SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Alogliptin/Metformin Hydrochloride 12.5 mg/1000 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains alogliptin benzoate equivalent to 12.5 mg alogliptin and 1000 mg metformin hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Pale yellow, oblong (approximately 22.3 mm long by 10.7 mm wide), biconvex, film-coated tablets with “12.5/1000” debossed on one side and “322M” debossed on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Alogliptin/Metformin Hydrochloride is indicated in the treatment of adult patients aged 18 years and older with type 2 diabetes mellitus:

- as an adjunct to diet and exercise to improve glycaemic control in adult patients, inadequately controlled on their maximal tolerated dose of metformin alone, or those already being treated with the combination of alogliptin and metformin.
- in combination with pioglitazone (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled on their maximal tolerated dose of metformin and pioglitazone.
- in combination with insulin (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control.

4.2 Posology and method of administration

Posology
For the different dose regimens Alogliptin/Metformin Hydrochloride is available in strengths of 12.5 mg/850 mg and 12.5 mg/1,000 mg film-coated tablets.

Adults (≥ 18 years old) with normal renal function(glomerular filtration rate (GFR)≥ 90 mL/min)
The dose should be individualised on the basis of the patient's current treatment regimen.

For patients inadequately controlled on the maximal tolerated dose of metformin hydrochloride alone, the recommended dose is one tablet of 12.5 mg/850 mg or 12.5 mg/1,000 mg twice daily, corresponding to 25 mg alogliptin plus 1,700 mg or 2,000 mg metformin hydrochloride daily, depending on the dose of metformin hydrochloride already being taken.

For patients inadequately controlled on dual therapy with a maximal tolerated dose of metformin and pioglitazone, the dose of pioglitazone should be maintained, and Alogliptin/Metformin Hydrochloride administered concomitantly; alogliptin should be dosed at 12.5 mg twice daily (25 mg total daily dose) and metformin hydrochloride at a similar dose (either 850 mg or 1,000 mg twice daily) to that already being taken.

Caution should be exercised when alogliptin is used in combination with metformin and a thiazolidinedione as an increased risk of hypoglycaemia has been observed with this triple therapy (see section 4.4). In case of hypoglycaemia, a lower dose of the thiazolidinedione or metformin may be considered.

For patients switching from separate tablets of alogliptin and metformin (as dual therapy or as part of triple therapy with insulin), both alogliptin and metformin should be dosed at the total daily dose already being taken; the individual dose of alogliptin should be halved as it will be taken twice daily whilst the dosing of metformin should remain unchanged.

For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin, the dose of Alogliptin/Metformin Hydrochloride should provide alogliptin dosed at 12.5 mg twice daily (25 mg total daily dose) and a dose of metformin similar to the dose already being taken.

A lower dose of insulin may be considered to reduce the risk of hypoglycaemia.

Maximum daily dose
The maximum recommended daily dose of 25 mg alogliptin should not be exceeded.

Special populations
Elderly (≥ 65 years old)
No dose adjustment is necessary based on age. However, dosing of alogliptin should be conservative in patients with advanced age due to the potential for decreased renal function in this population

Renal impairment
A GFR should be assessed before initiation of treatment with metformin containing medicinal 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 metformin in patients with GFR<60 mL/min.
If no adequate strength of Alogliptin/Metformin Hydrochloride is available, individual monocomponents should be used instead of the fixed dose combination.

GFR mL/min	Metformin	Alogliptin*
60-89	Maximum daily dose is 3,000 mg Dose reduction may be considered in relation to declining renal function.	No dose adjustment Maximum daily dose is 25 mg
45-59	Maximum daily dose is 2,000 mg The starting dose is at most half of the maximum dose.	Maximum daily dose is 12.5 mg
30-44	Maximum daily dose is 1,000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 12.5 mg
< 30	Metformin is contra-indicated	Maximum daily dose is 6.25 mg

* Alogliptin dose adjustment is based on a pharmacokinetic study where kidney function was assessed using creatinine clearance (CrCl) levels estimated from the Cockcroft-Gault equation.

Hepatic impairment
Alogliptin/Metformin Hydrochloride must not be used in patients with hepatic impairment (see sections 4.3, 4.4 and 5.2).

Paediatric population
The safety and efficacy of Alogliptin/Metformin Hydrochloride in children and adolescents < 18 years old have not been established. No data are available.

Method of administration

Oral use.

Alogliptin/Metformin Hydrochloride should be taken twice daily because of the pharmacokinetics of its metformin component. It should also be taken with meals to reduce the gastrointestinal adverse reactions associated with metformin. The tablets should be swallowed whole with water.

If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken at the same time. In that case, the missed dose should be skipped.

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 (DPP-4) 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)
- Acute conditions with the potential to alter renal function such as:
    - dehydration
    - severe infection
    - shock
- Acute or chronic disease which may cause tissue hypoxia (see section 4.4) such as:
    - cardiac or respiratory failure
    - recent myocardial infarction
    - shock
- Hepatic impairment (see section 4.4)
- Acute alcohol intoxication, alcoholism (see sections 4.4 and 4.5)

4.4 Special warnings and precautions for use

General

Alogliptin/Metformin Hydrochloride should not be used in patients with type 1 diabetes mellitus. Alogliptin/Metformin Hydrochloride is not a substitute for insulin in insulin-requiring patients.

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) Alogliptin/Metformin Hydrochloride 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 nonsteroidal anti-inflammatory drugs (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 Alogliptin/Metformin Hydrochloride and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (>5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

Administration of iodinated contrast agents

Intravascular administration of iodinated contrast media may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Alogliptin/Metformin Hydrochloride 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.

Renal function

GFR should be assessed before treatment initiation and regularly thereafter (see section 4.2). Metformin is contraindicated in patients with 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 nonsteroidal anti-inflammatory drug (NSAID).

Surgery

As Alogliptin/Metformin Hydrochloride contains metformin it must be discontinued at the time of surgery under general, spinal or epidural anesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Hepatic impairment

Alogliptin has not been studied in patients with severe hepatic impairment (Child-Pugh score >9) and is, therefore, not recommended for use in such patients (see sections 4.2, 4.3 and 5.2).

Use with other antihyperglycaemic medicinal products and hypoglycaemia

Insulin is known to cause hypoglycaemia. Therefore, a lower dose of insulin may be considered to reduce the risk of hypoglycaemia when this medicinal product is used in combination with Alogliptin/Metformin Hydrochloride (see section 4.2).

Due to the increased risk of hypoglycaemia in combination with pioglitazone, a lower dose of pioglitazone may be considered to reduce the risk of hypoglycaemia when this medicinal product is used in combination with Alogliptin/Metformin Hydrochloride (see section 4.2).

Combinations not studied

Alogliptin/Metformin Hydrochloride should not be used in combination with a sulphonylurea, as the safety and efficacy of this combination have not been fully established.

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

As Alogliptin/Metformin Hydrochloride contains metformin, any patient with type 2 diabetes mellitus previously well controlled on Alogliptin/Metformin Hydrochloride 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, Alogliptin/Metformin Hydrochloride must be stopped immediately, and other appropriate corrective measures initiated.

Hypersensitivity reactions

Hypersensitivity reactions, including anaphylactic reactions, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome and erythema multiforme have been observed for DPP-4 inhibitors and have been spontaneously reported for alogliptin in the post-marketing setting. In clinical studies of alogliptin, anaphylactic reactions were reported with a low incidence.

Acute pancreatitis

Use of DPP-4 inhibitors has been associated with a risk of developing acute pancreatitis. In a pooled analysis of the data from 13 studies, the overall rates of pancreatitis reports in patients treated with 25 mg alogliptin, 12.5 mg alogliptin, active control or placebo were 2, 1, 1 or 0 events per 1,000 patient years, respectively. In the cardiovascular outcomes study the rates of pancreatitis reports in patients treated with alogliptin or placebo were 3 or 2 events per 1,000 patient years, respectively. There have been spontaneously reported adverse reactions of acute pancreatitis in the post-marketing setting. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain, which may radiate to the back. If pancreatitis is suspected, Alogliptin/Metformin Hydrochloride should be discontinued; if acute pancreatitis is confirmed, Alogliptin/Metformin Hydrochloride should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Hepatic effects

Postmarketing reports of hepatic dysfunction including hepatic failure have been received. A causal relationship has not been established. Patients should be observed closely for possible liver abnormalities. Obtain liver function tests promptly in patients with symptoms suggestive of liver injury. If an abnormality is found and an alternative etiology is not established, consider discontinuation of alogliptin treatment.

Bullous Pemphigoid

There have been post-marketing reports of bullous pemphigoid in patients taking DPP-4 inhibitors including alogliptin. If bullous pemphigoid is suspected, alogliptin should be discontinued.

Vitamin B12 deficiency

Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with

risk factors known to cause vitamin B12 deficiency. If vitamin B12 deficiency is suspected (such as anaemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contra-indicated, with appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of 100 mg alogliptin once daily and 1,000 mg metformin hydrochloride twice daily for 6 days in healthy subjects had no clinically relevant effects on the pharmacokinetics of alogliptin or metformin.

Specific pharmacokinetic drug interaction studies have not been performed with Alogliptin/Metformin Hydrochloride. The following section outlines the interactions observed with the individual components of Alogliptin/Metformin Hydrochloride as reported in their respective Summary of Product Characteristics.

Interactions with metformin

Concomitant use not recommended
Alcohol
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting, malnutrition or hepatic impairment.

Iodinated contrast agents
Alogliptin/Metformin Hydrochloride 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 4.5.

Cationic medicinal products
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 (400 mg twice daily) increased metformin systemic exposure (area under the curve, 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.

Combination requiring precautions for use
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, angiotensin-converting enzyme (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.

Medicinal products with intrinsic hyperglycaemic activity
Glucocorticoids (given by systemic and local routes), beta-2-agonists and diuretics (see also section 4.4) have intrinsic hyperglycaemic activity. The patient should be informed, and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicinal products. If necessary, the dose of Alogliptin/Metformin Hydrochloride should be adjusted during therapy with the other medicinal product and upon its discontinuation.

ACE inhibitors
ACE inhibitors may decrease blood glucose levels. If necessary, the dose of Alogliptin/Metformin Hydrochloride should be adjusted during therapy with the other medicinal product and upon its discontinuation.

Effects of other medicinal products on alogliptin

Alogliptin is primarily excreted unchanged in the urine and metabolism by the cytochrome (CYP) P450 enzyme system is negligible (see section 5.2). Interactions with CYP inhibitors are thus not expected and have not been shown.

Results from clinical interaction studies also demonstrate that there are no clinically relevant effects of gemfibrozil (a CYP2C8/9 inhibitor), fluconazole (a CYP2C9 inhibitor), ketoconazole (a CYP3A4 inhibitor), cyclosporine (a p-glycoprotein inhibitor), voglibose (an alpha-glucosidase inhibitor), digoxin, metformin, cimetidine, pioglitazone or atorvastatin on the pharmacokinetics of alogliptin.

Effects of alogliptin on other medicinal products

In vitro studies suggest that alogliptin does not inhibit nor induce CYP 450 isoforms at concentrations achieved with the recommended dose of 25 mg alogliptin (see section 5.2). Interaction with substrates of CYP 450 isoforms are thus not expected and have not been shown. In studies *in vitro*, alogliptin was found to be neither a substrate nor an inhibitor of key transporters associated with disposition of the active submstance in the kidney: organic anion transporter-1, organic anion transporter-3 or organic cationic transporter-2 (OCT2). Furthermore, clinical data do not suggest interaction with p-glycoprotein inhibitors or substrates.

In clinical studies, alogliptin had no clinically relevant effect on the pharmacokinetics of caffeine, (R)-warfarin, pioglitazone, glyburide, tolbutamide, (S)-warfarin, dextromethorphan, atorvastatin, midazolam, an oral contraceptive (norethindrone and ethinyl oestradiol), digoxin, fexofenadine, metformin, or cimetidine, thus providing *in vivo* evidence of a low propensity to cause interaction with substrates of CYP1A2, CYP3A4, CYP2D6, CYP2C9, p-glycoprotein, and OCT2.

In healthy subjects, alogliptin had no effect on prothrombin time or International Normalised Ratio (INR) when administered concomitantly with warfarin.

Combination of alogliptin with other anti-diabetic medicinal products

Results from studies with metformin, pioglitazone (thiazolidinedione), voglibose (alpha-glucosidase inhibitor) and glyburide (sulphonylurea) have shown no clinically relevant pharmacokinetic interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Alogliptin/Metformin Hydrochloride in pregnant women. Studies in pregnant rats with alogliptin plus metformin as combination treatment have shown reproductive toxicity (see section 5.3) at approximately 5-20 times (for metformin and alogliptin respectively) the human exposure at the recommended dose.

Alogliptin/Metformin Hydrochloride should not be used during pregnancy.

Risk related to alogliptin
There are no data from the use of alogliptin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Risk related to metformin
A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at clinically relevant doses (see section 5.3).

Breast-feeding

No studies in lactating animals have been conducted with the combined active substances of Alogliptin/Metformin Hydrochloride. In studies performed with the individual active substances, both alogliptin and metformin were excreted in the milk of lactating rats. It is unknown whether alogliptin is excreted in human milk. Metformin is excreted in human milk in small amounts. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Alogliptin/Metformin Hydrochloride therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effect of Alogliptin/Metformin Hydrochloride on fertility in humans has not been studied. No adverse effects on fertility were observed in animal studies conducted with alogliptin or with metformin (see section 5.3).

4.7 Effects on ability to drive and use machines

Alogliptin/Metformin Hydrochloride has no or negligible influence on the ability to drive and use machines. However, patients should be alerted to the risk of hypoglycaemia especially when used in combination with insulin or pioglitazone.

4.8 Undesirable effects

Summary of the safety profile

Acute pancreatitis is a serious adverse reaction and is attributed to the alogliptin component of Alogliptin/Metformin Hydrochloride (see section 4.4). Hypersensitivity reactions, including Stevens-Johnson syndrome, anaphylactic reactions, and angioedema are serious and are attributed to the alogliptin component of Alogliptin/Metformin Hydrochloride (see section 4.4). Lactic acidosis is a serious adverse reaction, which may occur very rarely (<1/10,000) and is attributed to the metformin component of Alogliptin/Metformin Hydrochloride (see section 4.4). Other reactions such as upper respiratory tract infections, nasopharyngitis, headache, gastroenteritis, abdominal pain, diarrhoea, vomiting, gastritis, gastroesophageal reflux disease, pruritus, rash, hypoglycaemia may occur commonly (≥ 1/100 to < 1/10) (see section 4.4) which are attributed to Alogliptin/Metformin Hydrochloride.

Clinical studies conducted to support the efficacy and safety of Alogliptin/Metformin Hydrochloride involved the co-administration of alogliptin and metformin as separate tablets. However, the results of bioequivalence studies have demonstrated that Alogliptin/Metformin Hydrochloride film-coated tablets are bioequivalent to the corresponding doses of alogliptin and metformin co-administered as separate tablets.

The information provided is based on a total of 7,150 patients with type 2 diabetes mellitus, including 4,201 patients treated with alogliptin and metformin, who participated in 7 phase 3 double-blind, placebo- or active-controlled clinical studies. These studies evaluated the effects of co-administered alogliptin and metformin on glycaemic control and their safety as initial combination therapy, as dual therapy in patients initially treated with metformin alone, and as add-on therapy to a thiazolidinedione or insulin.

Tabulated list of adverse reactions

The adverse reactions are listed by system organ class and 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); very rare (<1/10,000), not known (cannot be estimated from available data).

System organ class **Adverse reaction**	**Frequency of adverse reactions**		
	Alogliptin	**Metformin**	**Alogliptin/Metformin Hydrochloride**
Infections and infestations			
upper respiratory tract infections	common		common
nasopharyngitis	common		common
Immune system disorders			
Hypersensitivity*	not known		
Metabolism and nutrition disorders			
lactic acidosis*		very rare	
vitamin B12 decrease/deficiency*		common	
Hypoglycaemia*	common		common
Nervous system disorders			
headache	common		common
metallic taste		common	

System organ class **Adverse reaction**	**Frequency of adverse reactions**		
	Alogliptin	**Metformin**	**Alogliptin/Metformin Hydrochloride**
Gastrointestinal disorders			
gastroenteritis			common
abdominal pain*	common	very common	common
Diarrhoea*	common	very common	common
Vomiting*		very common	common
gastritis			common
gastroesophageal reflux disease	common		common
loss of appetite		very common	
nausea		very common	
acute pancreatitis*	not known		
Hepatobiliary disorders			
hepatitis		very rare	
Liver function test abnormalities*		very rare	
hepatic dysfunction including hepatic failure*	not known		
Skin and subcutaneous tissue disorders			
pruritus	common	very rare	common
rash	common		common
erythema		very rare	
exfoliative skin conditions including Stevens-Johnson syndrome*	not known		
erythema multiforme*	not known		
Angioedema*	not known		
Urticaria	not known	very rare	
bullous pemphigoid*	not known		
Renal and urinary disorders			
interstitial nephritis	not known		
* see section 4.4 for further information			

Description of selected adverse reactions

Lactic acidosis: 0.03 cases/1,000 patient-years (see section 4.4).

Gastrointestinal symptoms occur most frequently during initiation of therapy and resolve spontaneously in most cases. These may be prevented by taking metformin in 2 daily doses during or after meals.

Isolated cases of hepatitis or liver function test abnormalities resolving on discontinuation of metformin have been reported.

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 at Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the GooglePlay or Apple App Store.

4.9 Overdose

No data are available with regard to overdose of Alogliptin/Metformin Hydrochloride.

Alogliptin

The highest doses of alogliptin administered in clinical studies were single doses of 800 mg to healthy subjects and doses of 400 mg once daily for 14 days to patients with type 2 diabetes mellitus (equivalent to 32 times and 16 times the recommended total daily dose of 25 mg alogliptin, respectively).

Metformin

A large overdose of metformin or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital.

Management

In the event of an overdose, appropriate supportive measures should be employed as dictated by the patient's clinical status.

Minimal quantities of alogliptin are removed by haemodialysis (approximately 7% of the substance was removed during a 3-hour haemodialysis session). Therefore, haemodialysis is of little clinical benefit in removing alogliptin in overdose. It is not known if alogliptin is removed by peritoneal dialysis.

The most effective method of removing lactate and metformin is haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Medicinal products used in diabetes; combinations of oral blood glucose lowering medicinal products.

ATC code: A10BD13.

Mechanism of action and pharmacodynamic effects

Alogliptin/Metformin Hydrochloride combines two antihyperglycaemic medicinal products with complementary and distinct mechanisms of action to improve glycaemic control in patients with type 2 diabetes mellitus: alogliptin, a

dipeptidyl-peptidase-4 (DPP-4) inhibitor, and metformin, a member of the biguanide class.

Alogliptin
Alogliptin is a potent and highly selective inhibitor of DPP-4, >10,000-fold more selective for DPP-4 than other related enzymes including DPP-8 and DPP-9. DPP-4 is the principal enzyme involved in the rapid degradation of the incretin hormones, glucagon-like peptide-1 (GLP-1) and GIP (glucose-dependent insulinotropic polypeptide), which are released by the intestine and levels are increased in response to a meal. GLP-1 and GIP increases insulin biosynthesis and secretion from pancreatic beta cells, while GLP-1 also inhibits glucagon secretion and hepatic glucose production. Alogliptin therefore improves glycaemic control via a glucose-dependent mechanism, whereby insulin release is enhanced and glucagon levels are suppressed when glucose levels are high.

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 3 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. It also 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 cholesterol and triglyceride levels.

Clinical efficacy

Clinical studies conducted to support the efficacy of Alogliptin/Metformin Hydrochloride involved the co-administration of alogliptin and metformin as separate tablets. However, the results of bioequivalence studies have demonstrated that Alogliptin/Metformin Hydrochloride film-coated tablets are bioequivalent to the corresponding doses of alogliptin and metformin co-administered as separate tablets.

The co-administration of alogliptin and metformin has been studied as dual therapy in patients initially treated with metformin alone, and as add-on therapy to a thiazolidinedione or insulin.

Administration of 25 mg alogliptin to patients with type 2 diabetes mellitus produced peak inhibition of DPP-4 within 1 to 2 hours and exceeded 93% both after a single 25 mg dose and after 14 days of once-daily dosing. Inhibition of DPP-4 remained above 81% at 24 hours after 14 days of dosing. When the 4-hour postprandial glucose concentrations were averaged across breakfast, lunch and dinner, 14 days of treatment with 25 mg alogliptin resulted in a mean placebo-corrected reduction from baseline of -35.2 mg/dL.

Both 25 mg alogliptin alone and in combination with 30 mg pioglitazone demonstrated significant decreases in postprandial glucose and postprandial glucagon whilst significantly increasing postprandial active GLP-1 levels at Week 16 compared to placebo ($p<0.05$). In addition, 25 mg alogliptin alone and in combination with 30 mg pioglitazone produced statistically significant ($p<0.001$) reductions in total triglycerides at Week 16 as measured by postprandial incremental $AUC_{(0-8)}$ change from baseline compared to placebo.

A total of 7,151 patients with type 2 diabetes mellitus, including 4,202 patients treated with alogliptin and metformin, participated in 7 phase 3 double-blind, placebo- or active-controlled clinical studies conducted to evaluate the effects of co-administered alogliptin and metformin on glycaemic control and their safety. In these studies, 696 alogliptin/metformin-treated patients were ≥ 65 years old.

Overall, treatment with the recommended total daily dose of 25 mg alogliptin in combination with metformin improved glycaemic control. This was determined by clinically relevant and statistically significant reductions in glycosylated haemoglobin (HbA1c) and fasting plasma glucose compared to control from baseline to study endpoint. Reductions in HbA1c were similar across different subgroups including renal impairment, age, gender and body mass index, while differences between races (e.g. White and non-White) were small. Clinically meaningful reductions in HbA1c compared to control were also observed regardless of baseline background treatment. Higher baseline HbA1c was associated with a greater reduction in HbA1c. Generally, the effects of alogliptin on body weight and lipids were neutral.

Alogliptin as add-on therapy to metformin

The addition of 25 mg alogliptin once daily to metformin hydrochloride therapy (mean dose = 1,847 mg) resulted in statistically significant improvements from baseline in HbA1c and fasting plasma glucose at Week 26 when compared to the addition of placebo (Table 5). Significantly more patients receiving 25 mg alogliptin (44.4%) achieved target HbA1c levels of ≤7.0% compared to those receiving placebo (18.3%) at Week 26 ($p<0.001$).

The addition of 25 mg alogliptin once daily to metformin hydrochloride therapy (mean dose = 1,835 mg) resulted in improvements from baseline in HbA1c at Week 52 and Week 104. At Week 52, the HbA1c reduction by 25 mg alogliptin plus metformin (-0.76%, Table 6) was similar to that produced by glipizide (mean dose = 5.2 mg) plus metformin hydrochloride therapy (mean dose = 1,824 mg, -0.73%). At Week 104, the HbA1c reduction by 25 mg alogliptin plus metformin (-0.72%, Table 6) was greater than that produced by glipizide plus metformin (-0.59%). Mean change from baseline in fasting plasma glucose at Week 52 for 25 mg alogliptin and metformin was significantly greater than that for glipizide and metformin ($p<0.001$). By Week 104, mean change from baseline in fasting plasma glucose for 25 mg alogliptin and metformin was -3.2 mg/dL compared with 5.4 mg/dL for glipizide and metformin. More patients receiving 25 mg alogliptin and metformin (48.5%) achieved target HbA1c levels of ≤7.0% compared to those receiving glipizide and metformin (42.8%) ($p=0.004$).

Co-administration of 12.5 mg alogliptin and 1,000 mg metformin hydrochloride twice daily resulted in statistically significant improvements from baseline in HbA1c and fasting plasma glucose at Week 26 when compared to either 12.5 mg alogliptin twice daily alone or 1,000 mg metformin hydrochloride twice daily alone. Significantly more patients receiving 12.5 mg alogliptin and 1.000 mg metformin hydrochloride twice daily (59.5%) achieved target HbA1c levels of < 7.0% compared to those receiving either 12.5 mg alogliptin twice daily alone (20.2%, $p<0.001$) or 1,000 mg metformin hydrochloride twice daily alone (34.3%, $p<0.001$) at Week 26.

Alogliptin as add-on therapy to metformin with a thiazolidinedione

The addition of 25 mg alogliptin once daily to pioglitazone therapy (mean dose = 35.0 mg, with or without metformin or a sulphonylurea) resulted in statistically significant improvements from baseline in HbA1c and fasting plasma glucose at Week 26 when compared to the addition of placebo (Table 5). Clinically meaningful reductions in HbA1c compared to placebo were also observed with 25 mg alogliptin regardless of whether patients were receiving concomitant metformin or sulphonylurea therapy. Significantly more patients receiving 25 mg alogliptin (49.2%) achieved target HbA1c levels of ≤7.0% compared to those receiving placebo (34.0%) at Week 26 ($p=0.004$).

The addition of 25 mg alogliptin once daily to 30 mg pioglitazone in combination with metformin hydrochloride therapy (mean dose = 1,867.9 mg) resulted in improvements from baseline in HbA1c at Week 52 that were both non-inferior and statistically superior to those produced by 45 mg pioglitazone in combination with metformin hydrochloride therapy (mean dose = 1,847.6 mg, Table 6). The significant reductions in HbA1c observed with 25 mg alogliptin plus 30 mg pioglitazone and metformin were consistent over the entire 52-week treatment period compared to 45 mg pioglitazone and metformin ($p<0.001$ at all time points). In addition, mean change from baseline in FPG at Week 52 for 25 mg alogliptin plus 30 mg pioglitazone and metformin was significantly greater than that for 45 mg pioglitazone and metformin ($p<0.001$). Significantly more patients receiving 25 mg alogliptin plus 30 mg pioglitazone and metformin (33.2%) achieved target HbA1c levels of ≤7.0% compared to those receiving 45 mg pioglitazone and metformin (21.3%) at Week 52 ($p<0.001$).

Alogliptin as add-on therapy to metformin with insulin

The addition of 25 mg alogliptin once daily to insulin therapy (mean dose = 56.5 IU, with or without metformin) resulted in statistically significant improvements from baseline in HbA1c and FPG at Week 26 when compared to the addition of placebo (Table 5). Clinically meaningful reductions in HbA1c compared to placebo were also observed with 25 mg alogliptin regardless of whether patients were receiving concomitant metformin therapy. More patients receiving 25 mg alogliptin (7.8%) achieved target HbA1c levels of ≤7.0% compared to those receiving placebo (0.8%) at Week 26.

Table 5: Change in HbA1c (%) from baseline with alogliptin 25 mg at Week 26 by placebo-controlled study (FAS, LOCF)

Study	Mean baseline HbA1c (%) (SD)	Mean change from baseline in HbA1c (%)[†] (SE)	Placebo-corrected change from baseline in HbA1c (%)[†] (2-sided 95% CI)
Add-on combination therapy placebo-controlled studies			
Alogliptin 25 mg once daily with metformin (n=203)	7.93 (0.799)	-0.59 (0.054)	-0.48* (-0.67, -0.30)
Alogliptin 25 mg once daily with a sulphonylurea (n=197)	8.09 (0.898)	-0.52 (0.058)	-0.53* (-0.73, -0.33)
Alogliptin 25 mg once daily with a thiazolidinedione ± metformin or a sulphonylurea (n=195)	8.01 (0.837)	-0.80 (0.056)	-0.61* (-0.80, -0.41)
Alogliptin 25 mg once daily with insulin ± metformin (n=126)	9.27 (1.127)	-0.71 (0.078)	-0.59* (-0.80, -0.37)

FAS = full analysis set
LOCF = last observation carried forward
[†] Least squares means adjusted for prior antihyperglycaemic therapy status and baseline values
* $p<0.001$ compared to placebo or placebo+combination treatment

Table 6: Change in HbA1c (%) from baseline with alogliptin 25 mg by active-controlled study (PPS, LOCF)

Study	Mean baseline HbA1c (%) (SD)	Mean change from baseline in HbA1c (%)[†] (SE)	Treatment-corrected change from baseline in HbA1c (%)[†] (1-sided CI)
Add-on combination therapy studies			
Alogliptin 25 mg once daily with metformin vs a sulphonylurea + metformin			
Change at Week 52 (n=382)	7.61 (0.526)	-0.76 (0.027)	-0.03 (-infinity, 0.059)
Change at Week 104 (n=382)	7.61 (0.526)	-0.72 (0.037)	-0.13* (-infinity, -0.006)
Alogliptin 25 mg once daily with a thiazolidinedione + metformin vs a titrating thiazolidinedione + metformin			
Change at Week 26 (n=303)	8.25 (0.820)	-0.89 (0.042)	-0.47* (-infinity, -0.35)
Change at Week 52 (n=303)	8.25 (0.820)	-0.70 (0.048)	-0.42* (-infinity, -0.28)

PPS = per protocol set
LOCF = last observation carried forward
*Non inferiority and superiority statistically demonstrated
[†] Least squares means adjusted for prior antihyperglycaemic therapy status and baseline values

Elderly (≥ 65 years old)
The efficacy and safety of the recommended doses of alogliptin and metformin in a subgroup of patients with type 2 diabetes mellitus and ≥ 65 years old were reviewed and found to be consistent with the profile obtained in patients < 65 years old.

Clinical safety

Cardiovascular Safety
In a pooled analysis of the data from 13 studies, the overall incidences of cardiovascular death, non fatal myocardial infarction and non-fatal stroke were comparable in patients treated with 25 mg alogliptin, active control or placebo.

In addition, a prospective randomised cardiovascular outcomes safety study was conducted with 5,380 patients with high underlying cardiovascular risk to examine the effect of alogliptin compared with placebo (when added to standard of care) on major adverse cardiovascular events (MACE) including time to the first occurrence of any event in the composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke in patients with a recent (15 to 90 days) acute coronary event. At baseline, patients had a mean age of 61 years, mean duration of diabetes of 9.2 years, and mean HbA1c of 8.0%.

The study demonstrated that alogliptin did not increase the risk of having a MACE compared to placebo [Hazard Ratio: 0.96; 1-sided 99% Confidence Interval: 0-1.16]. In the alogliptin group, 11.3% of patients experienced a MACE compared to 11.8% of patients in the placebo group.

Table 7. MACE Reported in cardiovascular outcomes study

	Number of Patients (%)	
	Alogliptin 25 mg	**Placebo**
	N=2,701	N=2,679
Primary Composite Endpoint [First Event of CV Death, Nonfatal MI and Nonfatal Stroke]	**305 (11.3)**	**316 (11.8)**
Cardiovascular Death*	89 (3.3)	111 (4.1)
Nonfatal Myocardial Infarction	187 (6.9)	173 (6.5)
Nonfatal Stroke	29 (1.1)	32 (1.2)
*Overall there were 153 subjects (5.7%) in the alogliptin group and 173 subjects (6.5%) in the placebo group who died (all-cause mortality)		

There were 703 patients who experienced an event within the secondary MACE composite endpoint (first event of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke and urgent revascularization due to unstable angina). In the alogliptin group, 12.7% (344 subjects) experienced an event within the secondary MACE composite endpoint, compared with 13.4% (359 subjects) in the placebo group [Hazard Ratio = 0.95; 1-sided 99% Confidence Interval: 0-1.14].

Hypoglycaemia
In a pooled analysis of the data from 12 studies, the overall incidence of any episode of hypoglycaemia was lower in patients treated with 25 mg alogliptin than in patients treated with 12.5 mg alogliptin, active control or placebo (3.6%, 4.6%, 12.9% and 6.2%, respectively). The majority of these episodes were mild to moderate in intensity. The overall incidence of episodes of severe hypoglycaemia was comparable in patients treated with 25 mg alogliptin or 12.5 mg alogliptin, and lower than the incidence in patients treated with active control or placebo (0.1%, 0.1%, 0.4% and 0.4%, respectively). In the prospective randomised controlled cardiovascular outcomes study, investigator reported events of hypoglycemia were similar in patients receiving placebo (6.5%) and patients receiving alogliptin (6.7%) in addition to standard of care.

In a clinical trial of alogliptin as mono-therapy, the incidence of hypoglycaemia was similar to that of placebo, and lower than placebo in another trial as add-on to a sulphonylurea.

Higher rates of hypoglycaemia were observed with triple therapy with a thiazolidinedione and metformin and in combination with insulin, as observed with other DPP-4 inhibitors.

Patients (≥ 65 years old) with type 2 diabetes mellitus are considered more susceptible to episodes of hypoglycaemia than patients < 65 years old. In a pooled analysis of the data from 12 studies, the overall incidence of any episode of hypoglycaemia was similar in patients ≥ 65 years old treated with 25 mg alogliptin (3.8%) to that in patients < 65 years old (3.6%).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Alogliptin/Metformin Hydrochloride in all subsets of the paediatric population in the treatment of 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 Alogliptin/Metformin Hydrochloride film-coated tablets are bioequivalent to the corresponding doses of alogliptin and metformin co-administered as separate tablets.

Co-administration of 100 mg alogliptin once daily and 1,000 mg metformin hydrochloride twice daily for 6 days in healthy subjects had no clinically relevant effects on the pharmacokinetics of alogliptin or metformin.

Administration of Alogliptin/Metformin Hydrochloride with food resulted in no change in total exposure (AUC) to alogliptin or metformin. However, mean peak plasma concentrations of alogliptin and metformin were decreased by 13% and 28% when Alogliptin/Metformin Hydrochloride was administered with food, respectively. There was no change in the time to peak plasma concentration (T_{max}) for alogliptin, but there was a delayed T_{max} for metformin of 1.5 hours. These changes are not likely to be clinically significant (see below).

Alogliptin/Metformin Hydrochloride should be taken twice daily because of the pharmacokinetics of its metformin component. It should also be taken with meals to reduce the gastrointestinal undesirable effects associated with metformin (see section 4.2).

The pharmacokinetics of Alogliptin/Metformin Hydrochloride in children and adolescents < 18 years old has not been established. No data are available (see section 4.2).

The following section outlines the pharmacokinetic properties of the individual components of Alogliptin/Metformin Hydrochloride as reported in their respective Summary of Product Characteristics.

Alogliptin

The pharmacokinetics of alogliptin has been shown to be similar in healthy subjects and in patients with type 2 diabetes mellitus.

Absorption

The absolute bioavailability of alogliptin is approximately 100%.

Administration with a high-fat meal resulted in no change in total and peak exposure to alogliptin. Alogliptin may, therefore, be administered with or without food.

After administration of single oral doses of up to 800 mg in healthy subjects, alogliptin was rapidly absorbed with peak plasma concentrations occurring 1 to 2 hours (median T_{max}) after dosing.

No clinically relevant accumulation after multiple dosing was observed in either healthy subjects or in patients with type 2 diabetes mellitus.

Total and peak exposure to alogliptin increased proportionately across single doses of 6.25 mg up to 100 mg alogliptin (covering the therapeutic dose range). The inter-subject coefficient of variation for alogliptin AUC was small (17%).

Distribution

Following a single intravenous dose of 12.5 mg alogliptin to healthy subjects, the volume of distribution during the terminal phase was 417 L indicating that the active substance is well distributed into tissues.

Alogliptin is 20-30% bound to plasma proteins.

Biotransformation

Alogliptin does not undergo extensive metabolism, 60-70% of the dose is excreted as unchanged active substance in the urine.

Two minor metabolites were detected following administration of an oral dose of [^{14}C] alogliptin, N-demethylated alogliptin, M-I (< 1% of the parent compound), and N-acetylated alogliptin, M-II (< 6% of the parent compound). M-I is an active metabolite and is a highly selective inhibitor of DPP-4 similar to alogliptin; M-II does not display any inhibitory activity towards DPP-4 or other DPP-related enzymes. *In vitro* data indicate that CYP2D6 and CYP3A4 contribute to the limited metabolism of alogliptin.

In vitro studies indicate that alogliptin does not induce CYP1A2, CYP2B6 and CYP2C9 and does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 at concentrations achieved with the recommended dose of 25 mg alogliptin. Studies *in vitro* have shown alogliptin to be a mild inducer of CYP3A4, but alogliptin has not been shown to induce CYP3A4 in studies in vivo.

In studies *in vitro*, alogliptin was not an inhibitor of the following renal transporters; OAT1, OAT3 and OCT2.

Alogliptin exists predominantly as the (R)-enantiomer (> 99%) and undergoes little or no chiral conversion *in vivo* to the (S)-enantiomer. The (S)-enantiomer is not detectable at therapeutic doses.

Elimination

Alogliptin was eliminated with a mean terminal half-life ($T_{1/2}$) of approximately 21 hours.

Following administration of an oral dose of [^{14}C] alogliptin, 76% of total radioactivity was eliminated in the urine and 13% was recovered in the faeces.

The average renal clearance of alogliptin (170 mL/min) was greater than the average estimated glomerular filtration rate (approx. 120 mL/min), suggesting some active renal excretion.

Time-dependency
Total exposure ($AUC_{(0\text{-}inf)}$) to alogliptin following administration of a single dose was similar to exposure during one dose interval ($AUC_{(0\text{-}24)}$) after 6 days of once daily dosing. This indicates no time-dependency in the kinetics of alogliptin after multiple dosing.

Special populations

Renal impairment
A single dose of 50 mg alogliptin was administered to 4 groups of patients with varying degrees of renal impairment (CrCl using the Cockcroft-Gault formula): mild (CrCl = > 50 to ≤ 80 mL/min), moderate (CrCl = ≥ 30 to ≤ 50 mL/min), severe (CrCl = < 30 mL/min) and end-stage renal disease on haemodialysis.

An approximate 1.7-fold increase in AUC for alogliptin was observed in patients with mild renal impairment. However, as the distribution of AUC values for alogliptin in these patients was within the same range as control subjects, no dose adjustment of alogliptin for patients with mild renal impairment is necessary (see section 4.2).

In patients with moderate or severe renal impairment, or end-stage renal disease on haemodialysis, an increase in systemic exposure to alogliptin of approximately 2- and 4-fold was observed, respectively. (Patients with end-stage renal disease underwent haemodialysis immediately after alogliptin dosing. Based on mean dialysate concentrations, approximately 7% of the active substance was removed during a 3-hour haemodialysis session.) Therefore, in order to maintain systemic exposures to alogliptin that are similar to those observed in patients with normal renal function, lower doses of alogliptin should be used in patients with moderate or severe renal impairment, or end-stage renal disease requiring dialysis (see above and section 4.2).

Hepatic impairment
Total exposure to alogliptin was approximately 10% lower and peak exposure was approximately 8% lower in patients with moderate hepatic impairment compared to control subjects. The magnitude of these reductions was not considered to be clinically relevant. Therefore, no dose adjustment of alogliptin is necessary for patients with mild to moderate hepatic impairment (Child-Pugh scores of 5 to 9). Alogliptin has not been studied in patients with severe hepatic impairment (Child-Pugh score > 9).

Age, gender, race, body weight
Age (65-81 years old), gender, race (white, black and Asian) and body weight did not have any clinically relevant effect on the pharmacokinetics of alogliptin. No dose adjustment is necessary (see section 4.2).

Paediatric population
The pharmacokinetics of alogliptin in children and adolescents < 18 years old has not been established. No data are available (see section 4.2 and above).

Metformin

Absorption

After an oral dose of metformin, the maximum plasma concentration (C_{max}) is reached in approximately 2.5 hours (T_{max}). Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride 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 recommended metformin doses and dosing schedules, steady-state plasma concentrations of metformin are reached within 24 to 48 hours and are generally less than 1 microgram/mL. In controlled clinical studies, maximum metformin plasma levels (C_{max}) did not exceed 4 microgram/mL even at maximum doses.

Food slightly delays and decreases the extent of the absorption of metformin. Following oral administration of an 850 mg metformin hydrochloride tablet, the peak plasma concentration was 40% lower, AUC was decreased by 25% and the time to peak plasma concentration (T_{max}) was prolonged by 35 minutes. The clinical relevance of these findings 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 volume of distribution (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 hours.

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 the plasma.

Alogliptin/Metformin Hydrochloride

Special populations

Renal impairment
Due to its metformin component, Alogliptin/Metformin Hydrochloride should not be used in patients with moderate or severe renal impairment, or end-stage renal disease requiring dialysis (see section 4.2).

Hepatic impairment
Alogliptin/Metformin Hydrochloride should not be used in patients with hepatic impairment (see section 4.2).

5.3 Preclinical safety data

Concomitant treatment with alogliptin and metformin did not produce new toxicities and no effects on the toxicokinetics of either compound were observed.

In rats no treatment-related foetal abnormalities occurred following concomitant administration at exposure margins of approximately 28- to 29-fold for alogliptin and 2- to 2.5-fold for metformin at the maximum recommended human dose of 25 mg/day and 2,000 mg/day, respectively. The combination revealed teratogenic potential in small numbers of foetuses (microphthalmia, small eye bulge and cleft palate) at higher doses of metformin (exposure margins of approximately 20-fold and 5- to 6-fold the maximum recommended human dose for alogliptin and metformin, respectively).

The following data are findings from studies performed with alogliptin or metformin individually.

Alogliptin

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and toxicology.

The no-observed-adverse-effect level (NOAEL) in the repeated dose toxicity studies in rats and dogs up to 26- and 39-weeks in duration, respectively, produced exposure margins that were approximately 147- and 227-fold, respectively, the exposure in humans at the recommended total daily dose of 25 mg alogliptin.

Alogliptin was not genotoxic in a standard battery of *in vitro* and *in vivo* genotoxicity studies.

Alogliptin was not carcinogenic in 2-year carcinogenicity studies conducted in rats and mice. Minimal to mild simple transitional cell hyperplasia was seen in the urinary bladder of male rats at the lowest dose used (27 times the human exposure) without establishment of a clear NOEL (no observed effect level).

No adverse effects of alogliptin were observed upon fertility, reproductive performance, or early embryonic development in rats up to a systemic exposure far above the human exposure at the recommended dose. Although fertility was not affected, a slight, statistical increase in the number of abnormal sperm was observed in males at an exposure far above the human exposure at the recommended dose.

Placental transfer of alogliptin occurs in rats.

Alogliptin was not teratogenic in rats or rabbits with a systemic exposure at the NOAELs far above the human exposure at the recommended dose. Higher doses of alogliptin were not teratogenic but resulted in maternal toxicity, and were associated with delayed and/or lack of ossification of bones and decreased foetal body weights.

In a pre- and postnatal development study in rats, exposures far above the human exposure at the recommended dose did not harm the developing embryo or affect offspring growth and development. Higher doses of alogliptin decreased offspring body weight and exerted some developmental effects considered secondary to the low body weight.

Studies in lactating rats indicate that alogliptin is excreted in milk.

No alogliptin-related effects were observed in juvenile rats following repeat-dose administration for 4 and 8 weeks.

Metformin

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol
Microcrystalline cellulose
Povidone K30
Crospovidone Type A
Magnesium stearate

Film-coating

Hypromellose
Talc
Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polychlorotrifluoroethylene (PCTFE)/polyvinyl chloride (PVC) blisters with push through aluminium lidding foil. Pack sizes of 10, 14, 20, 28, 56, 60, 98, 112, 120, 180, 196, 200 or multipacks containing 196 (2 packs of 98) film-coated tablets.

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

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 15475/0065

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10 DATE OF REVISION OF THE TEXT

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