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 in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:

- in patients inadequately controlled on their maximally tolerated dose of metformin

  alone
- in combination with other medicinal products for the treatment of diabetes, including insulin, in patients inadequately controlled with metformin and these

medicinal products (see sections 4.4, 4.5 and 5.1 for available data on different combinations)

- in patients already being treated with the combination of saxagliptin and metformin as separate tablets.

4.2 Posology and method of administration

Posology
Adults with normal renal function (GFR ≥ 90 mL/min)

For patients inadequately controlled on maximal tolerated dose of metformin monotherapy
Patients not adequately controlled on metformin alone should receive a dose of this medicinal product 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 this medicinal product 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 this medicinal product 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 this medicinal product 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 this medicinal product 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).

For patients inadequately controlled on dual combination therapy of dapagliflozin and metformin, or for patients switching from triple combination therapy of saxagliptin, metformin and dapagliflozin taken as separate tablets
The dose of this medicinal product 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.

Special populations
Renal impairment
No dose adjustment is recommended for patients with mild renal impairment (GFR 60-89 mL/min).

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months. The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of Komboglyze in patients with GFR < 60 mL/min.

If no adequate strength of Komboglyze is available, individual monocomponents should be used instead of the fixed dose combination.

Table 1 Dosage in patients with renal impairment

GFR mL/min	Metformin	Saxagliptin
60-89	Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.	Maximum total daily dose is 5 mg.
45-59	Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.	Maximum total daily dose is 5 mg.
30-44	Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.	Maximum total daily dose is 2.5 mg.
<30	Metformin is contraindicated.	Maximum total daily dose is 2.5 mg.

Hepatic impairment
This medicinal product must not be used in patients with hepatic impairment (see sections 4.3 and 4.5).

Elderly (≥ 65 years)
As metformin and saxagliptin are excreted by the kidney, this medicinal product 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, 4.4 and 5.2).

Paediatric population
The safety and efficacy of this medicinal product in children and adolescents 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

- Hypersensitivity to the active substances 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);
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis);
- Diabetic pre-coma;
- Severe renal failure (GFR < 30 mL/min) (see sections 4.2, 4.4 and 5.2);
- 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 4.5);
- Acute alcohol intoxication, alcoholism (see section 4.5);
- Breast-feeding (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.

Acute pancreatitis
Use of DPP4 inhibitors has been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis; persistent, severe abdominal pain. If pancreatitis is suspected, this medicinal product should be discontinued; if acute pancreatitis is confirmed, this medicinal product should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

In postmarketing experience of saxagliptin, there have been spontaneously reported adverse reactions of acute pancreatitis.

Lactic acidosis
Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever, heat, reduced fluid intake), Komboglyze should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in metformin-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections 4.3 and 4.5).

Patients and/or care-givers should be informed on the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking Komboglyze and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio.

Renal function
As metformin is excreted by the kidney, renal function should be assessed:
- Before initiation of treatment and regularly thereafter (see sections 4.2, 4.8, 5.1 and 5.2).
- For renal function with GFR levels approaching moderate renal impairment and in elderly patients, at least 2 to 4 times per year.
- In patients with moderate renal impairment that have GFR ≥ 30 to < 45 mL/min, in the absence of other conditions that may increase the risk of lactic acidosis, the dose is 2.5 mg/1000 mg or 2.5 mg/850 mg once daily. It is not recommended to initiate treatment in these patients. Treatment may be continued in the well-informed patients with close monitoring.
- Metformin is contraindicated in patients with a GFR < 30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function (see section 4.3).

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 NSAID.

Surgery
Komboglyze must be discontinued at the time of surgery with general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition provided that renal function has been re-evaluated and found to be stable.

Administration of iodinated contrast agents
Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. Komboglyze should be discontinued prior to, or at the time of, the imaging procedure and not

restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see sections 4.2 and 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). Skin lesions were not observed at an increased incidence in clinical trials. 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.

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

Hypersensitivity reactions
As this medicinal product 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 this medicinal product, 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 this medicinal product 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, this medicinal product must be stopped immediately and other appropriate corrective measures initiated.

Cardiac failure
In the SAVOR trial a small increase in the rate for hospitalisation for heart failure was observed in the saxagliptin treated patients compared to placebo, although a causal relationship has not been established (see section 5.1). Caution is warranted if this medicinal product is used in patients who have known risk factors for hospitalisation for heart failure, such as a history of heart failure or moderate to severe renal impairment. Patients should be advised of the characteristic symptoms of heart failure, and to immediately report such symptoms.

Arthralgia
Joint pain, which may be severe, has been reported in postmarketing reports for DPP4 inhibitors (see section 4.8). Patients experienced relief of symptoms after discontinuation of the medicinal product and some experienced recurrence of symptoms with reintroduction of the same or another DPP4 inhibitor. Onset of symptoms following initiation of drug therapy

may be rapid or may occur after longer periods of treatment. If a patient presents with severe joint pain, continuation of drug therapy should be individually assessed.

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

Use with potent CYP3A4 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.

Vitamin B_{12} decrease/deficiency
Metformin may reduce vitamin B_{12} serum levels. The risk of low vitamin B_{12} levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B_{12} deficiency. In case of suspicion of vitamin B_{12} deficiency (such as anaemia or neuropathy), vitamin B_{12} serum levels should be monitored. Periodic vitamin B_{12} monitoring could be necessary in patients with risk factors for vitamin B_{12} deficiency. Metformin therapy should be continued for as long as it is tolerated and not contraindicated and appropriate corrective treatment for vitamin B_{12} deficiency provided in line with current clinical guidelines.

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, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4, nor induced CYP1A2, 2B6, 2C9, or 3A4. In studies conducted in healthy subjects, neither the pharmacokinetics of saxagliptin nor its major metabolite, were meaningfully altered by metformin, glibenclamide, pioglitazone, digoxin, simvastatin, omeprazole, antacids or famotidine. In addition, saxagliptin did not meaningfully alter the pharmacokinetics of metformin, glibenclamide,

pioglitazone, digoxin, simvastatin, the active components of a combined oral contraceptive (ethinyl estradiol and norgestimate), diltiazem or ketoconazole.

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

Concomitant use not recommended

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.

Alcohol

Alcohol intoxication is associated with an increased risk of lactic acidosis, 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.

Iodinated contrast agents

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and increased risk of lactic acidosis. Komboglyze must be discontinued prior to, or at the time of the imaging procedure and not restarted until at least 48 hours after, provided

that renal function has been re-evaluated and found to be stable (see sections 4.2 and 4.4).

Combination requiring precautions for use
Glucocorticoids (given by systemic and local routes), beta-2 agonists, 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.

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.

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). This medicinal product should not be used during pregnancy. If the patient wishes to become pregnant, or if a pregnancy occurs, treatment with this medicinal product 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. This medicinal product must therefore not be used in women who are breast-feeding (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 has 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 randomised, controlled, double-blind clinical trials (including developmental and postmarketing experience), over 17,000 patients with type 2 diabetes have been treated with saxagliptin.

In a pooled analysis of 1,681 patients with type 2 diabetes including 882 patients treated with saxagliptin 5 mg, randomised in five double-blind, placebo-controlled clinical safety and efficacy studies conducted to evaluate the effects of saxagliptin on glycaemic control, 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 2.

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 2 Frequency of adverse reactions by system organ class

System organ class Adverse reaction	**Frequency of adverse reactions by treatment regimen** **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 3 shows additional adverse reactions which have been reported in postmarketing experience with saxagliptin. The frequencies are based on the experience from clinical trials.

Table 3 Frequency of additional adverse reactions by system organ class

System organ class Adverse Reaction	**Frequency of adverse reactions[1]**
Gastrointestinal disorders	
Nausea	Common
Pancreatitis	Uncommon
Constipation	Not known
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
Bullous pemphigoid	Not known

[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 2.

SAVOR trial results

The SAVOR trial included 8240 patients treated with saxagliptin 5 mg or 2.5 mg once daily and 8173 patients on placebo. The overall incidence of AEs in patients treated with saxagliptin in this trial was similar to placebo (72.5% versus 72.2%, respectively).

The incidence of adjudicated pancreatitis events was 0.3% in both saxagliptin-treated patients and placebo-treated patients in the intent-to-treat population.

The incidence of hypersensitivity reactions was 1.1% in both saxagliptin-treated patients and placebo-treated patients.

The overall incidence of reported hypoglycaemia (recorded in daily patient diaries) was 17.1% in subjects treated with saxagliptin and 14.8% among patients treated with placebo. The percent of subjects with reported on-treatment events of major hypoglycaemia (defined as an event that required assistance of another person) was higher in the saxagliptin group than in the placebo group (2.1% and 1.6%, respectively). The increased risk of overall hypoglycaemia and major hypoglycaemia observed in the saxagliptin-treated group occurred primarily in subjects treated with SU at baseline and not in subjects on insulin or metformin monotherapy at baseline. The increased risk of overall and major hypoglycaemia was primarily observed in subjects with A1C < 7% at baseline.

Decreased lymphocyte counts were reported in 0.5% of saxagliptin-treated patients and 0.4% of placebo-treated patients.

Hospitalisation for heart failure, occurred at a greater rate in the saxagliptin group (3.5%) compared with the placebo group (2.8%), with nominal statistical significance favouring placebo [HR = 1.27; 95% CI 1.07, 1.51); P = 0.007]. See also section 5.1.

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).

*Arthralgia has also been reported during postmarketing surveillance (see section 4.4).

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 hypoglycaemia was 10.1 % 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 postmarketing data
Table 4 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 4 The frequency of metformin adverse reactions identified from clinical trial and postmarketing data

System organ class Adverse reaction	**Frequency**
Metabolism and nutrition disorders	
Vitamin B_{12} decrease/deficiency	Common
Lactic acidosis	Very rare
Nervous system disorders	
Metallic taste	Common
Gastrointestinal disorders	
Gastrointestinal symptoms[1]	Very common
Hepatobiliary disorders	
Liver function disorders, hepatitis	Very rare
Skin and subcutaneous tissue disorders	
Urticaria, erythema, pruritus	Very rare

[1]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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme.
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 (DPP4) inhibitor, and metformin hydrochloride, a member of the biguanide class.

Saxagliptin
Saxagliptin is a highly potent (Ki: 1.3 nM), selective, reversible, competitive, DPP4 inhibitor. In patients with type 2 diabetes, administration of saxagliptin led to inhibition of DPP4 enzyme activity for a 24-hour period. After an oral glucose load, this DPP4 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, LDL-C and triglyceride levels.

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

Saxagliptin in combination with metformin for glycaemic control
The co-administration 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 5). 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 glycaemic 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.

Saxagliptin add-on to dapagliflozin plus metformin therapy
A 24-week randomised, double-blind, placebo-controlled study conducted in patients with type 2 diabetes mellitus compared saxagliptin 5 mg with placebo as add-on therapy in individuals with HbA1c 7-10.5% treated with dapagliflozin (SGLT2-inhibtor) and metformin. Patients who completed the initial 24-week study period were eligible to enter a controlled 28-week long-term study extension (52 weeks).

Individuals treated with saxagliptin added to dapagliflozin and metformin (n=153) achieved statistically significantly (p-value < 0.0001) greater reductions in HbA1c versus the group with placebo added to dapagliflozin plus metformin (n=162) at 24 weeks (see Table 5). The effect on HbA1c observed at Week 24 was sustained at Week 52. The safety profile of saxagliptin added to dapagliflozin plus metformin in the long-term treatment period was consistent with that observed in the 24-week treatment period in this study and in the trial in which saxagliptin and dapagliflozin were given concomitantly as add-on therapy to patients treated with metformin (described below).

Proportion of patients achieving HbA1c < 7%
The proportion of patients achieving HbA1c < 7% at Week 24 was higher in the saxagliptin 5 mg plus dapagliflozin plus metformin group 35.3% (95% CI [28.2, 42.4]) compared to the placebo plus dapagliflozin plus metformin group 23.1% (95% CI [16.9, 29.3]). The effect in HbA1c observed at Week 24 was sustained at Week 52.

Table 5 Key efficacy results in placebo-controlled, combination therapy studies of saxagliptin 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]:	9.4	-2.5	-0.5 (-0.7, -0.4) [4]
Overall population (n=306)	10.8	-3.3	-0.6 (-0.9, -0.3) [5]
Baseline HbA1c ≥ 10% stratum (n=107)			
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]
Saxa 5 mg daily add-on to metformin plus dapagliflozin Study CV181168 (n=315)	7.9	-0.5	-0.4 (-0.5, -0.2)[7]

n=Randomised 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 $\alpha = 0.05$).

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

Saxagliptin and dapagliflozin add-on to metformin therapy

A total of 534 adult patients with type 2 diabetes mellitus and inadequate glycaemic control on metformin alone (HbA1c 8%-12%), participated in this 24-week randomised, double-blind, active comparator-controlled trial to compare the combination of saxagliptin and dapagliflozin added concurrently to metformin, versus saxagliptin or dapagliflozin added to metformin. Patients were randomised to one of three double-blind treatment groups to receive saxagliptin 5 mg and dapagliflozin 10 mg added to metformin, saxagliptin 5 mg and placebo added to metformin, or dapagliflozin 10 mg and placebo added to metformin.

The saxagliptin and dapagliflozin group achieved significantly greater reductions in HbA1c versus either the saxagliptin group or dapagliflozin group at 24 weeks (see Table 6).

Table 6 HbA1c at Week 24 in active-controlled study comparing the combination of saxagliptin and dapagliflozin added concurrently to metformin with either saxagliptin or dapagliflozin added to metformin

Efficacy parameter	Saxagliptin 5 mg + dapagliflozin 10 mg + metformin N=179[2]	Saxagliptin 5 mg + metformin N=176[2]	Dapagliflozin 10 mg + metformin N=179[2]
HbA1c (%) at week 24[1]			
Baseline (mean)	8.93	9.03	8.87
Change from baseline (adjusted mean[3]) (95% Confidence interval [CI])	−1.47 (−1.62, −1.31)	−0.88 (−1.03, −0.72)	−1.20 (−1.35, −1.04)
Difference from saxagliptin + metformin (adjusted mean[3]) (95% CI)	−0.59[4] (−0.81, −0.37)	-	-
Difference from dapagliflozin + metformin (adjusted mean[3]) (95% CI)	−0.27[5] (−0.48, −0.05)	-	-

[1] LRM = Longitudinal repeated measures (using values prior to rescue).
[2] Randomised and treated patients with baseline and at least 1 post-baseline efficacy measurement.
[3] Least squares mean adjusted for baseline value.
[4] p-value < 0.0001.
[5] p-value=0.0166.

Proportion of patients achieving HbA1c < 7%
In the saxagliptin and dapagliflozin combination group, 41.4% (95% CI [34.5, 48.2]) of patients achieved HbA1c levels of less than 7% compared to 18.3% (95% CI [13.0, 23.5]) of patients in the saxagliptin group and 22.2% (95% CI [16.1, 28.3]) of patients in the dapagliflozin group.

Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus- Thrombolysis in Myocardial Infarction (SAVOR) Study
SAVOR was a CV outcome trial in 16,492 patients with HbA1c ≥ 6.5% and < 12% (12959 with established CV disease; 3533 with multiple risk factors only) who were randomised to saxagliptin (n=8280) or placebo (n=8212) added to regional standards of care for HbA1c and CV risk factors. The study population included those ≥ 65 years (n=8561) and ≥ 75 years (n=2330), with normal or mild renal impairment (n=13916) as well as moderate (n=2240) or severe (n=336) renal impairment.

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

After a mean follow up of 2 years, the trial met its primary safety endpoint demonstrating saxagliptin does not increase the cardiovascular risk in patients

with type 2 diabetes compared to placebo when added to current background therapy.

No benefit was observed for MACE or all-cause mortality.

Table 7 Primary and secondary clinical endpoints by treatment group in the SAVOR study*

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

* Intent-to-treat population

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

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

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

Events accumulated consistently over time, and the event rates for saxagliptin and placebo did not diverge notably over time.

¶ Significance not tested.

One component of the secondary composite endpoint, hospitalisation for heart failure, occurred at a greater rate in the saxagliptin group (3.5%) compared with the placebo group (2.8%), with nominal statistical significance favouring placebo [HR = 1.27; (95% CI 1.07, 1.51); P = 0.007]. Clinically relevant factors predictive of increased relative risk with saxagliptin treatment could not be definitively identified. Subjects at higher risk for hospitalisation for heart failure, irrespective of treatment assignment, could be identified by known risk factors for heart failure such as baseline history of heart failure or impaired renal function. However, subjects on saxagliptin with a history of heart failure or impaired renal function at baseline were not at an increased risk relative to placebo for the primary or secondary composite endpoints or all-cause mortality.

Another secondary endpoint, all-cause mortality, occurred at a rate of 5.1% in the saxagliptin group and 4.6% in the placebo group (see Table 7). CV deaths were balanced across the treatment groups. There was a numerical imbalance in non-CV death, with more events on saxagliptin (1.8%) than placebo (1.4%) [HR = 1.27; (95% CI 1.00, 1.62); P = 0.051].

A1c was lower with saxagliptin compared to placebo in an exploratory analysis.

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).

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

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

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 co-administration 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 DPP4 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 DPP4 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 DPP4 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. The study included patients with renal impairment classified on the basis of creatinine clearance as mild (approximately GFR $\geq$ 45 to < 90 mL/min), moderate (approximately GFR $\geq$ 30 to < 45 mL/min), or severe (approximately GFR < 30mL/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.

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 (≥ 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 this medicinal product 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

Co-administration 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.

Co-administration 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, co-administration 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 foetal body weight decrements of 7%, and a low incidence of delayed ossification of the foetal 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 $\geq$ 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 (RHD) of 5 mg/day.

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 post-natal 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

3 years

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

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

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited,
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CB2 0AA,
UK.

8 MARKETING AUTHORISATION NUMBER(S)

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