissue hypoxia such as:
  - cardiac or respiratory failure,
  - recent myocardial infarction,
  - shock;
- hepatic impairment (see sections 4.2 and 5.2);
- acute alcohol intoxication, alcoholism (see section 4.5);
- breastfeeding (see section 4.6).

## 4.4 Special warnings and precautions for use

General
Komboglyze should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Komboglyze is not a substitute for insulin in insulin-requiring patients.

Pancreatitis
In post-marketing experience with saxagliptin, there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of saxagliptin. If pancreatitis is suspected, Komboglyze and other potentially suspect medicinal products should be discontinued.

Lactic acidosis
Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin, a component of Komboglyze, accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any conditions associated with hypoxia.

*Diagnosis*
Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/l, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient hospitalised immediately (see section 4.9).

Renal function
As metformin is excreted by the kidney, serum creatinine concentrations should be determined regularly:
- at least once a year in patients with normal renal function
- at least two to four times a year in patients with serum creatinine levels at or above the upper limit of normal and in elderly patients.

Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy or when starting treatment with a nonsteroidal anti-inflammatory drug (NSAID).

Surgery
As Komboglyze contains metformin, the treatment should be discontinued 48 hours before elective surgery with general, spinal or epidural anaesthesia. Komboglyze should not usually be resumed earlier than 48 hours afterwards and only after renal function has been re-evaluated and found to be normal.

Administration of iodinated contrast agent
The intravascular administration of iodinated contrast agents in radiological studies can lead to renal failure which has been associated with lactic acidosis in patients receiving metformin. Therefore, Komboglyze must be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 4.5).

Skin disorders
Ulcerative and necrotic skin lesions have been reported in extremities of monkeys in non-clinical toxicology studies for saxagliptin (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 event (AE) for saxagliptin (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.

Hypersensitivity reactions
As Komboglyze contains saxagliptin, it should not be used in patients who have had any serious hypersensitivity reaction to a dipeptidyl peptidase 4 (DPP4) inhibitor.

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. If a serious hypersensitivity reaction to saxagliptin is suspected, discontinue Komboglyze, assess for other potential causes for the event, and institute alternative treatment for diabetes (see sections 4.3 and 4.8).

Change in clinical status of patients with previously controlled type 2 diabetes
As Komboglyze contains metformin, a patient with type 2 diabetes previously well controlled on Komboglyze who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, Komboglyze must be stopped immediately and other appropriate corrective measures initiated.

Elderly patients
Experience in patients aged 75 years and older is very limited with saxagliptin and caution should be exercised when treating this population (see section 5.2).

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 saxagliptin 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 saxagliptin (see section 4.5).

Use with medicinal products known to cause hypoglycaemia
Insulin and sulphonylureas are known to cause hypoglycaemia. Therefore, a lower dose of insulin or sulphonylurea may be required to reduce the risk of hypoglycaemia when used in combination with Komboglyze.

## 4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of multiple doses of saxagliptin (2.5 mg twice daily) and metformin (1,000 mg twice daily) did not meaningfully alter the pharmacokinetics of either saxagliptin or metformin in patients with type 2 diabetes.

There have been no formal interaction studies for Komboglyze. The following statements reflect the information available on the individual active substances.

Saxagliptin

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, 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 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.

Concomitant administration of saxagliptin with the moderate inhibitor of CYP3A4/5 diltiazem, increased the $C_{max}$ 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 $C_{max}$ 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 $C_{max}$ 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).

The co-administration 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 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.

Metformin

*Combinations not recommended*

There is increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic impairment) due to the metformin active substance of Komboglyze (see section 4.4). Consumption of alcohol and medicinal products containing alcohol should be avoided.

Cationic substances that are eliminated by renal tubular secretion (e.g., cimetidine) may interact with metformin by competing for common renal tubular transport systems. A study conducted in seven normal healthy volunteers showed that cimetidine, administered as 400 mg twice daily, increased metformin systemic exposure (AUC) by 50% and $C_{max}$ by 81%. Therefore, close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are co-administered.

The intravascular administration of iodinated contrast agents in radiological studies may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. Therefore Komboglyze must be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 4.4).

*Combination requiring precautions for use*
Glucocorticoids (given by systemic and local routes), beta-2agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring perfomed, especially at the beginning of treatment with such medicinal products. If necessary, the dose of the anti-hyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
The use of Komboglyze or saxagliptin has not been studied in pregnant women. Studies in animals have shown reproductive toxicity at high doses of saxagliptin alone or in combination with metformin (see section 5.3). The potential risk for humans is unknown. A limited amount of data suggest the use of metformin in pregnant women is not associated with an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development (see section 5.3). Komboglyze should not be used during pregnancy. If the patient wishes to become pregnant, or if a pregnancy occurs, treatment with Komboglyze should be discontinued and switched to insulin treatment as soon as possible.

Breast-feeding
Studies in animals have shown excretion of both saxagliptin and/or metabolite and metformin in milk. It is unknown whether saxagliptin is excreted in human milk, but metformin is excreted in human milk in small amounts. Komboglyze must therefore not be used in women who are breastfeeding (see section 4.3).

Fertility
The effect of saxagliptin on fertility in humans has not been studied. Effects on fertility were observed in male and female rats at high doses producing overt signs of toxicity (see section 5.3). For metformin, studies in animals have not shown reproductive toxicity (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Saxagliptin or metformin may have a negligible influence on the ability to drive and use machines. 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 Komboglyze is used in combination with other antidiabetic medicinal products known to cause hypoglycaemia (e.g. insulin, sulphonylureas).

## 4.8 Undesirable effects

There have been no therapeutic clinical trials conducted with Komboglyze tablets, however bioequivalence of Komboglyze with co-administered saxagliptin and metformin has been demonstrated (see section 5.2).

Saxagliptin
*Summary of the safety profile*
There were 4,148 patients with type 2 diabetes, including 3,021 patients treated with saxagliptin, randomised in six double-blind, controlled clinical safety and efficacy studies conducted to evaluate the effects of saxagliptin on glycaemic control.

In a pooled analysis, the overall incidence of AEs in patients treated with saxagliptin 5 mg was similar to placebo. Discontinuation of therapy due to AEs was higher in patients who received saxagliptin 5 mg as compared to placebo (3.3% as compared to 1.8%).

*Tabulated list of adverse reactions*

Adverse reactions reported in ≥ 5% of patients treated with saxagliptin 5 mg and more commonly than in patients treated with placebo or that were reported in ≥ 2% of patients treated with saxagliptin 5 mg and ≥ 1% more frequently compared to placebo are shown in Table 1.

The adverse reactions are listed by system organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to 1/100), rare (≥ 1/10,000 to 1/1,000), or very rare (< 1/10,000), not known (cannot be estimated from the available data).

**Table 1 Frequency of adverse reactions by system organ class**

| **System organ class**<br>Adverse reaction | **Frequency of adverse reactions by treatment regimen**<br><br>**Saxagliptin with metformin[1]** |
|---|---|
| **Infections and infestations** | |
| Upper respiratory infection | Common |
| Urinary tract infection | Common |
| Gastroenteritis | Common |
| Sinusitis | Common |
| Nasopharyngitis | Common[2] |
| **Nervous system disorders** | |
| Headache | Common |
| **Gastrointestinal disorders** | |
| Vomiting | Common |

[1]Includes saxagliptin in add-on to metformin and initial combination with metformin.

[2]Only in the initial combination therapy.

*Postmarketing experience from clinical trials and spontaneous reports*

Table 2 shows additional adverse reactions which have been reported in postmarketing experience with saxagliptin. The frequencies are based on the experience from clinical trials.

**Table 2 Frequency of additional adverse reactions by system organ class**

| **System organ class**<br>Adverse Reaction | **Frequency of adverse reactions[1]** |
|---|---|
| **Gastrointestinal disorders** | |
| Nausea | Common |
| Pancreatitis | Uncommon |
| **Immune system disorders** | |
| Hypersensitivity reactions[2] (see sections 4.3 and 4.4) | Uncommon |
| Anaphylactic reactions including anaphylactic shock (see sections 4.3 and 4.4) | Rare |
| **Skin and subcutaneous tissue disorders** | |
| Angioedema (see sections 4.3 and 4.4) | Rare |
| Dermatitis | Uncommon |
| Pruritus | Uncommon |
| Rash[2] | Common |
| Urticaria | Uncommon |

[1] Frequency estimates are based on the pooled analysis of the saxagliptin monotherapy, add-on to metformin and initial combination with metformin, add-on to sulphonylurea and add-on to thiazolidinedione clinical trials.

[2] These reactions were also identified in the pre-approval clinical trials, but do not meet the criteria for Table 1.

*Description of selected adverse reactions*

AEs, considered by the investigator to be at least possibly drug-related and reported in at least two more patients treated with saxagliptin 5 mg compared to control, are described below by treatment regimen.

As monotherapy: dizziness (common) and fatigue (common).

As add-on to metformin: dyspepsia (common) and myalgia (common).

As initial combination with metformin: gastritis (common), arthralgia (uncommon), myalgia (uncommon), and erectile dysfunction (uncommon).

As add-on to metformin and a sulphonylurea: dizziness (common), fatigue (common) and flatulence (common).

*Hypoglycaemia*
Adverse reactions of hypoglycaemia were based on all reports of hypoglycaemia; a concurrent glucose measurement was not required. The incidence of reported hypoglycaemia for saxagliptin 5 mg versus placebo given as add-on therapy to metformin was 5.8% versus 5%. The incidence of reported hypoglycaemia was 3.4% in treatment--naive patients given saxagliptin 5 mg plus metformin and 4.0% in patients given metformin alone. When used as add-on to insulin (with or without metformin), the overall incidence of reported hypoglycaemia was 18.4% for saxagliptin 5 mg and 19.9% for placebo.

When used as add-on to metformin plus a sulphonylurea, the overall incidence of reported hypoglycemia was 10.2 % for saxagliptin 5 mg and 6.3% for placebo.

*Investigations*
Across clinical studies, the incidence of laboratory AEs was similar in patients treated with saxagliptin 5 mg compared to patients treated with placebo. A small decrease in absolute lymphocyte count was observed. From a baseline mean absolute lymphocyte count of approximately 2,200 cells/µl, a mean decrease of approximately 100 cells/µl relative to placebo was observed in the placebo-controlled-pooled analysis. Mean absolute lymphocyte counts remained stable with daily dosing up to 102 weeks in duration. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions. The clinical significance of this decrease in lymphocyte count relative to placebo is not known.

Metformin
*Clinical trial data and post-marketing data*
Table 3 presents adverse reactions by system organ class and by frequency category. Frequency categories are based on information available from metformin Summary of Product Characteristics available in the European Union.

**Table 3 The frequency of metformin adverse reactions identified from clinical trial and postmarketing data**

| System organ class<br>Adverse reaction | Frequency |
|---|---|
| **Metabolism and nutrition disorders** | |
| Lactic acidosis | Very rare |
| Vitamin B12 deficiency[1] | Very rare |
| **Nervous system disorders** | |
| Metallic taste | Common |
| **Gastrointestinal disorders** | |
| Gastrointestinal symptoms[2] | Very common |
| **Hepatobiliary disorders** | |
| Liver function disorders, hepatitis | Very rare |
| **Skin and subcutaneous tissue disorders** | |
| Urticaria, erythema, pruritis | Very rare |

[1] Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency (e.g., megaloblastic anaemia).

[2] Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.

### 4.9 Overdose

No data are available with regard to overdose of Komboglyze.

Saxagliptin
Saxagliptin has been shown to be well-tolerated with no clinically meaningful effect on QTc interval or heart rate at oral doses up to 400 mg daily for 2 weeks (80 times the recommended dose). In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its major metabolite can be removed by haemodialysis (23% of dose over 4 hours).

Metformin
High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose lowering drugs, ATC code: A10BD10.

Mechanism of action and pharmacodynamic effects
Komboglyze combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: saxagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Saxagliptin
Saxagliptin is a highly potent (Ki: 1.3 nM), selective, reversible, competitive, DPP-4 inhibitor. In patients with type 2 diabetes, administration of saxagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load, this DPP-4 inhibition resulted in a 2-to 3-fold increase in circulating levels of active incretin hormones, including glucagon-like peptide-1 (GLP-1) and

glucose-dependent insulinotropic polypeptide (GIP), decreased glucagon concentrations and increased glucose-dependent beta-cell responsiveness, which resulted in higher insulin and C-peptide concentrations. The rise in insulin from pancreatic beta-cells and the decrease in glucagon from pancreatic alpha-cells were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal. Saxagliptin improves glycaemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes.

Metformin
Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via three mechanisms:
- by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis in muscle;
- by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation;
- by delaying intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDLc and triglyceride levels.

Clinical efficacy and safety
*Saxagliptin in combination with metformin*
The coadministration of saxagliptin and metformin has been studied in patients with type 2 diabetes inadequately controlled on metformin alone and in treatment-naive patients inadequately controlled on diet and exercise alone. 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 combination with metformin (initial or add-on therapy). Reductions in A1c were seen across subgroups including gender, age, race, and baseline BMI. Decrease in body weight in the treatment groups given saxagliptin in combination with metformin was similar to that in the groups given metformin alone. Saxagliptin plus metformin was not associated with significant changes from baseline in fasting serum lipids compared to metformin alone.

*Saxagliptin add-on to metformin therapy*
An add-on to metformin placebo-controlled study of 24-week duration was conducted to evaluate the efficacy and safety of saxagliptin in combination with metformin in patients with inadequate glycaemic control (HbA1c 7-10%) on metformin alone. Saxagliptin (n=186) provided significant improvements in HbA1c, FPG and PPG compared to placebo (n=175). Improvements in HbA1c, PPG, and FPG following treatment with saxagliptin 5 mg plus metformin were sustained up to Week 102. The HbA1c change for saxagliptin 5 mg plus metformin (n=31) compared to placebo plus metformin (n=15) was -0.8% at Week 102.

*Saxagliptin twice daily add-on to metformin therapy*
An add-on to metformin placebo-controlled study of 12-week duration was conducted to evaluate the efficacy and safety of saxagliptin 2.5 mg twice daily in combination with metformin in patients with inadequate glycaemic control (HbA1c 7-10%) on metformin alone. After 12 weeks, the saxagliptin group (n=74) had a greater HbA1c mean reduction from baseline than the placebo group (n=86) (-0.6% vs. -0.2%, respectively, difference of -0.34%, from a mean baseline HbA1c of 7.9% for the saxagliptin group and 8.0% for the placebo group), and a greater FPG reduction (-13.73 mg/dl versus –4.22 mg/dl) but without statistical significance (p=0.12, 95% CI [-21.68; 2.66]).

*Saxagliptin add-on to metformin compared with sulphonylurea add-on to metformin*
A 52-week study was conducted to evaluate the efficacy and safety of saxagliptin 5 mg in combination with metformin (428 patients) compared with sulphonylurea (glipizide, 5 mg titrated as needed to 20 mg, mean dose of 15 mg) in combination with metformin (430 patients) in 858 patients with inadequate glycaemic control (HbA1c 6.5%-10%) on metformin alone. The mean metformin dose was approximately 1900 mg in each treatment group. After 52 weeks, the saxagliptin and glipizide groups had similar mean reductions from baseline in HbA1c in the per-protocol analysis (-0.7% vs. -0.8%, respectively, mean baseline HbA1c of 7.5% for both groups). The intent-to-treat analysis showed consistent results. The reduction in FPG was slightly less in the saxagliptin-group and there were more discontinuations (3.5% vs. 1.2%) due to lack of efficacy based on FPG criteria during the first 24 weeks of the study. Saxagliptin also resulted in a significantly lower proportion of patients with hypoglycaemia, 3% (19 events in 13 subjects) vs. 36.3% (750 events in 156 patients) for glipizide. Patients treated with saxagliptin exhibited a significant decrease from baseline in body weight compared to a weight gain in patients administered glipizide (-1.1 vs. +1.1 kg).

*Saxagliptin add-on to metformin compared with sitagliptin add-on to metformin*
An 18-week study was conducted to evaluate the efficacy and safety of saxagliptin 5 mg in combination with metformin (403 patients), compared with sitagliptin 100 mg in combination with metformin (398 patients) in 801 patients with inadequate glycaemic control on metformin alone. After 18 weeks, saxagliptin was non-inferior to sitagliptin in mean reduction from baseline in HbA1c in both the per-protocol and the full analysis sets. The reductions from baseline in HbA1c respectively for saxagliptin and sitagliptin in the primary per-protocol analysis were -0.5% (mean and median) and -0.6% (mean and median). In the confirmatory full analysis set, mean reductions were -0.4% and -0.6% respectively for saxagliptin and sitagliptin, with median reductions of -0.5% for both groups.

*Saxagliptin in combination with metformin as initial therapy*
A 24-week study was conducted to evaluate the efficacy and safety of saxagliptin 5 mg in combination with metformin as initial combination therapy in treatment-naive patients with inadequate glycaemic control (HbA1c 8-12%). Initial therapy with the combination of saxagliptin 5 mg plus metformin (n=306) provided significant improvements in HbA1c, FPG and PPG compared to with either saxagliptin (n=317) or metformin (n=313) alone as initial therapy. Reductions in HbA1c from baseline to Week 24 were observed in all evaluated subgroups defined by baseline HbA1c, with greater reductions observed in patients with a baseline HbA1c ≥ 10% (see Table 4). Improvements in HbA1c, PPG, and FPG following initial therapy with saxagliptin 5 mg plus metformin were sustained up to Week 76. The HbA1c change for saxagliptin 5 mg plus metformin (n=177) compared to metformin plus placebo (n=147) was –0.5% at Week 76.

*Saxagliptin add-on combination therapy with insulin (with or without metformin)*
A total of 455 patients with type 2 diabetes participated in a 24-week randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of saxagliptin in combination with a stable dose of insulin (baseline mean: 54.2 Units) in patients with inadequate glycaemic control (HbA1c ≥ 7.5% and ≤ 11%) on insulin alone (n=141) or on insulin in combination with a stable dose of metformin (n=314). Saxagliptin 5 mg add-on to insulin with or without metformin provided significant improvements after 24 weeks in HbA1c and PPG compared with placebo add-on to insulin with or without metformin. Similar HbA1c reductions versus placebo were achieved for patients receiving saxagliptin 5 mg add-on to insulin regardless of metformin use (−0.4% for both subgroups). Improvements from baseline HbA1c were sustained in the saxagliptin add-on to insulin group compared to the placebo add-on to insulin group with or without metformin at Week 52. The HbA1c change for the saxagliptin group (n=244) compared to placebo (n=124) was -0.4% at Week 52.

*Saxagliptin add-on combination therapy with metformin and sulphonylurea*
A total of 257 patients with type 2 diabetes participated in a 24-week randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of saxagliptin (5 mg once daily) in combination with metformin plus sulphonylurea (SU) in patients with inadequate glycemic control (HbA1c ≥7% and ≤10%). Saxagliptin (n=127) provided significant improvements in HbA1c and PPG

compared with the placebo (n=128). The HbA1c change for saxagliptin compared to placebo was -0.7% at Week 24.

**Table 4 Key efficacy results in placebo-controlled, combination therapy studies of saxaglipin and metformin**

| | Mean baseline HbA1c (%) | Mean change[1] from baseline HbA1c (%) | Placebo-corrected mean change in HbA1c (%) (95% CI) |
|---|---|---|---|
| **ADD-ON/INITIAL COMBINATION WITH METFORMIN STUDIES** | | | |
| **24-weeks** | | | |
| Saxa 5 mg daily add-on to metformin; Study CV181014 (n=186) | 8.1 | -0.7 | -0.8 (-1.0, -0.6)[2] |
| Saxa 5 mg daily initial combination with metformin; Study CV181039[3]: | | | |
| Overall population (n=306) | 9.4 | -2.5 | -0.5 (-0.7, -0.4)[4] |
| Baseline HbA1c ≥ 10% stratum (n=107) | 10.8 | -3.3 | -0.6 (-0.9, -0.3)[5] |
| **12-weeks** | | | |
| Saxa 2.5 mg twice daily add-on to metformin; Study CV181080 (n=74) | 7.9 | -0.6 | -0.3 (-0.6,-0.1)[6] |
| **ADD-ON/COMBINATION STUDIES WITH ADDITIONAL THERAPIES** | | | |
| **Add on to insulin (+/- metformin)** | | | |
| Saxa 5 mg daily, Study CV181057: Overall population (n=300) | 8.7 | -0.7 | -0.4 (-0.6, -0.2)[2] |
| **24-weeks** | | | |
| Saxa 5 mg daily add on to metformin plus sulphonylurea; Study D1680L00006 (n=257) | 8.4 | -0.7 | -0.7 (-0.9, -0.5)[2] |

n=Randomized patients

[1] Adjusted mean change from baseline adjusted for baseline value (ANCOVA).

[2] $p < 0.0001$ compared to placebo.

[3] Metformin was uptitrated from 500 to 2000 mg per day as tolerated.

[4] Mean HbA1c change is the difference between the saxagliptin 5 mg + metformin and metformin alone groups ($p < 0.0001$).

[5] Mean HbA1c change is the difference between the saxagliptin 5 mg + metformin and metformin alone groups.

[6] p-value = 0.0063 (between group comparisons significant at $\alpha = 0.05$)

*Metformin*

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p=0.0034;
- a significant reduction of the absolute risk of any diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p=0.017;
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years, (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years (p=0.021);

- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years, (p=0.01).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Komboglyze in all subsets of the paediatric population in type 2 diabetes mellitus (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

The results of bioequivalence studies in healthy subjects demonstrated that Komboglyze combination tablets are bioequivalent to coadministration of corresponding doses of saxagliptin and metformin hydrochloride as individual tablets.

The following statements reflect the pharmacokinetic properties of the individual active substances of Komboglyze.

Saxagliptin
The pharmacokinetics of saxagliptin and its major metabolite were similar in healthy subjects and in patients with type 2 diabetes.

*Absorption*
Saxagliptin was rapidly absorbed after oral administration in the fasted state, with maximum plasma concentrations ($C_{max}$) of saxagliptin and its major metabolite attained within 2 and 4 hours ($T_{max}$), respectively. The $C_{max}$ and AUC values of saxagliptin and its major metabolite increased proportionally with the increment in the saxagliptin dose, and this dose-proportionality was observed in doses up to 400 mg. Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma AUC values for saxagliptin and its major metabolite were 78 ng·h/ml and 214 ng·h/ml, respectively. The corresponding plasma $C_{max}$ values were 24 ng/ml and 47 ng/ml, respectively. The intra-subject coefficients of variation for saxagliptin $C_{max}$ and AUC were less than 12%.

The inhibition of plasma DPP-4 activity by saxagliptin for at least 24 hours after oral administration of saxagliptin is due to high potency, high affinity, and extended binding to the active site.

*Interaction with food*
Food had relatively modest effects on the pharmacokinetics of saxagliptin in healthy subjects. Administration with food (a high-fat meal) resulted in no change in saxagliptin $C_{max}$ and a 27% increase in AUC compared with the fasted state. The time for saxagliptin to reach $C_{max}$ ($T_{max}$) was increased by approximately 0.5 hours with food compared with the fasted state. These changes were not considered to be clinically meaningful.

*Distribution*
The *in vitro* protein binding of saxagliptin and its major metabolite in human serum is negligible. Thus, changes in blood protein levels in various disease states (e.g., renal or hepatic impairment) are not expected to alter the disposition of saxagliptin.

*Biotransformation*
The biotransformation of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major metabolite of saxagliptin is also a selective, reversible, competitive DPP-4 inhibitor, half as potent as saxagliptin.

*Elimination*
The mean plasma terminal half-life ($t_{1/2}$) values for saxagliptin and its major metabolite are 2.5 hours and 3.1 hours respectively, and the mean $t_{1/2}$ value for plasma DPP-4 inhibition was 26.9 hours. Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50 mg dose of $^{14}$C-saxagliptin, 24%, 36%, and 75% of the dose was excreted in the urine as saxagliptin, its major

metabolite, and total radioactivity respectively. The average renal clearance of saxagliptin (~230 ml/min) was greater than the average estimated glomerular filtration rate (~120 ml/min), suggesting some active renal excretion. For the major metabolite, renal clearance values were comparable to estimated glomerular filtration rate. A total of 22% of the administered radioactivity was recovered in faeces representing the fraction of the saxagliptin dose excreted in bile and/or unabsorbed medicinal product from the gastrointestinal tract.

*Linearity*
The $C_{max}$ and AUC of saxagliptin and its major metabolite increased proportionally to the saxagliptin dose. No appreciable accumulation of either saxagliptin or its major metabolite was observed with repeated once-daily dosing at any dose level. No dose- and time-dependence was observed in the clearance of saxagliptin and its major metabolite over 14 days of once-daily dosing with saxagliptin at doses ranging from 2.5 mg to 400 mg.

Special populations
*Renal impairment*
A single-dose, open-label study was conducted to evaluate the pharmacokinetics of a 10 mg oral dose of saxagliptin in subjects with varying degrees of chronic renal impairment compared to subjects with normal renal function. In subjects with mild (> 50 to ≤ 80 ml/min), moderate (≥ 30 to ≤ 50 ml/min), or severe (19-30 ml/min) renal impairment the exposures to saxagliptin were 1.2-, 1.4- and 2.1-fold higher, respectively, and the exposures to BMS-510849 were 1.7-, 2.9-, and 4.5-fold higher, respectively, than those observed in subjects with normal renal function (> 80 ml/min).

*Hepatic impairment*
In subjects with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), or severe (Child-Pugh Class C) hepatic impairment the exposures to saxagliptin were 1.1-, 1.4- and 1.8-fold higher, respectively, and the exposures to BMS-510849 were 22%, 7%, and 33% lower, respectively, than those observed in healthy subjects.

*Elderly patients (≥ 65 years)*
Elderly patients (65-80 years) had about 60% higher saxagliptin AUC than young patients (18-40 years). This is not considered clinically meaningful, therefore, no dose adjustment for Komboglyze is recommended on the basis of age alone.

Metformin
*Absorption*
After an oral dose of metformin, $t_{max}$ is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 μg/ml. In controlled clinical trials, maximum metformin plasma levels ($C_{max}$) did not exceed 4 μg/ml, even at maximum doses.

*Interaction with food*
Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.

*Distribution*
Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean $V_d$ ranged between 63-276 l.

*Biotransformation*
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

*Elimination*
Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

## 5.3 Preclinical safety data

Coadministration of saxagliptin and metformin
A 3-month dog study and embryo-foetal development studies in rats and rabbits have been conducted with the combination of saxagliptin and metformin.

Coadministration of saxagliptin and metformin, to pregnant rats and rabbits during the period of organogenesis, was neither embryolethal nor teratogenic in either species when tested at doses yielding systemic exposures (AUC) up to 100 and 10 times the maximum recommended human doses (RHD; 5 mg saxagliptin and 2000 mg metformin), respectively, in rats; and 249 and 1.1 times the RHDs in rabbits. In rats, minor developmental toxicity was limited to an increased incidence of delayed ossification ("wavy ribs"); associated maternal toxicity was limited to weight decrements of 5-6% over the course of gestation days 13 through 18, and related reductions in maternal food consumption. In rabbits, coadministration was poorly tolerated in many mothers, resulting in death, moribundity or abortion. However, among surviving mothers with evaluable litters, maternal toxicity was limited to marginal reductions in body weight over the course of gestation days 21 to 29; and associated developmental toxicity in these litters was limited to fetal body weight decrements of 7%, and a low incidence of delayed ossification of the fetal hyoid.

A 3-month dog study was conducted with the combination of saxagliptin and metformin. No combination toxicity was observed at AUC exposures 68 and 1.5 times the RHDs for saxagliptin and metformin, respectively.

No animal studies have been conducted with the combination of products in Komboglyze to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on the findings in the studies with saxagliptin and metformin individually.

Saxagliptin
In cynomolgus monkeys saxagliptin produced reversible skin lesions (scabs, ulcerations and necrosis) in extremities (tail, digits, scrotum and/or nose) at doses ≥ 3 mg/kg/day. The no effect level (NOEL) for the lesions is 1 and 2 times the human exposure of saxagliptin and the major metabolite respectively, at the recommended human dose of 5 mg/day (RHD).

The clinical relevance of the skin lesions is not known, however clinical correlates to skin lesions in monkeys have not been observed in human clinical trials of saxagliptin.

Immune related findings of minimal, nonprogressive, lymphoid hyperplasia in spleen, lymph nodes and bone marrow with no adverse sequelae have been reported in all species tested at exposures starting from 7 times the RHD.

Saxagliptin produced gastrointestinal toxicity in dogs, including bloody/mucoid faeces and enteropathy at higher doses with a NOEL 4 and 2 times the human exposure for saxagliptin and the major metabolite, respectively, at RHD.

Saxagliptin was not genotoxic in a conventional battery of genotoxicity studies *in vitro* and *in vivo*. No carcinogenic potential was observed in two-year carcinogenicity assays with mice and rats.

Effects on fertility were observed in male and female rats at high doses producing overt signs of toxicity. Saxagliptin was not teratogenic at any doses evaluated in rats or rabbits. At high doses in rats, saxagliptin caused reduced ossification (a developmental delay) of the foetal pelvis and decreased foetal body weight (in the presence of maternal toxicity), with a NOEL 303 and 30 times the human exposure for saxagliptin and the major metabolite, respectively, at RHD. In rabbits, the effects of saxagliptin were limited to minor skeletal variations observed only at maternally toxic doses (NOEL 158 and 224 times the human exposure for saxagliptin and the major metabolite, respectively at RHD). In a pre- and postnatal developmental study in rats, saxagliptin caused decreased pup weight at maternally toxic doses, with NOEL 488 and 45 times the human exposure for saxagliptin and the major metabolite, respectively at RHD. The effect on offspring body weights were noted until postnatal day 92 and 120 in females and males, respectively.

Metformin
Preclinical data for metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core
Povidone K30
Magnesium stearate

Film coating
Polyvinyl alcohol
Macrogol 3350
Titanium dioxide (E171)
Talc (E553b)
Iron oxide red (E172)
Iron oxide yellow (E172)

Printing ink
Shellac
Indigo carmine aluminium lake (E132)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

36 months

### 6.4 Special precautions for storage

Store below 25°C.

### 6.5 Nature and contents of container

Alu/Alu blister.
Pack-sizes of 14, 28, 56 and 60 film-coated tablets in non-perforated blisters.
Multipacks containing 112 (2 packs of 56) and 196 (7 packs of 28) film-coated tablets in non-perforated blisters.
60x1 film-coated tablets in perforated unit dose blisters.
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/AstraZeneca EEIG
Bristol-Myers Squibb House
Uxbridge Business Park
Sanderson Road
Uxbridge
Middlesex
UB8 1DH
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/731/001
EU/1/11/731/002
EU/1/11/731/003
EU/1/11/731/004
EU/1/11/731/005
EU/1/11/731/006
EU/1/11/731/013

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 November, 2011

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

## 1. NAME OF THE MEDICINAL PRODUCT

Komboglyze 2.5 mg/1,000 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5 mg of saxagliptin (as hydrochloride) and 1,000 mg of metformin hydrochloride.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Pale yellow to light yellow, biconvex, oval shaped, film-coated tablets, with "2.5/1000" printed on one side and "4247" printed on the other side, in blue ink.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Komboglyze is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus inadequately controlled on their maximally tolerated dose of metformin alone or those already being treated with the combination of saxagliptin and metformin as separate tablets.

Komboglyze is also indicated in combination with insulin (ie, triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus when insulin and metformin alone do not provide adequate glycaemic control.

Komboglyze is also indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus when the maximally tolerated dose of both metformin and the sulphonylurea does not provide adequate glycaemic control.

### 4.2 Posology and method of administration

Posology
*For patients inadequately controlled on maximal tolerated dose of metformin monotherapy*
Patients not adequately controlled on metformin alone should receive a dose of Komboglyze equivalent to the total daily dose of saxagliptin 5 mg, dosed as 2.5 mg twice daily, plus the dose of metformin already being taken.

*For patients switching from separate tablets of saxagliptin and metformin*
Patients switching from separate tablets of saxagliptin and metformin should receive the doses of saxagliptin and metformin already being taken.

*For patients inadequately controlled on dual combination therapy of insulin and metformin, or, for patients controlled on triple combination therapy of insulin, and metformin plus saxagliptin as separate tablets.*

The dose of Komboglyze should provide saxagliptin 2.5 mg twice daily (5 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Komboglyze is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycaemia (see section 4.4).

*For patients inadequately controlled on dual combination therapy of a sulphonylurea and metformin, or for patients switching from triple combination therapy of saxagliptin, metformin and a sulphonylurea taken as separate tablets.*
The dose of Komboglyze should provide saxagliptin 2.5 mg twice daily (5 mg total daily dose), and a dose of metformin similar to the dose already being taken. When Komboglyze is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be required to reduce the risk of hypoglycaemia (see section 4.4).

*Special populations*
*Renal impairment*
No dose adjustment is recommended for patients with mild renal impairment. Komboglyze should not be used in patients with moderate to severe renal impairment (see sections 4.3, 4.4 and 5.2).

*Hepatic impairment*
Komboglyze should not be used in patients with hepatic impairment (see sections 4.3 and 5.2).

*Elderly (≥ 65 years)*
As metformin and saxagliptin are excreted by the kidney, Komboglyze should be used with caution in the elderly. Monitoring of renal function is necessary to prevent metformin-associated lactic acidosis, particularly in the elderly (see sections 4.3 and 4.4). Experience with saxagliptin in patients aged 75 years and older is very limited and caution should be exercised when treating this population (see sections 4.4 and 5.2).

*Paediatric population*
The safety and efficacy of Komboglyze in children from birth to < 18 years of age have not been established. No data are available.

Method of administration
Komboglyze should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin.

## 4.3 Contraindications

Komboglyze is contraindicated in patients with:

- hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1, or history of a serious hypersensitivity reaction, including anaphylactic reaction, anaphylactic shock, and angioedema, to any dipeptidyl peptidase 4 (DPP4) inhibitor (see sections 4.4 and 4.8);
- diabetic ketoacidosis, diabetic pre-coma;
- moderate and severe renal impairment (creatinine clearance < 60 ml/min) (see section 4.4);
- acute conditions with the potential to alter renal function such as:
  - dehydration,
  - severe infection,
  - shock;
- acute or chronic disease which may cause tissue hypoxia such as:
  - cardiac or respiratory failure,
  - recent myocardial infarction,
  - shock;
- hepatic impairment (see sections 4.2 and 5.2);
- acute alcohol intoxication, alcoholism (see section 4.5);
- breastfeeding (see section 4.6).

## 4.4 Special warnings and precautions for use

General
Komboglyze should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

Komboglyze is not a substitute for insulin in insulin-requiring patients.

Pancreatitis
In post-marketing experience with saxagliptin, there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of saxagliptin. If pancreatitis is suspected, Komboglyze and other potentially suspect medicinal products should be discontinued.

Lactic acidosis
Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin, a component of Komboglyze, accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any conditions associated with hypoxia.

*Diagnosis*
Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/l, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient hospitalised immediately (see section 4.9).

Renal function
As metformin is excreted by the kidney, serum creatinine concentrations should be determined regularly:
- at least once a year in patients with normal renal function
- at least two to four times a year in patients with serum creatinine levels at or above the upper limit of normal and in elderly patients.

Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy or when starting treatment with a nonsteroidal anti-inflammatory drug (NSAID).

Surgery
As Komboglyze contains metformin, the treatment should be discontinued 48 hours before elective surgery with general, spinal or epidural anaesthesia. Komboglyze should not usually be resumed earlier than 48 hours afterwards and only after renal function has been re-evaluated and found to be normal.

Administration of iodinated contrast agent
The intravascular administration of iodinated contrast agents in radiological studies can lead to renal failure which has been associated with lactic acidosis in patients receiving metformin. Therefore, Komboglyze must be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 4.5).

Skin disorders
Ulcerative and necrotic skin lesions have been reported in extremities of monkeys in non-clinical toxicology studies for saxagliptin (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 event (AE) for saxagliptin (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.

Hypersensitivity reactions
As Komboglyze contains saxagliptin, it should not be used in patients who have had any serious hypersensitivity reaction to a dipeptidyl peptidase 4 (DPP4) inhibitor.

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. If a serious hypersensitivity reaction to saxagliptin is suspected, discontinue Komboglyze, assess for other potential causes for the event, and institute alternative treatment for diabetes (see sections 4.3 and 4.8).

Change in clinical status of patients with previously controlled type 2 diabetes
As Komboglyze contains metformin, a patient with type 2 diabetes previously well controlled on Komboglyze who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, Komboglyze must be stopped immediately and other appropriate corrective measures initiated.

Elderly patients
Experience in patients aged 75 years and older is very limited with saxagliptin and caution should be exercised when treating this population (see section 5.2).

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 saxagliptin 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 saxagliptin (see section 4.5).

Use with medicinal products known to cause hypoglycaemia
Insulin and sulphonylureas are known to cause hypoglycaemia. Therefore, a lower dose of insulin or sulphonylurea may be required to reduce the risk of hypoglycaemia when used in combination with Komboglyze.

## 4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of multiple doses of saxagliptin (2.5 mg twice daily) and metformin (1,000 mg twice daily) did not meaningfully alter the pharmacokinetics of either saxagliptin or metformin in patients with type 2 diabetes.

There have been no formal interaction studies for Komboglyze. The following statements reflect the information available on the individual active substances.

Saxagliptin

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, 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 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.

Concomitant administration of saxagliptin with the moderate inhibitor of CYP3A4/5 diltiazem, increased the $C_{max}$ 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 $C_{max}$ 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 $C_{max}$ 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).

The co-administration 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 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.

Metformin

*Combinations not recommended*

There is increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic impairment) due to the metformin active substance of Komboglyze (see section 4.4). Consumption of alcohol and medicinal products containing alcohol should be avoided.

Cationic substances that are eliminated by renal tubular secretion (e.g., cimetidine) may interact with metformin by competing for common renal tubular transport systems. A study conducted in seven normal healthy volunteers showed that cimetidine, administered as 400 mg twice daily, increased metformin systemic exposure (AUC) by 50% and $C_{max}$ by 81%. Therefore, close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are co-administered.

The intravascular administration of iodinated contrast agents in radiological studies may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. Therefore Komboglyze must be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 4.4).

*Combination requiring precautions for use*
Glucocorticoids (given by systemic and local routes), beta-2agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring perfomed, especially at the beginning of treatment with such medicinal products. If necessary, the dose of the anti-hyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
The use of Komboglyze or saxagliptin has not been studied in pregnant women. Studies in animals have shown reproductive toxicity at high doses of saxagliptin alone or in combination with metformin (see section 5.3). The potential risk for humans is unknown. A limited amount of data suggest the use of metformin in pregnant women is not associated with an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development (see section 5.3). Komboglyze should not be used during pregnancy. If the patient wishes to become pregnant, or if a pregnancy occurs, treatment with Komboglyze should be discontinued and switched to insulin treatment as soon as possible.

Breast-feeding
Studies in animals have shown excretion of both saxagliptin and/or metabolite and metformin in milk. It is unknown whether saxagliptin is excreted in human milk, but metformin is excreted in human milk in small amounts. Komboglyze must therefore not be used in women who are breastfeeding (see section 4.3).

Fertility
The effect of saxagliptin on fertility in humans has not been studied. Effects on fertility were observed in male and female rats at high doses producing overt signs of toxicity (see section 5.3). For metformin, studies in animals have not shown reproductive toxicity (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Saxagliptin or metformin may have a negligible influence on the ability to drive and use machines. 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 Komboglyze is used in combination with other antidiabetic medicinal products known to cause hypoglycaemia (e.g. insulin, sulphonylureas).

## 4.8 Undesirable effects

There have been no therapeutic clinical trials conducted with Komboglyze tablets, however bioequivalence of Komboglyze with co-administered saxagliptin and metformin has been demonstrated (see section 5.2).

Saxagliptin
*Summary of the safety profile*
There were 4,148 patients with type 2 diabetes, including 3,021 patients treated with saxagliptin, randomised in six double-blind, controlled clinical safety and efficacy studies conducted to evaluate the effects of saxagliptin on glycaemic control.

In a pooled analysis, the overall incidence of AEs in patients treated with saxagliptin 5 mg was similar to placebo. Discontinuation of therapy due to AEs was higher in patients who received saxagliptin 5 mg as compared to placebo (3.3% as compared to 1.8%).

*Tabulated list of adverse reactions*

Adverse reactions reported in ≥ 5% of patients treated with saxagliptin 5 mg and more commonly than in patients treated with placebo or that were reported in ≥ 2% of patients treated with saxagliptin 5 mg and ≥ 1% more frequently compared to placebo are shown in Table 1.

The adverse reactions are listed by system organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to 1/100), rare (≥ 1/10,000 to 1/1,000), or very rare (< 1/10,000), not known (cannot be estimated from the available data).

**Table 1 Frequency of adverse reactions by system organ class**

| **System organ class**<br>Adverse reaction | **Frequency of adverse reactions by treatment regimen**<br><br>**Saxagliptin with metformin[1]** |
|---|---|
| **Infections and infestations** | |
| Upper respiratory infection | Common |
| Urinary tract infection | Common |
| Gastroenteritis | Common |
| Sinusitis | Common |
| Nasopharyngitis | Common[2] |
| **Nervous system disorders** | |
| Headache | Common |
| **Gastrointestinal disorders** | |
| Vomiting | Common |

[1]Includes saxagliptin in add-on to metformin and initial combination with metformin.

[2]Only in the initial combination therapy.

*Postmarketing experience from clinical trials and spontaneous reports*

Table 2 shows additional adverse reactions which have been reported in postmarketing experience with saxagliptin. The frequencies are based on the experience from clinical trials.

**Table 2 Frequency of additional adverse reactions by system organ class**

| **System organ class**<br>Adverse Reaction | **Frequency of adverse reactions[1]** |
|---|---|
| **Gastrointestinal disorders** | |
| Nausea | Common |
| Pancreatitis | Uncommon |
| **Immune system disorders** | |
| Hypersensitivity reactions[2] (see sections 4.3 and 4.4) | Uncommon |
| Anaphylactic reactions including anaphylactic shock (see sections 4.3 and 4.4) | Rare |
| **Skin and subcutaneous tissue disorders** | |
| Angioedema (see sections 4.3 and 4.4) | Rare |
| Dermatitis | Uncommon |
| Pruritus | Uncommon |
| Rash[2] | Common |
| Urticaria | Uncommon |

[1] Frequency estimates are based on the pooled analysis of the saxagliptin monotherapy, add-on to metformin and initial combination with metformin, add-on to sulphonylurea and add-on to thiazolidinedione clinical trials.

[2] These reactions were also identified in the pre-approval clinical trials, but do not meet the criteria for Table 1.

*Description of selected adverse reactions*

AEs, considered by the investigator to be at least possibly drug-related and reported in at least two more patients treated with saxagliptin 5 mg compared to control, are described below by treatment regimen.

As monotherapy: dizziness (common) and fatigue (common).

As add-on to metformin: dyspepsia (common) and myalgia (common).

As initial combination with metformin: gastritis (common), arthralgia (uncommon), myalgia (uncommon), and erectile dysfunction (uncommon).

As add-on to metformin and a sulphonylurea: dizziness (common), fatigue (common) and flatulence (common).

*Hypoglycaemia*
Adverse reactions of hypoglycaemia were based on all reports of hypoglycaemia; a concurrent glucose measurement was not required. The incidence of reported hypoglycaemia for saxagliptin 5 mg versus placebo given as add-on therapy to metformin was 5.8% versus 5%. The incidence of reported hypoglycaemia was 3.4% in treatment--naive patients given saxagliptin 5 mg plus metformin and 4.0% in patients given metformin alone. When used as add on to insulin (with or without metformin), the overall incidence of reported hypoglycaemia was 18.4% for saxagliptin 5 mg and 19.9% for placebo.

When used as add-on to metformin plus a sulphonylurea, the overall incidence of reported hypoglycemia was 10.2 % for saxagliptin 5 mg and 6.3% for placebo.

*Investigations*
Across clinical studies, the incidence of laboratory AEs was similar in patients treated with saxagliptin 5 mg compared to patients treated with placebo. A small decrease in absolute lymphocyte count was observed. From a baseline mean absolute lymphocyte count of approximately 2,200 cells/µl, a mean decrease of approximately 100 cells/µl relative to placebo was observed in the placebo-controlled-pooled analysis. Mean absolute lymphocyte counts remained stable with daily dosing up to 102 weeks in duration. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions. The clinical significance of this decrease in lymphocyte count relative to placebo is not known.

Metformin
*Clinical trial data and post-marketing data*
Table 3 presents adverse reactions by system organ class and by frequency category. Frequency categories are based on information available from metformin Summary of Product Characteristics available in the European Union.

**Table 3 The frequency of metformin adverse reactions identified from clinical trial and postmarketing data**

| System organ class<br>Adverse reaction | Frequency |
|---|---|
| **Metabolism and nutrition disorders** | |
| Lactic acidosis | Very rare |
| Vitamin B12 deficiency[1] | Very rare |
| **Nervous system disorders** | |
| Metallic taste | Common |
| **Gastrointestinal disorders** | |
| Gastrointestinal symptoms[2] | Very common |
| **Hepatobiliary disorders** | |
| Liver function disorders, hepatitis | Very rare |
| **Skin and subcutaneous tissue disorders** | |
| Urticaria, erythema, pruritis | Very rare |

[1] Long-term treatment with metformin has been associated with a decrease in vitamin B12 absorption which may very rarely result in clinically significant vitamin B12 deficiency (e.g., megaloblastic anaemia).

[2] Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.

### 4.9 Overdose

No data are available with regard to overdose of Komboglyze.

Saxagliptin
Saxagliptin has been shown to be well-tolerated with no clinically meaningful effect on QTc interval or heart rate at oral doses up to 400 mg daily for 2 weeks (80 times the recommended dose). In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its major metabolite can be removed by haemodialysis (23% of dose over 4 hours).

Metformin
High overdose or concomitant risks of metformin may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose lowering drugs, ATC code: A10BD10.

Mechanism of action and pharmacodynamic effects
Komboglyze combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: saxagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Saxagliptin
Saxagliptin is a highly potent (Ki: 1.3 nM), selective, reversible, competitive, DPP-4 inhibitor. In patients with type 2 diabetes, administration of saxagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load, this DPP-4 inhibition resulted in a 2-to 3-fold increase in circulating levels of active incretin hormones, including glucagon-like peptide-1 (GLP-1) and

glucose-dependent insulinotropic polypeptide (GIP), decreased glucagon concentrations and increased glucose-dependent beta-cell responsiveness, which resulted in higher insulin and C-peptide concentrations. The rise in insulin from pancreatic beta-cells and the decrease in glucagon from pancreatic alpha-cells were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal. Saxagliptin improves glycaemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes.

Metformin
Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via three mechanisms:
- by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis in muscle;
- by modestly increasing insulin sensitivity, improving peripheral glucose uptake and utilisation;
- by delaying intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDLc and triglyceride levels.

Clinical efficacy and safety
*Saxagliptin in combination with metformin*
The coadministration of saxagliptin and metformin has been studied in patients with type 2 diabetes inadequately controlled on metformin alone and in treatment-naive patients inadequately controlled on diet and exercise alone. 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 combination with metformin (initial or add-on therapy). Reductions in A1c were seen across subgroups including gender, age, race, and baseline BMI. Decrease in body weight in the treatment groups given saxagliptin in combination with metformin was similar to that in the groups given metformin alone. Saxagliptin plus metformin was not associated with significant changes from baseline in fasting serum lipids compared to metformin alone.

*Saxagliptin add-on to metformin therapy*
An add-on to metformin placebo-controlled study of 24-week duration was conducted to evaluate the efficacy and safety of saxagliptin in combination with metformin in patients with inadequate glycaemic control (HbA1c 7-10%) on metformin alone. Saxagliptin (n=186) provided significant improvements in HbA1c, FPG and PPG compared to placebo (n=175). Improvements in HbA1c, PPG, and FPG following treatment with saxagliptin 5 mg plus metformin were sustained up to Week 102. The HbA1c change for saxagliptin 5 mg plus metformin (n=31) compared to placebo plus metformin (n=15) was –0.8% at Week 102.

*Saxagliptin twice daily add-on to metformin therapy*
An add-on to metformin placebo-controlled study of 12-week duration was conducted to evaluate the efficacy and safety of saxagliptin 2.5 mg twice daily in combination with metformin in patients with inadequate glycaemic control (HbA1c 7-10%) on metformin alone. After 12 weeks, the saxagliptin group (n=74) had a greater HbA1c mean reduction from baseline than the placebo group (n=86) (-0.6% vs. -0.2%, respectively, difference of –0.34%, from a mean baseline HbA1c of 7.9% for the saxagliptin group and 8.0% for the placebo group), and a greater FPG reduction (-13.73 mg/dl versus –4.22 mg/dl) but without statistical significance (p=0.12, 95% CI [-21.68; 2.66]).

*Saxagliptin add-on to metformin compared with sulphonylurea add-on to metformin*
A 52-week study was conducted to evaluate the efficacy and safety of saxagliptin 5 mg in combination with metformin (428 patients) compared with sulphonylurea (glipizide, 5 mg titrated as needed to 20 mg, mean dose of 15 mg) in combination with metformin (430 patients) in 858 patients with inadequate glycaemic control (HbA1c 6.5%-10%) on metformin alone. The mean metformin dose was approximately 1900 mg in each treatment group. After 52 weeks, the saxagliptin and glipizide groups had similar mean reductions from baseline in HbA1c in the per-protocol analysis (-0.7% vs. -0.8%, respectively, mean baseline HbA1c of 7.5% for both groups). The intent-to-treat analysis showed consistent results. The reduction in FPG was slightly less in the saxagliptin-group and there were more discontinuations (3.5% vs. 1.2%) due to lack of efficacy based on FPG criteria during the first 24 weeks of the study. Saxagliptin also resulted in a significantly lower proportion of patients with hypoglycaemia, 3% (19 events in 13 subjects) vs. 36.3% (750 events in 156 patients) for glipizide. Patients treated with saxagliptin exhibited a significant decrease from baseline in body weight compared to a weight gain in patients administered glipizide (-1.1 vs. +1.1 kg).

*Saxagliptin add-on to metformin compared with sitagliptin add-on to metformin*
An 18-week study was conducted to evaluate the efficacy and safety of saxagliptin 5 mg in combination with metformin (403 patients), compared with sitagliptin 100 mg in combination with metformin (398 patients) in 801 patients with inadequate glycaemic control on metformin alone. After 18 weeks, saxagliptin was non-inferior to sitagliptin in mean reduction from baseline in HbA1c in both the per-protocol and the full analysis sets. The reductions from baseline in HbA1c respectively for saxagliptin and sitagliptin in the primary per-protocol analysis were -0.5% (mean and median) and -0.6% (mean and median). In the confirmatory full analysis set, mean reductions were -0.4% and -0.6% respectively for saxagliptin and sitagliptin, with median reductions of -0.5% for both groups.

*Saxagliptin in combination with metformin as initial therapy*
A 24-week study was conducted to evaluate the efficacy and safety of saxagliptin 5 mg in combination with metformin as initial combination therapy in treatment-naive patients with inadequate glycaemic control (HbA1c 8-12%). Initial therapy with the combination of saxagliptin 5 mg plus metformin (n=306) provided significant improvements in HbA1c, FPG and PPG compared to with either saxagliptin (n=317) or metformin (n=313) alone as initial therapy. Reductions in HbA1c from baseline to Week 24 were observed in all evaluated subgroups defined by baseline HbA1c, with greater reductions observed in patients with a baseline HbA1c $\geq$ 10% (see Table 4). Improvements in HbA1c, PPG, and FPG following initial therapy with saxagliptin 5 mg plus metformin were sustained up to Week 76. The HbA1c change for saxagliptin 5 mg plus metformin (n=177) compared to metformin plus placebo (n=147) was –0.5% at Week 76.

*Saxagliptin add-on combination therapy with insulin (with or without metformin)*
A total of 455 patients with type 2 diabetes participated in a 24-week randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of saxagliptin in combination with a stable dose of insulin (baseline mean: 54.2 Units) in patients with inadequate glycaemic control (HbA1c $\geq$ 7.5% and $\leq$ 11%) on insulin alone (n=141) or on insulin in combination with a stable dose of metformin (n=314). Saxagliptin 5 mg add-on to insulin with or without metformin provided significant improvements after 24 weeks in HbA1c and PPG compared with placebo add-on to insulin with or without metformin. Similar HbA1c reductions versus placebo were achieved for patients receiving saxagliptin 5 mg add-on to insulin regardless of metformin use (−0.4% for both subgroups). Improvements from baseline HbA1c were sustained in the saxagliptin add-on to insulin group compared to the placebo add-on to insulin group with or without metformin at Week 52. The HbA1c change for the saxagliptin group (n=244) compared to placebo (n=124) was -0.4% at Week 52.

*Saxagliptin add-on combination therapy with metformin and sulphonylurea*
A total of 257 patients with type 2 diabetes participated in a 24-week randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of saxagliptin (5 mg once daily) in combination with metformin plus sulphonylurea (SU) in patients with inadequate glycemic control (HbA1c $\geq$7% and $\leq$10%). Saxagliptin (n=127) provided significant improvements in HbA1c and PPG

compared with the placebo (n=128). The HbA1c change for saxagliptin compared to placebo was -0.7% at Week 24.

**Table 4 Key efficacy results in placebo-controlled, combination therapy studies of saxaglipin and metformin**

| | Mean baseline HbA1c (%) | Mean change[1] from baseline HbA1c (%) | Placebo-corrected mean change in HbA1c (%) (95% CI) |
|---|---|---|---|
| **ADD-ON/INITIAL COMBINATION WITH METFORMIN STUDIES** | | | |
| **24-weeks** | | | |
| Saxa 5 mg daily add-on to metformin; Study CV181014 (n=186) | 8.1 | -0.7 | -0.8 (-1.0, -0.6)[2] |
| Saxa 5 mg daily initial combination with metformin; Study CV181039[3] | | | |
| Overall population (n=306) | 9.4 | -2.5 | -0.5 (-0.7, -0.4)[4] |
| Baseline HbA1c ≥ 10% stratum (n=107) | 10.8 | -3.3 | -0.6 (-0.9, -0.3)[5] |
| **12-weeks** | | | |
| Saxa 2.5 mg twice daily add-on to metformin; Study CV181080 (n=74) | 7.9 | -0.6 | -0.3 (-0.6,-0.1)[6] |
| **ADD-ON/COMBINATION STUDIES WITH ADDITIONAL THERAPIES** | | | |
| **Add on to insulin (+/- metformin)** | | | |
| Saxa 5 mg daily, Study CV181057: Overall population (n=300) | 8.7 | -0.7 | -0.4 (-0.6, -0.2)[2] |
| **24-weeks** | | | |
| Saxa 5 mg daily add on to metformin plus sulphonylurea; Study D1680L00006 (n=257) | 8.4 | -0.7 | -0.7 (-0.9, -0.5)[2] |

n=Randomized patients

[1] Adjusted mean change from baseline adjusted for baseline value (ANCOVA).

[2] $p < 0.0001$ compared to placebo.

[3] Metformin was uptitrated from 500 to 2000 mg per day as tolerated.

[4] Mean HbA1c change is the difference between the saxagliptin 5 mg + metformin and metformin alone groups ($p < 0.0001$).

[5] Mean HbA1c change is the difference between the saxagliptin 5 mg + metformin and metformin alone groups.

[6] p-value = 0.0063 (between group comparisons significant at $\alpha = 0.05$)

*Metformin*

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), p=0.0023, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p=0.0034;
- a significant reduction of the absolute risk of any diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p=0.017;
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years, (p=0.011), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years (p=0.021);

- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years, (p=0.01).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Komboglyze in all subsets of the paediatric population in type 2 diabetes mellitus (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

The results of bioequivalence studies in healthy subjects demonstrated that Komboglyze combination tablets are bioequivalent to coadministration of corresponding doses of saxagliptin and metformin hydrochloride as individual tablets.

The following statements reflect the pharmacokinetic properties of the individual active substances of Komboglyze.

Saxagliptin
The pharmacokinetics of saxagliptin and its major metabolite were similar in healthy subjects and in patients with type 2 diabetes.

*Absorption*
Saxagliptin was rapidly absorbed after oral administration in the fasted state, with maximum plasma concentrations ($C_{max}$) of saxagliptin and its major metabolite attained within 2 and 4 hours ($T_{max}$), respectively. The $C_{max}$ and AUC values of saxagliptin and its major metabolite increased proportionally with the increment in the saxagliptin dose, and this dose-proportionality was observed in doses up to 400 mg. Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma AUC values for saxagliptin and its major metabolite were 78 ng·h/ml and 214 ng·h/ml, respectively. The corresponding plasma $C_{max}$ values were 24 ng/ml and 47 ng/ml, respectively. The intra-subject coefficients of variation for saxagliptin $C_{max}$ and AUC were less than 12%.

The inhibition of plasma DPP-4 activity by saxagliptin for at least 24 hours after oral administration of saxagliptin is due to high potency, high affinity, and extended binding to the active site.

*Interaction with food*
Food had relatively modest effects on the pharmacokinetics of saxagliptin in healthy subjects. Administration with food (a high-fat meal) resulted in no change in saxagliptin $C_{max}$ and a 27% increase in AUC compared with the fasted state. The time for saxagliptin to reach $C_{max}$ ($T_{max}$) was increased by approximately 0.5 hours with food compared with the fasted state. These changes were not considered to be clinically meaningful.

*Distribution*
The *in vitro* protein binding of saxagliptin and its major metabolite in human serum is negligible. Thus, changes in blood protein levels in various disease states (e.g., renal or hepatic impairment) are not expected to alter the disposition of saxagliptin.

*Biotransformation*
The biotransformation of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major metabolite of saxagliptin is also a selective, reversible, competitive DPP-4 inhibitor, half as potent as saxagliptin.

*Elimination*
The mean plasma terminal half-life ($t_{1/2}$) values for saxagliptin and its major metabolite are 2.5 hours and 3.1 hours respectively, and the mean $t_{1/2}$ value for plasma DPP-4 inhibition was 26.9 hours. Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50 mg dose of $^{14}$C-saxagliptin, 24%, 36%, and 75% of the dose was excreted in the urine as saxagliptin, its major

metabolite, and total radioactivity respectively. The average renal clearance of saxagliptin (~230 ml/min) was greater than the average estimated glomerular filtration rate (~120 ml/min), suggesting some active renal excretion. For the major metabolite, renal clearance values were comparable to estimated glomerular filtration rate. A total of 22% of the administered radioactivity was recovered in faeces representing the fraction of the saxagliptin dose excreted in bile and/or unabsorbed medicinal product from the gastrointestinal tract.

*Linearity*
The $C_{max}$ and AUC of saxagliptin and its major metabolite increased proportionally to the saxagliptin dose. No appreciable accumulation of either saxagliptin or its major metabolite was observed with repeated once-daily dosing at any dose level. No dose- and time-dependence was observed in the clearance of saxagliptin and its major metabolite over 14 days of once-daily dosing with saxagliptin at doses ranging from 2.5 mg to 400 mg.

Special populations
*Renal impairment*
A single-dose, open-label study was conducted to evaluate the pharmacokinetics of a 10 mg oral dose of saxagliptin in subjects with varying degrees of chronic renal impairment compared to subjects with normal renal function. In subjects with mild (> 50 to ≤ 80 ml/min), moderate (≥ 30 to ≤ 50 ml/min), or severe (19-30 ml/min) renal impairment the exposures to saxagliptin were 1.2-, 1.4- and 2.1-fold higher, respectively, and the exposures to BMS-510849 were 1.7-, 2.9-, and 4.5-fold higher, respectively, than those observed in subjects with normal renal function (> 80 ml/min).

*Hepatic impairment*
In subjects with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), or severe (Child-Pugh Class C) hepatic impairment the exposures to saxagliptin were 1.1-, 1.4- and 1.8-fold higher, respectively, and the exposures to BMS-510849 were 22%, 7%, and 33% lower, respectively, than those observed in healthy subjects.

*Elderly patients (≥ 65 years)*
Elderly patients (65-80 years) had about 60% higher saxagliptin AUC than young patients (18-40 years). This is not considered clinically meaningful, therefore, no dose adjustment for Komboglyze is recommended on the basis of age alone.

Metformin
*Absorption*
After an oral dose of metformin, $t_{max}$ is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 μg/ml. In controlled clinical trials, maximum metformin plasma levels ($C_{max}$) did not exceed 4 μg/ml, even at maximum doses.

*Interaction with food*
Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40% lower plasma peak concentration, a 25% decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.

*Distribution*
Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean $V_d$ ranged between 63-276 l.

*Biotransformation*
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

*Elimination*
Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

## 5.3 Preclinical safety data

Coadministration of saxagliptin and metformin
A 3-month dog study and embryo-foetal development studies in rats and rabbits have been conducted with the combination of saxagliptin and metformin.

Coadministration of saxagliptin and metformin, to pregnant rats and rabbits during the period of organogenesis, was neither embryolethal nor teratogenic in either species when tested at doses yielding systemic exposures (AUC) up to 100 and 10 times the maximum recommended human doses (RHD; 5 mg saxagliptin and 2000 mg metformin), respectively, in rats; and 249 and 1.1 times the RHDs in rabbits. In rats, minor developmental toxicity was limited to an increased incidence of delayed ossification ("wavy ribs"); associated maternal toxicity was limited to weight decrements of 5-6% over the course of gestation days 13 through 18, and related reductions in maternal food consumption. In rabbits, coadministration was poorly tolerated in many mothers, resulting in death, moribundity or abortion. However, among surviving mothers with evaluable litters, maternal toxicity was limited to marginal reductions in body weight over the course of gestation days 21 to 29; and associated developmental toxicity in these litters was limited to fetal body weight decrements of 7%, and a low incidence of delayed ossification of the fetal hyoid.

A 3-month dog study was conducted with the combination of saxagliptin and metformin. No combination toxicity was observed at AUC exposures 68 and 1.5 times the RHDs for saxagliptin and metformin, respectively.

No animal studies have been conducted with the combination of products in Komboglyze to evaluate carcinogenesis, mutagenesis, or impairment of fertility. The following data are based on the findings in the studies with saxagliptin and metformin individually.

Saxagliptin
In cynomolgus monkeys saxagliptin produced reversible skin lesions (scabs, ulcerations and necrosis) in extremities (tail, digits, scrotum and/or nose) at doses ≥ 3 mg/kg/day. The no effect level (NOEL) for the lesions is 1 and 2 times the human exposure of saxagliptin and the major metabolite respectively, at the recommended human dose of 5 mg/day (RHD).

The clinical relevance of the skin lesions is not known, however clinical correlates to skin lesions in monkeys have not been observed in human clinical trials of saxagliptin.

Immune related findings of minimal, nonprogressive, lymphoid hyperplasia in spleen, lymph nodes and bone marrow with no adverse sequelae have been reported in all species tested at exposures starting from 7 times the RHD.

Saxagliptin produced gastrointestinal toxicity in dogs, including bloody/mucoid faeces and enteropathy at higher doses with a NOEL 4 and 2 times the human exposure for saxagliptin and the major metabolite, respectively, at RHD.

Saxagliptin was not genotoxic in a conventional battery of genotoxicity studies *in vitro* and *in vivo*. No carcinogenic potential was observed in two-year carcinogenicity assays with mice and rats.

Effects on fertility were observed in male and female rats at high doses producing overt signs of toxicity. Saxagliptin was not teratogenic at any doses evaluated in rats or rabbits. At high doses in rats, saxagliptin caused reduced ossification (a developmental delay) of the foetal pelvis and decreased foetal body weight (in the presence of maternal toxicity), with a NOEL 303 and 30 times the human exposure for saxagliptin and the major metabolite, respectively, at RHD. In rabbits, the effects of saxagliptin were limited to minor skeletal variations observed only at maternally toxic doses (NOEL 158 and 224 times the human exposure for saxagliptin and the major metabolite, respectively at RHD). In a pre- and postnatal developmental study in rats, saxagliptin caused decreased pup weight at maternally toxic doses, with NOEL 488 and 45 times the human exposure for saxagliptin and the major metabolite, respectively at RHD. The effect on offspring body weights were noted until postnatal day 92 and 120 in females and males, respectively.

Metformin
Preclinical data for metformin reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core
Povidone K30
Magnesium stearate

Film coating
Polyvinyl alcohol
Macrogol 3350
Titanium dioxide (E171)
Talc (E553b)
Iron oxide yellow (E172)

Printing ink
Shellac
Indigo carmine aluminium lake (E132)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

36 months

### 6.4 Special precautions for storage

Store below 25°C.

### 6.5 Nature and contents of container

Alu/Alu blister.
Pack-sizes of 14, 28, 56 and 60 film-coated tablets in non-perforated blisters.
Multipacks containing 112 (2 packs of 56) and 196 (7 packs of 28) film-coated tablets in non-perforated blisters.
60x1 film-coated tablets in perforated unit dose blisters.
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/AstraZeneca EEIG
Bristol-Myers Squibb House
Uxbridge Business Park
Sanderson Road
Uxbridge
Middlesex
UB8 1DH
United Kingdom

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/731/007
EU/1/11/731/008
EU/1/11/731/009
EU/1/11/731/010
EU/1/11/731/011
EU/1/11/731/012
EU/1/11/731/014

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 November, 2011

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

## A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

## A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Bristol-Myers Squibb S.r.l.
Contrada Fontana del Ceraso
IT-03012 Anagni (FR)
Italy

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted annually until renewal.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON** Komboglyze 2.5 mg/850 mg film-coated tablets

## 1. NAME OF THE MEDICINAL PRODUCT

Komboglyze 2.5 mg/850 mg film-coated tablets
saxagliptin/metformin hydrochloride

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2.5 mg of saxagliptin (as hydrochloride) and 850 mg of metformin hydrochloride.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
56 film-coated tablets
60 film-coated tablets
Multipack: 112 (2 packs of 56) film-coated tablets
Multipack: 196 (7 packs of 28) film-coated tablets
60x1 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/AstraZeneca EEIG
Bristol-Myers Squibb House
Uxbridge Business Park
Sanderson Road
Uxbridge
Middlesex
UB8 1DH
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/731/001 28 film coated tablets
EU/1/11/731/002 56 film coated tablets
EU/1/11/731/003 60 film coated tablets
EU/1/11/731/004 112 (2 packs of 56) film coated tablets
EU/1/11/731/005 196 (7 packs of 28) film coated tablets
EU/1/11/731/006 60x1 film coated tablets
EU/1/11/731/013 14 film coated tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Komboglyze 2.5 mg/850 mg

**PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING**

**CARTON** Komboglyze 2.5 mg/850 mg film-coated tablets

## 1. NAME OF THE MEDICINAL PRODUCT

Komboglyze 2.5 mg/850 mg film-coated tablets
saxagliptin/metformin hydrochloride

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2.5 mg of saxagliptin (as hydrochloride) and 850 mg of metformin hydrochloride.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets. Component of a multipack, can't be sold separately.
28 film-coated tablets. Component of a multipack, can't be sold separately.

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/AstraZeneca EEIG
Bristol-Myers Squibb House
Uxbridge Business Park
Sanderson Road
Uxbridge
Middlesex
UB8 1DH
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Komboglyze 2.5 mg/850 mg

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON** Komboglyze 2.5 mg/1,000 mg film-coated tablets

## 1. NAME OF THE MEDICINAL PRODUCT

Komboglyze 2.5 mg/1,000 mg film-coated tablets
saxagliptin/metformin hydrochloride

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2.5 mg of saxagliptin (as hydrochloride) and 1,000 mg of metformin hydrochloride.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
56 film-coated tablets
60 film-coated tablets
Multipack: 112 (2 packs of 56) film-coated tablets
Multipack: 196 (7 packs of 28) film-coated tablets
60x1 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/AstraZeneca EEIG
Bristol-Myers Squibb House
Uxbridge Business Park
Sanderson Road
Uxbridge
Middlesex
UB8 1DH
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/731/007 28 film coated tablets
EU/1/11/731/008 56 film coated tablets
EU/1/11/731/009 60 film coated tablets
EU/1/11/731/010 112 (2 packs of 56) film coated tablets
EU/1/11/731/011 196 (7 packs of 28) film coated tablets
EU/1/11/731/012 60x1 film coated tablets
EU/1/11/731/014 14 film coated tablets

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Komboglyze 2.5 mg/1,000 mg

**PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING**

**CARTON** Komboglyze 2.5 mg/1000 mg film-coated tablets

## 1. NAME OF THE MEDICINAL PRODUCT

Komboglyze 2.5 mg/1000 mg film-coated tablets
saxagliptin/metformin hydrochloride

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2.5 mg of saxagliptin (as hydrochloride) and 1000 mg of metformin hydrochloride.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets. Component of a multipack, can't be sold separately.
28 film-coated tablets. Component of a multipack, can't be sold separately.

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Store below 25°C.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/AstraZeneca EEIG
Bristol-Myers Squibb House
Uxbridge Business Park
Sanderson Road
Uxbridge
Middlesex
UB8 1DH
United Kingdom

## 12. MARKETING AUTHORISATION NUMBER(S)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Komboglyze 2.5 mg/1000 mg

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS (PERFORATED/NON-PERFORATED)** for Komboglyze 2.5 mg/850 mg tablets

## 1. NAME OF THE MEDICINAL PRODUCT

Komboglyze 2.5 mg/850 mg tablets
saxagliptin/metformin HCl

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/AstraZeneca EEIG

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS (PERFORATED/NON-PERFORATED)** for Komboglyze 2.5 mg/1,000 mg tablets

## 1. NAME OF THE MEDICINAL PRODUCT

Komboglyze 2.5 mg/1,000 mg tablets
saxagliptin/metformin HCl

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb/AstraZeneca EEIG

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

# B. PACKAGE LEAFLET

**Package leaflet: Information for the patient**

**Komboglyze 2.5 mg/850 mg film-coated tablets**
saxagliptin/metformin

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

**What is in this leaflet**:


## 1. What Komboglyze is and what it is used for

Komboglyze contains two different substances called

saxagliptin, part of a class of medicines called DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors), and
metformin, part of a class of medicines called biguanides.

Both belong to a group of medicines called oral anti-diabetics.

**What Komboglyze is used for**
Komboglyze is used to treat a type of diabetes called 'type 2 diabetes'.

**How Komboglyze works**
Saxagliptin and metformin work together to control your blood sugar. They increase the levels of insulin after a meal. They also lower the amount of sugar made by your body. Along with diet and exercise, this helps lower your blood sugar. Komboglyze can be used alone or together with insulin.

To control your diabetes, you still need to diet and exercise, even when you are taking this medicine. So it is important to keep following the advice about diet and exercise from your doctor or nurse.

## 2. What you need to know before you take Komboglyze

**Do not take Komboglyze**
- If you are allergic to saxagliptin, metformin or any of the other ingredients of this medicine (listed in section 6);
- If you have had a serious allergic (hypersensitive) reaction to any other similar medications that you take to control your blood sugar.
  Symptoms of a serious allergic reaction may include:
  - Rash
  - Raised red patches on your skin (hives)

- Swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing.
- If you have these symptoms, stop taking Komboglyze and call your doctor or nurse right away.

– If you have ever had a diabetic coma;
– If you have a condition called 'diabetic ketoacidosis', a problem you can get with diabetes. The signs include rapid weight loss, feeling sick or being sick;
– If you have problems with your kidneys or liver;
– If you have recently had a heart attack or if you have heart failure or serious problems with your blood circulation or difficulties in breathing which could be a sign of heart problems;
– If you have a severe infection or are dehydrated (have lost a lot of water from your body);
– If you are breast-feeding (see also "Pregnancy and breast-feeding");
– If you drink a large amount of alcohol (either every day or only from time to time) (please see section "Komboglyze with alcohol");
– If you are going to have an X-ray where you will be injected with a dye. You will need to tell your doctor and stop taking Komboglyze at the time of the X-ray and for 2 or more days after, depending on how your kidneys are working.

Do not take Komboglyze if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Komboglyze.

**Warnings and precautions:**
Talk to your doctor or pharmacist before taking Komboglyze
– If you have type 1 diabetes (your body does not produce any insulin). Komboglyze should not be used to treat this condition;
– If you are taking insulin or an antidiabetic medicine known as 'sulphonylurea', your doctor may want to reduce your dose of insulin or the sulphonylurea when you take either of them together with Komboglyze, in order to avoid low blood sugar;
– If you have had allergic reactions to any other medicines that you take to control the amount of sugar in your blood;
– If you have a problem or take a medicine that can lower your body's defence against infections;
– If you are going to have an operation under anaesthetic. You should stop at least 48 hours before planned surgery with general anaesthesia and should not start again until at least 48 hours afterwards; follow your doctor's instructions before stopping and re-starting your medicine.

If you have symptoms of acute pancreatitis, like persistent, severe abdominal pain, you should consult your doctor.

Diabetic skin lesions are a common complication of diabetes. Rash has been seen with saxagliptin and with certain anti-diabetic medicines in the same class as saxagliptin. Follow the recommendations for skin and foot care that your doctor or nurse gave you.

If any of the above apply to you, or if you are not sure talk to your doctor or pharmacist before taking Komboglyze.

**Kidney tests or checks**
During treatment with Komboglyze:
- your doctor will check how well your kidneys are working
- they will do this at least once a year.

Your kidneys will be checked more often if:
- you are elderly
- your kidneys are not working as well as they should be (or are at risk of getting worse).

**Children and adolescents**
Komboglyze is not recommended for use in children and adolescents under 18 years. It is not known if this medicine is safe and effective when used in children and adolescents under 18 years of age.

**Other medicines and Komboglyze**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines:
- medicines containing alcohol
- cimetidine, a medicine used to treat stomach problems
- ketoconazole which is used to treat fungal infections
- bronchodilators (beta-2 agonists) which are used to treat asthma
- water tablets ('diuretics') which are used to increase the amount of water you produce
- diltiazem which is used for high blood pressure
- rifampicin, an antibiotic used to treat infections such as tuberculosis
- corticosteroids, which are used to treat inflammation in diseases like asthma and arthritis
- carbamazepine, phenobarbital or phenytoin, which are used to control fits (seizures) or long-term pain.

If any of the above apply to you, or if you are not sure, talk to your doctor or pharmacist before taking Komboglyze.

**Komboglyze with alcohol**
Avoid alcohol while taking Komboglyze since alcohol may increase the risk of lactic acidosis (please see section 4 "Possible side effects").

**Pregnancy and breast-feeding**
Do not take Komboglyze if you are pregnant or might become pregnant. This is because it may affect the baby.

Do not take Komboglyze if you are breast-feeding or plan to breast-feed. This is because metformin passes into human milk in small amounts.

Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**
Saxagliptin and metformin may have a negligible influence on the ability to drive and use machines. If you feel dizzy while taking Komboglyze do not drive or use any tools or machines. Hypoglycaemia may affect your ability to drive and use machines or work with safe foothold and there is a risk of hypoglycaemia when taking this medicine in combination with medicines known to cause hypoglycaemia such as insulin and sulphonylureas.

## 3. How to take Komboglyze

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

If your doctor prescribes Komboglyze together with insulin, remember to take this other medicine as directed by your doctor to achieve the best results for your health.

**How much to take**
- The amount of Komboglyze that you will take varies depending on your condition and the doses you currently take of metformin and/or individual tablets of saxagliptin and metformin. Your doctor will tell you exactly the dose of Komboglyze to take.
- The recommended dosing is one tablet twice a day.

**How to take this medicine**
- Take this medicine by mouth.
- Take with a meal to lower your chance of getting an upset stomach.

**Diet and exercise**
To control your diabetes, you still need to diet and exercise, even when you are taking this medicine. So it is important to keep following the advice about diet and exercise from your doctor or nurse. In particular, if you are following a diabetic weight control diet, keep on with this while you are taking Komboglyze.

**If you take more Komboglyze than you should**
If you take more Komboglyze tablets than you should, talk to a doctor or go to a hospital straight away. Take the medicine pack with you.

**If you forget to take Komboglyze**
- If you forget to take a dose of Komboglyze, take it as soon as you remember. However if it is time for your next dose, skip the missed dose and take your next dose at the usual time.
- Do not take a double dose of Komboglyze to make up for a forgotten dose.

**If you stop taking Komboglyze**
Keep taking Komboglyze until your doctor tells you to stop. This is to help keep your blood sugar under control.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Metformin, one of the substances in Komboglyze, can cause a very rare (affects less than 1 user in 10,000) but serious side effect called **'lactic acidosis'**. This is a build-up of lactic acid in the blood that can cause death. Lactic acidosis is a medical emergency and must be treated in a hospital. This particularly happens in patients whose kidneys are not working properly.

Stop taking Komboglyze and see a doctor straight away if you notice any of the following signs of 'lactic acidosis'**:**

- feeling cold or uncomfortable
- feeling or being very sick or stomach pain
- weight loss which you cannot explain
- muscle cramps
- rapid breathing.

**Other side effects of Komboglyze include:**
Common (affects 1 to 10 users in 100)
- headache
- muscle pain (myalgia)
- being sick or indigestion (dyspepsia)
- infection of the structures that carry urine (urinary tract infection)
- infection of the upper airways
- inflamed nose or throat such as with a cold or sore throat
- inflamed stomach (gastritis) or gut, sometimes caused by an infection (gastro-enteritis)
- infection of your sinuses, sometimes with a feeling of pain and fullness behind your cheeks and eyes (sinusitis)
- flatulence

- dizziness
- tiredness (fatigue).

Uncommon (affects 1 to 10 users in 1,000)
- joint pain (arthralgia)
- difficulties in getting or maintaining an erection (erectile dysfunction).

**Side effects seen when taking saxagliptin alone:**
Common
- dizziness
- tiredness (fatigue).

Some patients have had a small reduction in the number of one type of white blood cells (lymphocytes) shown in a blood test. In addition, some patients have reported rash and skin reactions (hypersensitivity) while taking saxagliptin.

During post-approval use of saxagliptin, additional side effects have been reported that include serious allergic reactions (anaphylaxis), and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing. If you have an allergic reaction, stop taking Komboglyze and call your doctor right away. Your doctor may prescribe a medicine to treat your allergic reaction and a different medicine for your diabetes.

Cases of inflammation of the pancreas (pancreatitis) have been reported (frequency uncommon). Pancreatitis can be a serious, potentially life-threatening medical condition. Call your doctor if you experience severe and persistent stomach pain, with or without vomiting, because you could have pancreatitis.

**Side effects seen when taking metformin alone:**
Very common (affects more than 1 user in 10)
- nausea, vomiting
- diarrhoea or stomach pain
- loss of appetite.

Common
- a metallic taste in your mouth.

Very rare
- decreased vitamin B12 levels
- liver problems (hepatitis)
- redness of the skin (rash) or itching.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

## 5. How to store Komboglyze

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and the carton after EXP. The expiry date refers to the last day of that month.

Store below 25°C.

Do not use this medicine if the package is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

## 6. Contents of the pack and other information

**What Komboglyze contains**
The active substances are saxagliptin and metformin hydrochloride. Each film-coated tablet contains 2.5 mg saxagliptin (as hydrochloride) and 850 mg metformin hydrochloride.

The other ingredients (excipients) are:
- Tablet core: povidone K30, magnesium stearate.
- Film-coating: polyvinyl alcohol, macrogol 3350, titanium dioxide (E171), talc (E553b), iron oxide red (E172), iron oxide yellow (E172)
- Printing ink: shellac, indigo carmine aluminium lake (E132)

**What Komboglyze looks like and contents of the pack**
- Komboglyze 2.5 mg/850 mg film-coated tablets ('tablets') are light brown to brown and round, with "2.5/850" printed on one side and "4246" printed on the other side, in blue ink.
- Komboglyze is available in aluminum foil blister. The pack-sizes are 14, 28, 56 and 60 film-coated tablets in non-perforated blisters, multipacks containing 112 (2 packs of 56) and 196 (7 packs of 28) film-coated tablets in non-perforated blisters and 60x1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed in your country.

**Marketing Authorisation Holder and Manufacturer**

Marketing Authorisation Holder
Bristol-Myers Squibb/AstraZeneca EEIG
Bristol-Myers Squibb House
Uxbridge Business Park
Sanderson Road
Uxbridge
Middlesex
UB8 1DH
United Kingdom

Manufacturer
Bristol-Myers Squibb Company
Contrada Fontana del Ceraso
IT-03012 Anagni (FR)
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**Luxembourg/Luxemburg**
Bristol-Myers Squibb Belgium S.A./N.V.
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**България**
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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

**Package leaflet: Information for the patient**
**Komboglyze 2.5 mg/1,000 mg film-coated tablets**
saxagliptin/metformin

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

**What is in this leaflet**:


## 1. What Komboglyze is and what it is used for

Komboglyze contains two different substances called

saxagliptin, part of a class of medicines called DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors), and
metformin, part of a class of medicines called biguanides.

Both belong to a group of medicines called oral anti-diabetics.

**What Komboglyze is used for**
Komboglyze is used to treat a type of diabetes called 'type 2 diabetes'.

**How Komboglyze works**
Saxagliptin and metformin work together to control your blood sugar. They increase the levels of insulin after a meal. They also lower the amount of sugar made by your body. Along with diet and exercise, this helps lower your blood sugar. Komboglyze can be used alone or together with insulin.

To control your diabetes, you still need to diet and exercise, even when you are taking this medicine. So it is important to keep following the advice about diet and exercise from your doctor or nurse.

## 2. What you need to know before you take Komboglyze

**Do not take Komboglyze**
- If you are allergic to saxagliptin, metformin or any of the other ingredients of this medicine (listed in section 6);
- If you have had a serious allergic (hypersensitive) reaction to any other similar medications that you take to control your blood sugar.
  Symptoms of a serious allergic reaction may include:
  - Rash
  - Raised red patches on your skin (hives)

- Swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing.
- If you have these symptoms, stop taking Komboglyze and call your doctor or nurse right away.

– If you have ever had a diabetic coma;
– If you have a condition called 'diabetic ketoacidosis', a problem you can get with diabetes. The signs include rapid weight loss, feeling sick or being sick;
– If you have problems with your kidneys or liver;
– If you have recently had a heart attack or if you have heart failure or serious problems with your blood circulation or difficulties in breathing which could be a sign of heart problems;
– If you have a severe infection or are dehydrated (have lost a lot of water from your body);
– If you are breast-feeding (see also "Pregnancy and breast-feeding");
– If you drink a large amount of alcohol (either every day or only from time to time) (please see section "Komboglyze with alcohol");
– If you are going to have an X-ray where you will be injected with a dye. You will need to tell your doctor and stop taking Komboglyze at the time of the X-ray and for 2 or more days after, depending on how your kidneys are working.

Do not take Komboglyze if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Komboglyze.

**Warnings and precautions:**
Talk to your doctor or pharmacist before taking Komboglyze
– If you have type 1 diabetes (your body does not produce any insulin). Komboglyze should not be used to treat this condition;
– If you are taking insulin or an antidiabetic medicine known as 'sulphonylurea', your doctor may want to reduce your dose of insulin or the sulphonylurea when you take either of them together with Komboglyze, in order to avoid low blood sugar;
– If you have had allergic reactions to any other medicines that you take to control the amount of sugar in your blood;
– If you have a problem or take a medicine that can lower your body's defence against infections;
– If you are going to have an operation under anaesthetic. You should stop at least 48 hours before planned surgery with general anaesthesia and should not start again until at least 48 hours afterwards; follow your doctor's instructions before stopping and re-starting your medicine.

If you have symptoms of acute pancreatitis, like persistent, severe abdominal pain, you should consult your doctor.

Diabetic skin lesions are a common complication of diabetes. Rash has been seen with saxagliptin and with certain anti-diabetic medicines in the same class as saxagliptin. Follow the recommendations for skin and foot care that your doctor or nurse gave you.

If any of the above apply to you, or if you are not sure talk to your doctor or pharmacist before taking Komboglyze.

**Kidney tests or checks**
During treatment with Komboglyze:
- your doctor will check how well your kidneys are working
- they will do this at least once a year.

Your kidneys will be checked more often if:
- you are elderly
- your kidneys are not working as well as they should be (or are at risk of getting worse).

**Children and adolescents**
Komboglyze is not recommended for use in children and adolescents under 18 years. It is not known if this medicine is safe and effective when used in children and adolescents under 18 years of age.

**Other medicines and Komboglyze**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines.

In particular, tell your doctor or pharmacist if you are taking any of the following medicines:
- medicines containing alcohol
- cimetidine, a medicine used to treat stomach problems
- ketoconazole which is used to treat fungal infections
- bronchodilators (beta-2 agonists) which are used to treat asthma
- water tablets ('diuretics') which are used to increase the amount of water you produce
- diltiazem which is used for high blood pressure
- rifampicin, an antibiotic used to treat infections such as tuberculosis
- corticosteroids, which are used to treat inflammation in diseases like asthma and arthritis
- carbamazepine, phenobarbital or phenytoin, which are used to control fits (seizures) or long-term pain.

If any of the above apply to you, or if you are not sure, talk to your doctor or pharmacist before taking Komboglyze.

**Komboglyze with alcohol**
Avoid alcohol while taking Komboglyze since alcohol may increase the risk of lactic acidosis (please see section 4 "Possible side effects").

**Pregnancy and breast-feeding**
Do not take Komboglyze if you are pregnant or might become pregnant. This is because it may affect the baby.

Do not take Komboglyze if you are breast-feeding or plan to breast-feed. This is because metformin passes into human milk in small amounts.

Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**
Saxagliptin and metformin may have a negligible influence on the ability to drive and use machines. If you feel dizzy while taking Komboglyze do not drive or use any tools or machines. Hypoglycaemia may affect your ability to drive and use machines or work with safe foothold and there is a risk of hypoglycaemia when taking this medicine in combination with medicines known to cause hypoglycaemia such as insulin and sulphonylureas.

## 3. How to take Komboglyze

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

If your doctor prescribes Komboglyze together with insulin, remember to take this other medicine as directed by your doctor to achieve the best results for your health.

**How much to take**
- The amount of Komboglyze that you will take varies depending on your condition and the doses you currently take of metformin and/or individual tablets of saxagliptin and metformin. Your doctor will tell you exactly the dose of Komboglyze to take.
- The recommended dosing is one tablet twice a day.

**How to take this medicine**
- Take this medicine by mouth.
- Take with a meal to lower your chance of getting an upset stomach.

**Diet and exercise**
To control your diabetes, you still need to diet and exercise, even when you are taking this medicine. So it is important to keep following the advice about diet and exercise from your doctor or nurse. In particular, if you are following a diabetic weight control diet, keep on with this while you are taking Komboglyze.

**If you take more Komboglyze than you should**
If you take more Komboglyze tablets than you should, talk to a doctor or go to a hospital straight away. Take the medicine pack with you.

**If you forget to take Komboglyze**
- If you forget to take a dose of Komboglyze, take it as soon as you remember. However if it is time for your next dose, skip the missed dose and take your next dose at the usual time.
- Do not take a double dose of Komboglyze to make up for a forgotten dose.

**If you stop taking Komboglyze**
Keep taking Komboglyze until your doctor tells you to stop. This is to help keep your blood sugar under control.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Metformin, one of the substances in Komboglyze, can cause a very rare (affects less than 1 user in 10,000) but serious side effect called **'lactic acidosis'**. This is a build-up of lactic acid in the blood that can cause death. Lactic acidosis is a medical emergency and must be treated in a hospital. This particularly happens in patients whose kidneys are not working properly.

Stop taking Komboglyze and see a doctor straight away if you notice any of the following signs of 'lactic acidosis'**:**

- feeling cold or uncomfortable
- feeling or being very sick or stomach pain
- weight loss which you cannot explain
- muscle cramps
- rapid breathing.

**Other side effects of Komboglyze include:**
Common (affects 1 to 10 users in 100)
- headache
- muscle pain (myalgia)
- being sick or indigestion (dyspepsia)
- infection of the structures that carry urine (urinary tract infection)
- infection of the upper airways
- inflamed nose or throat such as with a cold or sore throat
- inflamed stomach (gastritis) or gut, sometimes caused by an infection (gastro-enteritis)
- infection of your sinuses, sometimes with a feeling of pain and fullness behind your cheeks and eyes (sinusitis)
- flatulence

- dizziness
- tiredness (fatigue).

Uncommon (affects 1 to 10 users in 1,000)
- joint pain (arthralgia)
- difficulties in getting or maintaining an erection (erectile dysfunction).

**Side effects seen when taking saxagliptin alone:**
Common
- dizziness
- tiredness (fatigue).

Some patients have had a small reduction in the number of one type of white blood cells (lymphocytes) shown in a blood test. In addition, some patients have reported rash and skin reactions (hypersensitivity) while taking saxagliptin.

During post-approval use of saxagliptin, additional side effects have been reported that include serious allergic reactions (anaphylaxis), and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing. If you have an allergic reaction, stop taking Komboglyze and call your doctor right away. Your doctor may prescribe a medicine to treat your allergic reaction and a different medicine for your diabetes.

Cases of inflammation of the pancreas (pancreatitis) have been reported (frequency uncommon). Pancreatitis can be a serious, potentially life-threatening medical condition. Call your doctor if you experience severe and persistent stomach pain, with or without vomiting, because you could have pancreatitis.

**Side effects seen when taking metformin alone:**
Very common (affects more than 1 user in 10)
- nausea, vomiting
- diarrhoea or stomach pain
- loss of appetite.

Common
- a metallic taste in your mouth.

Very rare
- decreased vitamin B12 levels
- liver problems (hepatitis)
- redness of the skin (rash) or itching.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

## 5. How to store Komboglyze

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and the carton after EXP. The expiry date refers to the last day of that month.

Store below 25°C.

Do not use this medicine if the package is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

## 6. Contents of the pack and other information

**What Komboglyze contains**
The active substances are saxagliptin and metformin hydrochloride. Each film-coated tablet contains 2.5 mg saxagliptin (as hydrochloride) and 1,000 mg metformin hydrochloride.

The other ingredients (excipients) are:
- Tablet core: povidone K30, magnesium stearate.
- Film-coating: polyvinyl alcohol, macrogol 3350, titanium dioxide (E171), talc (E553b), iron oxide yellow (E172)
- Printing ink: shellac, indigo carmine aluminium lake (E132)

**What Komboglyze looks like and contents of the pack**
- Komboglyze 2.5 mg/1,000 mg film-coated tablets ('tablets') are pale yellow to light yellow and oval, with "2.5/1000" printed on one side and "4247" printed on the other side, in blue ink.
- Komboglyze is available in aluminum foil blister. The pack-sizes are 14, 28, 56 and 60 film-coated tablets in non-perforated blisters, multipacks containing 112 (2 packs of 56) and 196 (7 packs of 28) film-coated tablets in non-perforated blisters and 60x1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed in your country.

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