Proposed packaging material		
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Name & Date	ASR (07 November 2022)	

KOMBIGLYZE™ XR 5 mg/500 mg

(saxagliptin/metformin HCl extended release)

Film-coated tablet

Qualitative and quantitative composition

KOMBIGLYZE XR is available for oral administration as tablets containing either 5.58 mg saxagliptin hydrochloride (anhydrous) equivalent to 5 mg saxagliptin and 500 mg metformin hydrochloride (KOMBIGLYZE XR 5 mg/500 mg).

Pharmaceutical form

KOMBIGLYZE XR 5 mg/500 mg are light brown to brown, biconvex, capsule shaped, film-coated tablet, with 5/500 printed on one side and 4221 printed on the other side, in blue ink.

Therapeutic indication

KOMBIGLYZE XR is indicated as an adjunct to diet and exercise to improve glycemic control in adults 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.

KOMBIGLYZE XR is not indicated for initial treatment of type 2 diabetes mellitus.

Posology and method of administration

Posology

Recommended Dosage

The dosage of antihyperglycemic therapy with KOMBIGLYZE XR should be individualized on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended dose of saxagliptin and metformin extended-release. KOMBIGLYZE XR should generally be administered once daily with the evening meal, with gradual dose titration to reduce the gastrointestinal side effects associated with metformin, as appropriate. The following dosage forms are available:

- KOMBIGLYZE XR (saxagliptin/metformin HCl extended-release) tablets 5 mg/500 mg

For patients inadequately controlled on maximal tolerated dose of metformin monotherapy
Patients not adequately controlled on metformin alone should receive a dose of KOMBIGLYZE XR equivalent to the total daily dose of saxagliptin 5 mg 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.

No studies have been performed specifically examining the safety and efficacy of KOMBIGLYZE XR in patients previously treated with other antihyperglycemic agents and switched to KOMBIGLYZE XR. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring as changes in glycemic control can occur.

Patients should be informed that KOMBIGLYZE XR tablets must be swallowed whole and never crushed, cut, or chewed. Occasionally, the inactive ingredients of KOMBIGLYZE XR will be eliminated in the feces as a soft, hydrated mass that may resemble the original tablet.

Special populations
Renal impairment

Assess renal function prior to initiation of KOMBIGLYZE and periodically thereafter (see Special warnings and special precautions for use, Renal function and Pharmacokinetic properties, Renal impairment).

Mild renal impairment

No dosage adjustment is required for patients with mild renal impairment (eGFR 60-89 mL/min/1.73 m2 (by Modified Diet in Renal Disease [MDRD] eGFR equation).

Moderate renal impairment

No dosage adjustment is required for patients with eGFR ≥ 45 mL/min/1.73 m2. It is not recommended to initiate treatment with KOMBIGLYZE in patients with eGFR <45 mL/min/1.73 m2.

Severe renal impairment

KOMBIGLYZE XR is contraindicated in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m2) (see Contraindications)..

Hepatic impairment
KOMBIGLYZE XR should not be used in patients with hepatic impairment.

Pediatric and adolescent
Safety and effectiveness of KOMBIGLYZE XR in pediatric and adolescent patients have not been established.

Geriatric

Because saxagliptin and metformin are eliminated in part by the kidney, and because elderly patients are more likely to have decreased renal function, KOMBIGLYZE XR should be used with caution as age increases (see *Special warnings and precautions for use*).

Contraindication

KOMBIGLYZE XR is contraindicated in patients with:

- hypersensitivity to the active substance(s) or to any of the excipients, or history of a serious hypersensitivity reaction, including anaphylactic reaction, anaphylactic shock, and angioedema, to any dipeptidyl peptidase 4 (DPP4) inhibitor (see sections Special warnings and precautions for use and Undesirable effects);
- diabetic ketoacidosis, diabetic pre-coma;
- Severe renal impairment (eGFR <30 mL/min/1.73 m2) (see sections Special warnings and precautions for use);
- 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 Posology and method of administration, Contraindication and Pharmacokinetic properties);
- acute alcohol intoxication, alcoholism (see section Interaction with other medicinal products and other forms of interaction);
- breastfeeding (see section Fertility, pregnancy and lactation).

Special warnings and precautions for use

General

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

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, KOMBIGLYZE XR and other potentially suspect medicinal products should be discontinued.

In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes

Mellitus-Thrombolysis in Myocardial Infarction (SAVOR) Trial, the incidence of adjudicated pancreatitis events was 0.3% in both saxagliptin-treated patients and placebo-treated patients in the intent-to-treat population (see *Clinical experience)*

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 KOMBIGLYZE XR, 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 Overdose).

Renal function

As metformin is excreted by the kidney and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function, assess renal function prior to initiation of KOMBIGLYZE XR and then periodically thereafter:

- at least annually
- at least two to four times per year in patients with renal function where eGFR levels are approaching 45 mL/min/1.73 m2 and in elderly patients.

It is not recommended to initiate treatment with KOMBIGLYZE XR in patients with eGFR <45 mL/min/1.73 m2. If during treatment eGFR falls to levels persistently below 45 mL/min/1.73 m2, assess the benefit and risk of continuing therapy and limit the maximum dose of KOMBIGLYZE to 2.5 mg/1000 mg once daily. KOMBIGLYZE is contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73 m2) (see Contraindications).

Surgery

As KOMBIGLYZE XR contains metformin, the treatment should be discontinued 48 hours before elective surgery with general, spinal or epidural anaesthesia. KOMBIGLYZE XR 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, KOMBIGLYZE XR 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 Interaction with other medicinal products and other forms of interaction*).

Skin disorders

Ulcerative and necrotic skin lesions have been reported in extremities of monkeys in non-clinical toxicology studies for saxagliptin (*see section Preclinical safety data*). 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 Undesirable effects*). 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 KOMBIGLYZE XR 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 KOMBIGLYZE XR, assess for other potential causes for the event, and institute alternative treatment for diabetes (*see sections Contraindications and Undesirable effects*).

Change in clinical status of patients with previously controlled type 2 diabetes

As KOMBIGLYZE XR contains metformin, a patient with type 2 diabetes previously well controlled on KOMBIGLYZE XR 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, KOMBIGLYZE XR 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 Pharmacokinetic properties).

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

saxagliptin in the SAVOR study that were 65 years and over was 4290 and the number of subjects that were 75 years and over was 1169

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 Interaction with other medicinal products and other forms of interaction)

Cardiac Failure

In the SAVOR trial an increase in the rate of hospitalization for heart failure was observed in the saxagliptin treated patients compared to placebo, although a causal relationship has not been established. Caution is warranted if Kombiglyze XR is used in patients who have known risk factors for hospitilisation 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. (see *Pharmacodynamic Properties, Cardiovascular Safety Study*)

Arthralgia

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

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 Kombiglyze XR and bullous pemphigoid is suspected, Kombiglyze XR should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment

Interaction with other medicinal products and other forms of interaction

There have been no formal interaction studies for KOMBIGLYZE XR. 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 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 Special warnings and precautions for use).

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

KOMBIGLYZE XR (see *Special warnings and precautions for use*). 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 KOMBIGLYZE XR 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 *Special warnings and precautions for use*).

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.

Fertility, pregnancy and lactation

Pregnancy
The use of KOMBIGLYZE XR 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 *Preclinical safety data*). 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 *Preclinical safety data*). KOMBIGLYZE XR should not be used during pregnancy. If the patient wishes to become pregnant, or if a pregnancy occurs, treatment with KOMBIGLYZE XR should be discontinued and switched to insulin treatment as soon as possible.

Breastfeeding
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. KOMBIGLYZE XR must therefore not be used in women who are breastfeeding (see *Contraindications*).

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 *Preclinical safety data*). For metformin, studies in animals have not shown reproductive toxicity (see *Preclinical safety data*).

Effects on ability to drive and to 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.

Undesirable effects

Clinical experience

In randomized, controlled, double-blind clinical trials, over 17.000 patients with type 2 diabetes have been treated with saxagliptin.

Adverse reactions associated with saxagliptin in the SAVOR trial

The SAVOR trial included 8240 patients treated with saxagliptin 5 mg or 2.5 mg once daily and 8173 patients on placebo. The mean duration of saxagliptin exposure regardless of interruptions was 1.8 years. A total of 3698 subjects (45%) were treated with saxagliptin for between 2 and 3 years.

The overall incidence of adverse events in patients treated with saxagliptin in this trial was similar to placebo (72.5% versus 72.2%, respectively). Discontinuation of therapy due to adverse events was similar between the two treatment groups (4.9% in the saxagliptin group and 5.0% in the placebo group).

The cardiovascular safety of saxagliptin was evaluated in the SAVOR trial which established that saxagliptin did not increase the cardiovascular risk (CV death, nonfatal MI, or nonfatal ischemic stroke) in patients with type 2 diabetes mellitus (T2DM) compared to placebo when added to current background therapy (Hazard Ratio [HR] 1.00; 95% Confidence Interval [CI]: 0.89, 1.12; P<0.001 for non-inferiority) (see *Cardiovascular safety*).

In the SAVOR trial, 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.

Hypoglycemia

In the SAVOR trial, the overall incidence of reported hypoglycemia (recorded in daily patient diaries) was 17.1% in saxagliptin-treated patients and 14.8% in placebo-treated patients.

The percent of subjects with reported on-treatment events of major hypoglycemia (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 and major hypoglycemia was primarily observed in subjects with A1C <7% at baseline.

There have been no therapeutic clinical trials conducted with KOMBIGLYZE XR tablets; however bioequivalence of KOMBIGLYZE XR with co-administered saxagliptin and metformin has been demonstrated (see *Pharmacokinetic properties*).

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 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.

Post marketing experience from clinical trials and spontaneous reports

Table 2 shows additional adverse reactions which have been reported in post marketing 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 Adverse Reaction	**Frequency of adverse reactions[1]**
Gastrointestinal disorders	
Nausea	Common
Pancreatitis	Uncommon
Immune system disorders	
Hypersensitivity reactions[2] (see sections Contraindications and Special warnings and precautions for use)	Uncommon
Anaphylactic reactions including anaphylactic shock (see sections Contraindications and Special warnings and precautions for use)	Rare
Skin and subcutaneous tissue disorders	
Angioedema (see sections Contraindications and Special warnings and precautions for use)	Rare
Dermatitis	Uncommon
Pruritus	Uncommon
Rash[2]	Common
Urticaria	Uncommon
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	Common

[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).

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.

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.

In the SAVOR trial, decreased lymphocyte counts were reported in 0.5% of saxagliptin treated patients and 0.4% of placebo-treated patients.

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 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.

Postmarketing experience

During postmarketing experience, the following adverse reactions have been reported with use of saxagliptin: acute pancreatitis, arthralgia, bullous pemphigoid and hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency

Overdose

No data are available with regard to overdose of KOMBIGLYZE XR.

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.

Pharmacological properties

Pharmacodynamic properties

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

Mechanism of action and pharmacodynamic effects

KOMBIGLYZE XR 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 safety and efficacy

Saxagliptin in combination with metformin immediate-release

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 immediate-release 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 add-on to metformin immediate-release compared with sulphonylurea add-on to metformin immediate-release

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 immediate-release compared with sitagliptin add-on to metformin immediate-release
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.

Metformin immediate-release
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).

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

Patients were randomly assigned to placebo (n=8212) or saxagliptin (5 mg or 2.5 mg for patients with moderate or severe renal insufficiency) once daily (n=8280). Randomization to

the saxagliptin and placebo groups was stratified by CV risk with 3533 patients (21.4%) with CV risk factors only and 12,959 patients (78.6%) with established CVD and by renal impairment including 13,916 subjects (84.4%) with normal renal function to mild impairment, 2240 subjects (13.6%) with moderate impairment, and 336 subjects (2.0%) with severe renal impairment. Patients with established CVD were defined by a history of ischemic heart disease, peripheral vascular disease, or ischemic stroke. Patients with CV risk factors only had age as a CV risk factor (men ≥55 years and women ≥60 years) plus at least one additional risk factor of dyslipidemia, hypertension, or current cigarette smoking.

The demographics and baseline characteristics of subjects were balanced between the saxagliptin and placebo groups. The study population was 67% male and 33% female with a mean age at randomization of 65 years. Of the 16,492 patients randomized, 8561 (52%) patients were 65 years and over and 2330 (14%) were 75 years and over.

All study subjects had a mean duration of T2DM of 12 years (median = 10.3) and a mean A1C level of 8.0% (median = 7.6%). Overall, 25% of subjects had baseline A1C levels <7%. Subjects were followed for a mean duration of 2 (median = 2.0) years.

Concomitant medication use was similar for the two treatment groups. Overall, the use of diabetes medications was consistent with local treatment practice and the saxagliptin clinical program (metformin 69%, insulin 41%, sulfonylureas 40%, and TZDs 6%). The use of CVD medications was also consistent with local treatment practice (ACE inhibitors or ARBs 79%, statins 78%, aspirin 75%, beta blockers 62%, and nonaspirin antiplatelet medications 24%). Approximately 6% of subjects were treated with diet and exercise only at baseline. Concomitant medications were managed throughout the trial to local guideline targets for glycemic control and CV risk reduction in order to minimize differences between the two treatment groups, particularly for glycemic control.

The primary safety and efficacy 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 ischemic stroke.

The primary safety objective of this trial was to establish that the upper bound of the 2-sided 95% CI for the estimated risk ratio comparing the incidence of the composite endpoint of CV death, non-fatal MI or non-fatal ischemic stroke observed with saxagliptin to that observed in the placebo group was <1.3.

The primary efficacy objective was to determine, as a superiority assessment, whether treatment with saxagliptin, compared with placebo when added to current background therapy, resulted in a significant reduction in the primary MACE endpoint.

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

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

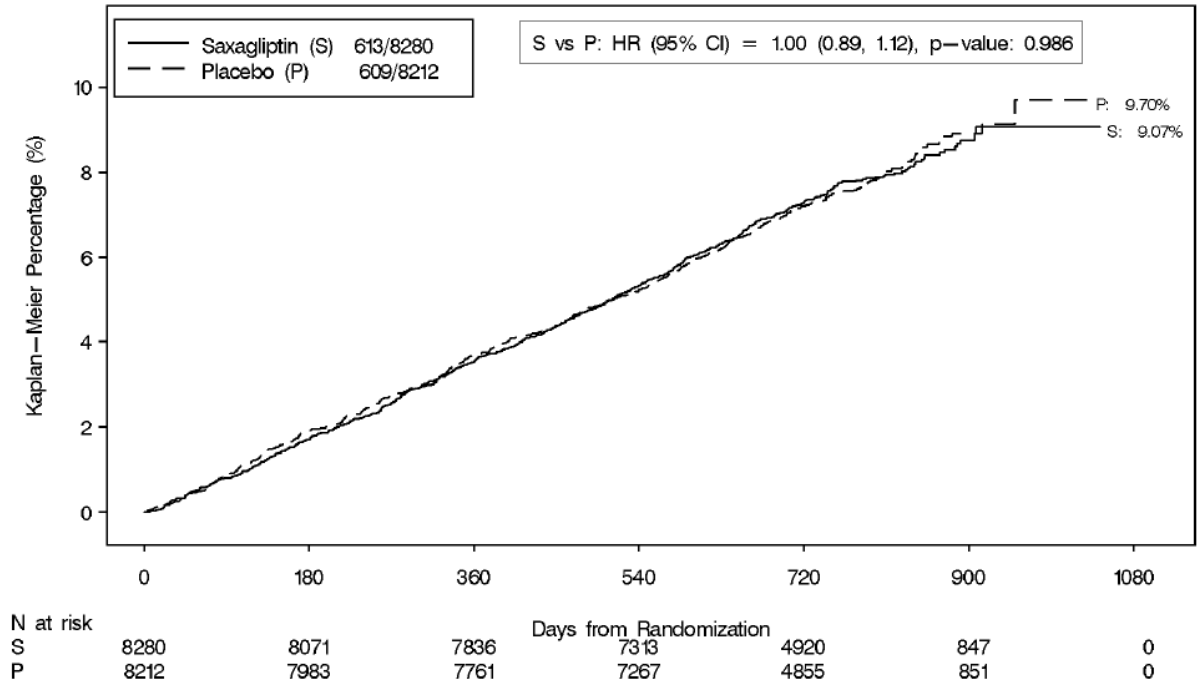
The primary efficacy endpoint did not demonstrate a statistically significant difference in major adverse coronary events for saxagliptin compared to placebo when added to current background therapy in patients with T2DM.

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

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

* Intent-to-treat population
† Hazard ratio adjusted for baseline renal function category and baseline CVD risk category.
‡ P-value <0.001 for non-inferiority (based on HR <1.3) compared to placebo.
§ P-value = 0.99 for superiority (based on HR <1.0) compared to placebo.
¶ Significance not tested.

Figure 7 Cumulative percent of time to first CV event for primary composite endpoint*



* Intent-to-treat population

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

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

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

Despite active management of concomitant antidiabetic therapy in both study arms, mean A1C levels were lower in the saxagliptin group compared to the placebo group at Year 1 (7.6% versus 7.9%, difference of -0.35% [95% CI: -0.38, -0.31]) and at Year 2 (7.6% versus 7.9%, difference of -0.30% [95% CI: -0.34, -0.26]). The proportions of subjects with A1C <7% in the saxagliptin group compared to the placebo group were 38% versus 27% at Year 1 and 38% versus 29% at Year 2.

Compared to placebo, saxagliptin resulted in less need for the initiation of new or increases in current oral diabetes medications or insulin. The improvements in A1C and the proportion of subjects reaching A1C targets among saxagliptin-treated subjects were observed despite lower rates of upward adjustments in diabetes medications or initiation of new diabetes medications or insulin compared with placebo.

Pharmacokinetic properties

The results of bioequivalence studies in healthy subjects demonstrated that KOMBIGLYZE XR 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 KOMBIGLYZE XR.

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
Saxagliptin
A single-dose, open-label study was conducted to evaluate the pharmacokinetics of saxagliptin (10-mg dose) in subjects with varying degrees of chronic renal impairment compared to subjects with normal renal function.
The degree of renal impairment did not affect the Cmax of saxagliptin or its major metabolite. In subjects with renal impairment with CrCL>50 mL/min (corresponding to eGFR ≥45 mL/min/1.73 m2) the AUC values of saxagliptin and its major metabolite were 1.2- and 1.7-fold higher, respectively, than AUC values in subjects with normal renal function. Because increases of this magnitude are not clinically relevant, dosage adjustment in these patients is not recommended.
In subjects with renal impairment with CrCL≤50 mL/min (corresponding to eGFR <45 mL/min/1.73 m2) or in subjects with ESRD on hemodialysis, the AUC values of saxagliptin

and its major metabolite were up to 2.1- and 4.5-fold higher, respectively, than AUC values in subjects with normal renal function. In these patients, the recommended dose is 2.5 mg once daily (see *Posology and method of administration* and *Special warnings and special precautions for use, Renal function*).
Saxagliptin is removed by hemodialysis.

Metformin hydrochloride
In patients with renal impairment, the plasma and blood half-life of metformin is prolonged in proportion to the decrease in 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 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 KOMBIGLYZE XR 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.

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 KOMBIGLYZE XR 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.

List of excipients

KOMBIGLYZE XR contains the following inactive ingredients: carboxymethylcellulose sodium, hypromellose 2208, and magnesium stearate. The 5 mg/500 mg strength tablet of KOMBIGLYZE XR also contains microcrystalline cellulose and hypermellose 2910. In addition, the film coatings contain the following inactive ingredients: polyvinyl alcohol, polyethylene glycol 3350, titanium dioxide, talc, and iron oxides.

Incompatibilities
None

Shelf Life
3 years

Special precautions for storage
Store below 30°C

Pack size
KOMBIGLYZE XR 5 mg/500 mg: Box of 4 blisters @ 7 film-coated tablets
(Reg. No.: DKI1359602217A1)

HARUS DENGAN RESEP DOKTER

Manufactured by

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