ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ristfor 50 mg/850 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains sitagliptin phosphate monohydrate equivalent to 50 mg of sitagliptin and 850 mg of metformin hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Capsule-shaped, pink film-coated tablet with "515" debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For adult patients with type 2 diabetes mellitus:

Ristfor is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.

Ristfor is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.

Ristfor is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist.

Ristfor is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control.

4.2 Posology and method of administration

Posology
The dose of antihyperglycaemic therapy with Ristfor should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin.

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

For patients inadequately controlled on maximal tolerated dose of metformin monotherapy
For patients not adequately controlled on metformin alone, the usual starting dose should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken.

For patients switching from co-administration of sitagliptin and metformin
For patients switching from co-administration of sitagliptin and metformin, Ristfor should be initiated at the dose of sitagliptin and metformin already being taken.

For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a sulphonylurea
The dose should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Ristfor is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be required to reduce the risk of hypoglycaemia (see section 4.4).

For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a PPARγ agonist
The dose should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken.

For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin
The dose should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Ristfor is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycaemia (see section 4.4).

For the different doses on metformin, Ristfor is available in strengths of 50 mg sitagliptin and 850 mg metformin hydrochloride or 1,000 mg metformin hydrochloride.

All patients should continue their recommended diet with an adequate distribution of carbohydrate intake during the day.

Special populations
Renal impairment
No dose adjustment is needed for patients with mild renal impairment (glomerular filtration rate [GFR] ≥ 60 mL/min). A GFR should be assessed before initiation of treatment with metformin-containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin in patients with GFR < 60 mL/min.

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

GFR mL/min	**Metformin**	**Sitagliptin**
60-89	*Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.*	*Maximum daily dose is 100 mg.*
45-59	*Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.*	*Maximum daily dose is 100 mg.*
30-44	*Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.*	*Maximum daily dose is 50 mg.*

< 30	*Metformin is contraindicated.*	*Maximum daily dose is 25 mg.*

Hepatic impairment
Ristfor must not be used in patients with hepatic impairment (see section 5.2).

Elderly
As metformin and sitagliptin are excreted by the kidney, Ristfor should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly (see sections 4.3 and 4.4).

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

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

4.3 Contraindications

Ristfor is contraindicated in patients with:

- hypersensitivity to the active substances or to any of the excipients listed in section 6.1 (see sections 4.4 and 4.8);
- any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis);
- diabetic pre-coma;
- severe renal failure (GFR< 30 mL/min) (see section 4.4);
- acute conditions with the potential to alter renal function such as:
  - dehydration,
  - severe infection,
  - shock,
  - intravascular administration of iodinated contrast agents (see section 4.4);
- acute or chronic disease which may cause tissue hypoxia such as:
  - cardiac or respiratory failure,
  - recent myocardial infarction,
  - shock;
- hepatic impairment;
- acute alcohol intoxication, alcoholism;
- breast-feeding.

4.4 Special warnings and precautions for use

General
Ristfor should not be used in patients with type 1 diabetes and must not be used for the treatment of diabetic ketoacidosis.

Acute pancreatitis
Use of DPP-4 inhibitors has been associated with a risk of developing 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 sitagliptin (with or without supportive treatment), but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, Ristfor and other potentially suspect medicinal products should be discontinued; if acute pancreatitis is confirmed, Ristfor should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Lactic acidosis
Lactic acidosis, a 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 vomiting, diarrhoea, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

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

Patients and/or care-givers should be informed of 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 metformin 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.

Renal function
GFR should be assessed before treatment initiation and regularly thereafter (see section 4.2). Ristfor is contraindicated in patients with GFR < 30 mL/min and should be temporarily discontinued during conditions with the potential to alter renal function (see section 4.3).

Hypoglycaemia
Patients receiving Ristfor in combination with a sulphonylurea or with insulin may be at risk for hypoglycaemia. Therefore, a reduction in the dose of the sulphonylurea or insulin may be necessary.

Hypersensitivity reactions
Post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin have been reported. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, Ristfor should be discontinued, other potential causes of the event should be assessed, and alternative treatment for diabetes should be instituted (see section 4.8).

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

Surgery
Ristfor must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. 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.

Administration of iodinated contrast agent
Intravascular administration of iodinated contrast agents may lead to contrast-induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Ristfor 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 4.3 and 4.5).

Change in clinical status of patients with previously controlled type 2 diabetes
A patient with type 2 diabetes previously well controlled on Ristfor 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, treatment must be stopped immediately and other appropriate corrective measures initiated.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of multiple doses of sitagliptin (50 mg twice daily) and metformin (1,000 mg twice daily) did not meaningfully alter the pharmacokinetics of either sitagliptin or metformin in patients with type 2 diabetes.

Pharmacokinetic drug interaction studies with Ristfor have not been performed; however, such studies have been conducted with the individual active substances, sitagliptin and metformin.

Concomitant use not recommended

Alcohol
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

Iodinated contrast agents
Ristfor 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 4.3 and 4.4).

Combinations 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, 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.

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use. Close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when such products are co-administered.

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 performed, 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.

ACE-inhibitors may decrease the blood glucose levels. If necessary, the dose of the anti-hyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

Effects of other medicinal products on sitagliptin
In vitro and clinical data described below suggest that the risk for clinically meaningful interactions following co-administration of other medicinal products is low.

In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin is CYP3A4, with contribution from CYP2C8. In patients with normal renal function, metabolism, including via CYP3A4, plays only a small role in the clearance of sitagliptin. Metabolism may play a more significant role in the elimination of sitagliptin in the setting of severe renal impairment or end-stage renal disease (ESRD). For this reason, it is possible that potent CYP3A4 inhibitors (i.e., ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the pharmacokinetics of sitagliptin in patients with severe renal impairment or ESRD. The effects of potent CYP3A4 inhibitors in the setting of renal impairment have not been assessed in a clinical study.

In vitro transport studies showed that sitagliptin is a substrate for p-glycoprotein and organic anion transporter-3 (OAT3). OAT3 mediated transport of sitagliptin was inhibited *in vitro* by probenecid, although the risk of clinically meaningful interactions is considered to be low. Concomitant administration of OAT3 inhibitors has not been evaluated *in vivo*.

Ciclosporin: A study was conducted to assess the effect of ciclosporin, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Co-administration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of ciclosporin increased the AUC and C_{max} of sitagliptin by approximately 29 % and 68 %, respectively. These changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

Effects of sitagliptin on other medicinal products
Digoxin: Sitagliptin had a small effect on plasma digoxin concentrations. Following administration of 0.25 mg digoxin concomitantly with 100 mg of sitagliptin daily for 10 days, the plasma AUC of digoxin was increased on average by 11 %, and the plasma C_{max} on average by 18 %. No dose adjustment of digoxin is recommended. However, patients at risk of digoxin toxicity should be monitored for this when sitagliptin and digoxin are administered concomitantly.

In vitro data suggest that sitagliptin does not inhibit nor induce CYP450 isoenzymes. In clinical studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing *in vivo* evidence of a low propensity for causing interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT). Sitagliptin may be a mild inhibitor of p-glycoprotein *in vivo*.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of sitagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses of sitagliptin (see section 5.3).

A limited amount of data suggests 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 also section 5.3).

Ristfor should not be used during pregnancy. If a patient wishes to become pregnant or if a pregnancy occurs, treatment should be discontinued and the patient switched to insulin treatment as soon as possible.

Breast-feeding
No studies in lactating animals have been conducted with the combined active substances of this medicinal product. In studies performed with the individual active substances, both sitagliptin and metformin are excreted in the milk of lactating rats. Metformin is excreted in human milk in small

amounts. It is not known whether sitagliptin is excreted in human milk. Ristfor must therefore not be used in women who are breast-feeding (see section 4.3).

Fertility
Animal data do not suggest an effect of treatment with sitagliptin on male and female fertility. Human data are lacking.

4.7 Effects on ability to drive and use machines

Ristfor has no or negligible influence on the ability to drive and use machines. However, when driving or using machines, it should be taken into account that dizziness and somnolence have been reported with sitagliptin.

In addition, patients should be alerted to the risk of hypoglycaemia when Ristfor is used in combination with a sulphonylurea or with insulin.

4.8 Undesirable effects

Summary of the safety profile
There have been no therapeutic clinical trials conducted with Ristfor tablets however bioequivalence of Ristfor with co-administered sitagliptin and metformin has been demonstrated (see section 5.2). Serious adverse reactions including pancreatitis and hypersensitivity reactions have been reported. Hypoglycaemia has been reported in combination with sulphonylurea (13.8%) and insulin (10.9%).

Sitagliptin and metformin
Tabulated list of adverse reactions
Adverse reactions are listed below as MedDRA preferred term by system organ class and absolute frequency (Table 1). 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) and not known (cannot be estimated from the available data).

Table 1: The frequency of adverse reactions identified from placebo-controlled clinical studies of sitagliptin and metformin alone, and post-marketing experience

Adverse reaction	**Frequency of adverse reaction**
Blood and lymphatic system disorders	
thrombocytopenia	Rare
Immune system disorders	
hypersensitivity reactions including anaphylactic responses[*,†]	Frequency not known
Metabolism and nutrition disorders	
hypoglycaemia[†]	Common
Nervous system disorders	
somnolence	Uncommon
Respiratory, thoracic and mediastinal disorders	
interstitial lung disease[*]	Frequency not known
Gastrointestinal disorders	
diarrhoea	Uncommon
nausea	Common

Adverse reaction	Frequency of adverse reaction
flatulence	Common
constipation	Uncommon
upper abdominal pain	Uncommon
vomiting	Common
acute pancreatitis[*,†,‡]	Frequency not known
fatal and non-fatal haemorrhagic and necrotizing pancreatitis[*,†]	Frequency not known
Skin and subcutaneous tissue disorders	
pruritus[*]	Uncommon
angioedema[*,†]	Frequency not known
rash[*,†]	Frequency not known
urticaria[*,†]	Frequency not known
cutaneous vasculitis[*,†]	Frequency not known
exfoliative skin conditions including Stevens-Johnson syndrome[*,†]	Frequency not known
bullous pemphigoid[*]	Frequency not known
Musculoskeletal and connective tissue disorders	
arthralgia[*]	Frequency not known
myalgia[*]	Frequency not known
pain in extremity[*]	Frequency not known
back pain[*]	Frequency not known
arthropathy[*]	Frequency not known
Renal and urinary disorders	
impaired renal function[*]	Frequency not known
acute renal failure[*]	Frequency not known

[*] Adverse reactions were identified through post-marketing surveillance.
[†] **See section 4.4.**
[‡] See *TECOS Cardiovascular Safety Study* below.

Description of selected adverse reactions
Some adverse reactions were observed more frequently in studies of combination use of sitagliptin and metformin with other anti-diabetic medicinal products than in studies of sitagliptin and metformin alone. These included hypoglycaemia (frequency very common with sulphonylurea or insulin), constipation (common with sulphonylurea), peripheral oedema (common with pioglitazone), and headache and dry mouth (uncommon with insulin).

Sitagliptin
In monotherapy studies of sitagliptin 100 mg once daily alone compared to placebo, adverse reactions reported were headache, hypoglycaemia, constipation, and dizziness.

Among these patients, adverse events reported regardless of causal relationship to medicinal product occurring in at least 5 % included upper respiratory tract infection and nasopharyngitis. In addition, osteoarthritis and pain in extremity were reported with frequency uncommon (> 0.5 % higher among sitagliptin users than that in the control group).

Metformin
Gastrointestinal symptoms were reported very commonly in clinical studies and post-marketing use of metformin. 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. Additional adverse reactions associated with metformin include metallic taste (common); lactic acidosis, liver function disorders, hepatitis, urticaria, erythema, and pruritus (very rare). 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). Frequency categories are based on information available from metformin Summary of Product Characteristics available in the EU.

TECOS Cardiovascular Safety Study
The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with sitagliptin, 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 mL/min/1.73 m^2), and 7,339 patients treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for HbA_{1c} and CV risk factors. The overall incidence of serious adverse events in patients receiving sitagliptin was similar to that in patients receiving placebo.

In the intention-to-treat population, among patients who were using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 2.7 % in sitagliptin-treated patients and 2.5 % in placebo-treated patients; among patients who were not using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 1.0 % in sitagliptin-treated patients and 0.7 % in placebo-treated patients. The incidence of adjudication-confirmed pancreatitis events was 0.3 % in sitagliptin-treated patients and 0.2 % in placebo-treated patients.

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 national reporting system listed in Appendix V.

4.9 Overdose

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

A large overdose of metformin (or co-existing risks of lactic acidosis) may lead to lactic acidosis which is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

In clinical studies, approximately 13.5 % of the dose was removed over a 3- to 4-hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose lowering drugs, ATC code: A10BD07

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

Sitagliptin

Mechanism of action

Sitagliptin phosphate is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. When blood glucose levels are low, insulin release is not enhanced and glucagon secretion is not suppressed. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations. Sitagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulphonylureas or meglitinides, biguanides, peroxisome proliferator-activated receptor gamma (PPARγ) agonists, alpha-glucosidase inhibitors, and amylin analogues.

In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Co-administration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations.

Clinical efficacy and safety

Overall, sitagliptin improved glycaemic control when used as monotherapy or in combination treatment.

In clinical trials, sitagliptin as monotherapy improved glycaemic control with significant reductions in haemoglobin A_{1c} (HbA_{1c}) and fasting and postprandial glucose. Reduction in fasting plasma glucose (FPG) was observed at 3 weeks, the first time point at which FPG was measured. The observed incidence of hypoglycaemia in patients treated with sitagliptin was similar to placebo. Body weight did not increase from baseline with sitagliptin therapy. Improvements in surrogate markers of beta cell function, including HOMA-β (Homeostasis Model Assessment-β), proinsulin to insulin ratio, and measures of beta cell responsiveness from the frequently-sampled meal tolerance test were observed.

Studies of sitagliptin in combination with metformin

In a 24-week, placebo-controlled clinical study to evaluate the efficacy and safety of the addition of sitagliptin 100 mg once daily to ongoing metformin, sitagliptin provided significant improvements in glycaemic parameters compared with placebo. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo. In this study there was a similar incidence of hypoglycaemia reported for patients treated with sitagliptin or placebo.

In a 24-week placebo-controlled factorial study of initial therapy, sitagliptin 50 mg twice daily in combination with metformin (500 mg or 1,000 mg twice daily) provided significant improvements in glycaemic parameters compared with either monotherapy. The decrease in body weight with the combination of sitagliptin and metformin was similar to that observed with metformin alone or placebo; there was no change from baseline for patients on sitagliptin alone. The incidence of hypoglycaemia was similar across treatment groups.

Study of sitagliptin in combination with metformin and a sulphonylurea

A 24-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to glimepiride (alone or in combination with metformin). The addition of

sitagliptin to glimepiride and metformin provided significant improvements in glycaemic parameters. Patients treated with sitagliptin had a modest increase in body weight (+1.1 kg) compared to those given placebo.

Study of sitagliptin in combination with metformin and a PPARγ agonist
A 26-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to the combination of pioglitazone and metformin. The addition of sitagliptin to pioglitazone and metformin provided significant improvements in glycaemic parameters. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo. The incidence of hypoglycaemia was also similar in patients treated with sitagliptin or placebo.

Study of sitagliptin in combination with metformin and insulin
A 24-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to insulin (at a stable dose for at least 10 weeks) with or without metformin (at least 1,500 mg). In patients taking pre-mixed insulin, the mean daily dose was 70.9 U/day. In patients taking non-pre-mixed (intermediate/long-acting) insulin, the mean daily dose was 44.3 U/day. Data from the 73 % of patients who were taking metformin are presented in Table 2. The addition of sitagliptin to insulin provided significant improvements in glycaemic parameters. There was no meaningful change from baseline in body weight in either group.

Table 2: HbA_{1c} results in placebo-controlled combination therapy studies of sitagliptin and metformin*

Study	Mean baseline HbA_{1c} (%)	Mean change from baseline HbA_{1c} (%)	Placebo-corrected mean change in HbA_{1c} (%) (95 % CI)
Sitagliptin 100 mg once daily added to ongoing metformin therapy‖ (N=453)	8.0	-0.7†	-0.7†,‡ (-0.8, -0.5)
Sitagliptin 100 mg once daily added to ongoing glimepiride + metformin therapy‖ (N=115)	8.3	-0.6†	-0.9†,‡ (-1.1, -0.7)
Sitagliptin 100 mg once daily added to ongoing pioglitazone + metformin therapy¶ (N=152)	8.8	-1.2†	-0.7†,‡ (-1.0, -0.5)
Sitagliptin 100 mg once daily added to ongoing insulin + metformin therapy ‖ (N=223)	8.7	-0.7§	-0.5§,‡ (-0.7, -0.4)
Initial Therapy (twice daily)‖: Sitagliptin 50 mg + metformin 500 mg (N=183)	8.8	-1.4†	-1.6†,‡ (-1.8, -1.3)

Study	Mean baseline HbA_{1c} (%)	Mean change from baseline HbA_{1c} (%)	Placebo-corrected mean change in HbA_{1c} (%) (95 % CI)
Initial Therapy (twice daily)[‖]: Sitagliptin 50 mg + metformin 1,000 mg (N=178)	8.8	-1.9[†]	-2.1[†,‡] (-2.3, -1.8)

* All Patients Treated Population (an intention-to-treat analysis).
[†] Least squares means adjusted for prior antihyperglycaemic therapy status and baseline value.
[‡] p< 0.001 compared to placebo or placebo + combination treatment.
[‖] HbA_{1c} (%) at week 24.
[¶] HbA_{1c} (%) at week 26.
[§] Least squares mean adjusted for insulin use at Visit 1 (pre-mixed vs. non-pre-mixed [intermediate- or long-acting]), and baseline value.

In a 52-week study, comparing the efficacy and safety of the addition of sitagliptin 100 mg once daily or glipizide (a sulphonylurea) in patients with inadequate glycaemic control on metformin monotherapy, sitagliptin was similar to glipizide in reducing HbA_{1c} (-0.7 % mean change from baselines at week 52, with baseline HbA_{1c} of approximately 7.5 % in both groups). The mean glipizide dose used in the comparator group was 10 mg per day with approximately 40 % of patients requiring a glipizide dose of ≤ 5 mg/day throughout the study. However, more patients in the sitagliptin group discontinued due to lack of efficacy than in the glipizide group. Patients treated with sitagliptin exhibited a significant mean decrease from baseline in body weight (-1.5 kg) compared to a significant weight gain in patients administered glipizide (+1.1 kg). In this study, the proinsulin to insulin ratio, a marker of efficiency of insulin synthesis and release, improved with sitagliptin and deteriorated with glipizide treatment. The incidence of hypoglycaemia in the sitagliptin group (4.9 %) was significantly lower than that in the glipizide group (32.0 %).

A 24-week placebo-controlled study involving 660 patients was designed to evaluate the insulin-sparing efficacy and safety of sitagliptin (100 mg once daily) added to insulin glargine with or without metformin (at least 1,500 mg) during intensification of insulin therapy. Among patients taking metformin, baseline HbA_{1c} was 8.70 % and baseline insulin dose was 37 IU/day. Patients were instructed to titrate their insulin glargine dose based on fingerstick fasting glucose values. Among patients taking metformin, at Week 24, the increase in daily insulin dose was 19 IU/day in patients treated with sitagliptin and 24 IU/day in patients treated with placebo. The reduction in HbA_{1c} for patients treated with sitagliptin, metformin, and insulin was -1.35 % compared to -0.90 % for patients treated with placebo, metformin, and insulin, a difference of -0.45 % [95 % CI: -0.62, -0.29]. The incidence of hypoglycaemia was 24.9 % for patients treated with sitagliptin, metformin, and insulin and 37.8 % for patients treated with placebo, metformin, and insulin. The difference was mainly due to a higher percentage of patients in the placebo group experiencing 3 or more episodes of hypoglycaemia (9.1 vs. 19.8 %). There was no difference in the incidence of severe hypoglycaemia.

Metformin

Mechanism of action

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).

Clinical efficacy and safety
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.

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).

The TECOS was a randomised study in 14,671 patients in the intention-to-treat population with an HbA_{1c} of ≥ 6.5 to 8.0 % with established CV disease who received sitagliptin (7,332) 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 mL/min/1.73 m^2) or placebo (7,339) added to usual care targeting regional standards for HbA_{1c} and CV risk factors. Patients with an eGFR < 30 mL/min/1.73 m^2 were not to be enrolled in the study. The study population included 2,004 patients ≥ 75 years of age and 3,324 patients with renal impairment (eGFR < 60 mL/min/1.73 m^2).

Over the course of the study, the overall estimated mean (SD) difference in HbA_{1c} between the sitagliptin and placebo groups was 0.29 % (0.01), 95 % CI (-0.32, -0.27); p < 0.001.

The primary cardiovascular endpoint was a composite of the first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for unstable angina. Secondary cardiovascular endpoints included the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; first occurrence of the individual components of the primary composite; all-cause mortality; and hospital admissions for congestive heart failure.

After a median follow up of 3 years, sitagliptin, when added to usual care, did not increase the risk of major adverse cardiovascular events or the risk of hospitalisation for heart failure compared to usual care without sitagliptin in patients with type 2 diabetes (Table 3).

Table 3: Rates of Composite Cardiovascular Outcomes and Key Secondary Outcomes

	Sitagliptin 100 mg		**Placebo**			
	N (%)	**Incidence rate per 100 patient-years***	**N (%)**	**Incidence rate per 100 patient-years***	**Hazard Ratio (95% CI)**	**p-value†**
Analysis in the Intention-to-Treat Population						
Number of patients	**7,332**		**7,339**		0.98 (0.89–1.08)	<0.001

	Sitagliptin 100 mg		Placebo		Hazard Ratio (95% CI)	p-value[†]
	N (%)	Incidence rate per 100 patient-years*	N (%)	Incidence rate per 100 patient-years*		
Primary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for unstable angina)	839 (11.4)	4.1	851 (11.6)	4.2		
Secondary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke)	745 (10.2)	3.6	746 (10.2)	3.6	0.99 (0.89–1.10)	<0.001
Secondary Outcome						
Cardiovascular death	380 (5.2)	1.7	366 (5.0)	1.7	1.03 (0.89-1.19)	0.711
All myocardial infarction (fatal and non-fatal)	300 (4.1)	1.4	316 (4.3)	1.5	0.95 (0.81–1.11)	0.487
All stroke (fatal and non-fatal)	178 (2.4)	0.8	183 (2.5)	0.9	0.97 (0.79–1.19)	0.760
Hospitalisation for unstable angina	116 (1.6)	0.5	129 (1.8)	0.6	0.90 (0.70–1.16)	0.419
Death from any cause	547 (7.5)	2.5	537 (7.3)	2.5	1.01 (0.90–1.14)	0.875
Hospitalisation for heart failure[‡]	228 (3.1)	1.1	229 (3.1)	1.1	1.00 (0.83–1.20)	0.983

***** Incidence rate per 100 patient-years is calculated as 100 × (total number of patients with ≥ 1 event during eligible exposure period per total patient-years of follow-up).

[†] Based on a Cox model stratified by region. For composite endpoints, the p-values correspond to a test of non-inferiority seeking to show that the hazard ratio is less than 1.3. For all other endpoints, the p-values correspond to a test of differences in hazard rates.

[‡] The analysis of hospitalisation for heart failure was adjusted for a history of heart failure at baseline.

Paediatric population

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

5.2 Pharmacokinetic properties

Ristfor

A bioequivalence study in healthy subjects demonstrated that the Ristfor (sitagliptin/metformin hydrochloride) combination tablets are bioequivalent to co-administration of sitagliptin phosphate and metformin hydrochloride as individual tablets.

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

Sitagliptin

Absorption

Following oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8.52 μM•hr, C_{max} was 950 nM. The absolute bioavailability of sitagliptin is approximately 87 %. Since co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.

Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for C_{max} and C_{24hr} (C_{max} increased in a greater than dose-proportional manner and C_{24hr} increased in a less than dose-proportional manner).

Distribution
The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 litres. The fraction of sitagliptin reversibly bound to plasma proteins is low (38 %).

Biotransformation
Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79 % of sitagliptin is excreted unchanged in the urine.

Following a [^{14}C]sitagliptin oral dose, approximately 16 % of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

In vitro data showed that sitagliptin is not an inhibitor of CYP isoenzymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4 and CYP1A2.

Elimination
Following administration of an oral [^{14}C]sitagliptin dose to healthy subjects, approximately 100 % of the administered radioactivity was eliminated in faeces (13 %) or urine (87 %) within one week of dosing. The apparent terminal $t_{½}$ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours. Sitagliptin accumulates only minimally with multiple doses. The renal clearance was approximately 350 mL/min.

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, ciclosporin, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin. Sitagliptin is not a substrate for OCT2 or OAT1 or PEPT1/2 transporters. *In vitro*, sitagliptin did not inhibit OAT3 (IC50=160 μM) or p-glycoprotein (up to 250 μM) mediated transport at therapeutically relevant plasma concentrations. In a clinical study sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of p-glycoprotein.

Characteristics in patients
The pharmacokinetics of sitagliptin were generally similar in healthy subjects and in patients with type 2 diabetes.

Renal impairment
A single-dose, open-label study was conducted to evaluate the pharmacokinetics of a reduced dose of sitagliptin (50 mg) in patients with varying degrees of chronic renal impairment compared to normal healthy control subjects. The study included patients with mild, moderate, and severe renal impairment, as well as patients with ESRD on haemodialysis. In addition, the effects of renal impairment on sitagliptin pharmacokinetics in patients with type 2 diabetes and mild, moderate, or severe renal impairment (including ESRD) were assessed using population pharmacokinetic analyses.

Compared to normal healthy control subjects, plasma AUC of sitagliptin was increased by approximately 1.2-fold and 1.6-fold in patients with mild renal impairment (GFR ≥ 60 to < 90 mL/min) and patients with moderate renal impairment (GFR ≥ 45 to < 60 mL/min), respectively.

Because increases of this magnitude are not clinically relevant, dosage adjustment in these patients is not necessary.

Plasma AUC of sitagliptin was increased approximately 2-fold in patients with moderate renal impairment (GFR ≥ 30 to < 45 mL/min), and approximately 4-fold in patients with severe renal impairment (GFR < 30 mL/min), including patients with ESRD on haemodialysis. Sitagliptin was modestly removed by haemodialysis (13.5 % over a 3- to 4-hour haemodialysis session starting 4 hours post-dose).

Hepatic impairment
No dose adjustment for sitagliptin is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score ≤ 9). There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score > 9). However, because sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin.

Elderly
No dose adjustment is required based on age. Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 years) had approximately 19 % higher plasma concentrations of sitagliptin compared to younger subjects.

Paediatric
No studies with sitagliptin have been performed in paediatric patients.

Other patient characteristics
No dose adjustment is necessary based on gender, race, or body mass index (BMI). These characteristics had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

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 5 μg/mL, even at maximum doses.

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 Vd ranged between 63 – 276 L.

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

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

5.3 Preclinical safety data

No animal studies have been conducted with Ristfor.

In 16-week studies in which dogs were treated with either metformin alone or a combination of metformin and sitagliptin, no additional toxicity was observed from the combination. The NOEL in these studies was observed at exposures to sitagliptin of approximately 6 times the human exposure and to metformin of approximately 2.5 times the human exposure.

The following data are findings in studies performed with sitagliptin or metformin individually.

Sitagliptin
Renal and liver toxicity were observed in rodents at systemic exposure values 58 times the human exposure level, while the no-effect level was found at 19 times the human exposure level. Incisor teeth abnormalities were observed in rats at exposure levels 67 times the clinical exposure level; the no-effect level for this finding was 58-fold based on the 14-week rat study. The relevance of these findings for humans is unknown. Transient treatment-related physical signs, some of which suggest neural toxicity, such as open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture were observed in dogs at exposure levels approximately 23 times the clinical exposure level. In addition, very slight to slight skeletal muscle degeneration was also observed histologically at doses resulting in systemic exposure levels of approximately 23 times the human exposure level. A no-effect level for these findings was found at an exposure 6-fold the clinical exposure level.

Sitagliptin has not been demonstrated to be genotoxic in preclinical studies. Sitagliptin was not carcinogenic in mice. In rats, there was an increased incidence of hepatic adenomas and carcinomas at systemic exposure levels 58 times the human exposure level. Since hepatotoxicity has been shown to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumours in rats was likely secondary to chronic hepatic toxicity at this high dose. Because of the high safety margin (19-fold at this no-effect level), these neoplastic changes are not considered relevant for the situation in humans.

No treatment related effects on fertility were observed in male and female rats given sitagliptin prior to and throughout mating.

In a pre-/post-natal development study performed in rats sitagliptin showed no adverse effects.

Reproductive toxicity studies showed a slight treatment-related increased incidence of foetal rib malformations (absent, hypoplastic and wavy ribs) in the offspring of rats at systemic exposure levels more than 29 times the human exposure levels. Maternal toxicity was seen in rabbits at more than 29 times the human exposure levels. Because of the high safety margins, these findings do not suggest a relevant risk for human reproduction. Sitagliptin is secreted in considerable amounts into the milk of lactating rats (milk/plasma ratio: 4:1).

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
microcrystalline cellulose (E460)
povidone K29/32 (E1201)
sodium lauril sulfate
sodium stearyl fumarate

Film coating
poly(vinyl alcohol)
macrogol 3350
talc (E553b)
titanium dioxide (E171)
iron oxide red (E172)
iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Opaque blisters (PVC/PE/PVDC and aluminium).
Packs of 14, 28, 56, 60, 112, 168, 180, 196 film-coated tablets, multi-packs containing 196 (2 packs of 98) and 168 (2 packs of 84) film-coated tablets. Pack of 50 x 1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/620/001
EU/1/10/620/002
EU/1/10/620/003
EU/1/10/620/004
EU/1/10/620/005
EU/1/10/620/006
EU/1/10/620/007
EU/1/10/620/008
EU/1/10/620/017
EU/1/10/620/019
EU/1/10/620/020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 March 2010
Date of latest renewal: 16 December 2014

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Ristfor 50 mg/1,000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains sitagliptin phosphate monohydrate equivalent to 50 mg of sitagliptin and 1,000 mg of metformin hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Capsule-shaped, red film-coated tablet with "577" debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For adult patients with type 2 diabetes mellitus:

Ristfor is indicated as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin.

Ristfor is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.

Ristfor is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist.

Ristfor is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control.

4.2 Posology and method of administration

Posology
The dose of antihyperglycaemic therapy with Ristfor should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability while not exceeding the maximum recommended daily dose of 100 mg sitagliptin.

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

For patients inadequately controlled on maximal tolerated dose of metformin monotherapy
For patients not adequately controlled on metformin alone, the usual starting dose should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken.

For patients switching from co-administration of sitagliptin and metformin
For patients switching from co-administration of sitagliptin and metformin, Ristfor should be initiated at the dose of sitagliptin and metformin already being taken.

For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a sulphonylurea
The dose should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Ristfor is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be required to reduce the risk of hypoglycaemia (see section 4.4).

For patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a PPARγ agonist
The dose should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken.

For patients inadequately controlled on dual combination therapy with insulin and the maximal tolerated dose of metformin
The dose should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. When Ristfor is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycaemia (see section 4.4).

For the different doses on metformin, Ristfor is available in strengths of 50 mg sitagliptin and 850 mg metformin hydrochloride or 1,000 mg metformin hydrochloride.

All patients should continue their recommended diet with an adequate distribution of carbohydrate intake during the day.

Special populations
Renal impairment
No dose adjustment is needed for patients with mild renal impairment (glomerular filtration rate [GFR] ≥ 60 mL/min). A GFR should be assessed before initiation of treatment with metformin-containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses. Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin in patients with GFR < 60 mL/min.

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

GFR mL/min	**Metformin**	**Sitagliptin**
60-89	*Maximum daily dose is 3000 mg. Dose reduction may be considered in relation to declining renal function.*	*Maximum daily dose is 100 mg.*
45-59	*Maximum daily dose is 2000 mg. The starting dose is at most half of the maximum dose.*	*Maximum daily dose is 100 mg.*
30-44	*Maximum daily dose is 1000 mg. The starting dose is at most half of the maximum dose.*	*Maximum daily dose is 50 mg.*

< 30	*Metformin is contraindicated.*	*Maximum daily dose is 25 mg.*

Hepatic impairment
Ristfor must not be used in patients with hepatic impairment (see section 5.2).

Elderly
As metformin and sitagliptin are excreted by the kidney, Ristfor should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly (see sections 4.3 and 4.4).

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

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

4.3 Contraindications

Ristfor is contraindicated in patients with:

- hypersensitivity to the active substances or to any of the excipients listed in section 6.1 (see sections 4.4 and 4.8);
- any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis);
- diabetic pre-coma;
- severe renal failure (GFR< 30 mL/min) (see section 4.4);
- acute conditions with the potential to alter renal function such as:
  - dehydration,
  - severe infection,
  - shock,
  - intravascular administration of iodinated contrast agents (see section 4.4);
- acute or chronic disease which may cause tissue hypoxia such as:
  - cardiac or respiratory failure,
  - recent myocardial infarction,
  - shock;
- hepatic impairment;
- acute alcohol intoxication, alcoholism;
- breast-feeding.

4.4 Special warnings and precautions for use

General
Ristfor should not be used in patients with type 1 diabetes and must not be used for the treatment of diabetic ketoacidosis.

Acute pancreatitis
Use of DPP-4 inhibitors has been associated with a risk of developing 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 sitagliptin (with or without supportive treatment), but very rare cases of necrotising or haemorrhagic pancreatitis and/or death have been reported. If pancreatitis is suspected, Ristfor and other potentially suspect medicinal products should be discontinued; if acute pancreatitis is confirmed, Ristfor should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

Lactic acidosis
Lactic acidosis, a 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 vomiting, diarrhoea, fever or reduced fluid intake), metformin should be temporarily discontinued and contact with a health care professional is recommended.

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

Patients and/or care-givers should be informed of 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 metformin 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.

Renal function
GFR should be assessed before treatment initiation and regularly thereafter (see section 4.2). Ristfor is contraindicated in patients with GFR < 30 mL/min and should be temporarily discontinued during conditions with the potential to alter renal function (see section 4.3).

Hypoglycaemia
Patients receiving Ristfor in combination with a sulphonylurea or with insulin may be at risk for hypoglycaemia. Therefore, a reduction in the dose of the sulphonylurea or insulin may be necessary.

Hypersensitivity reactions
Post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin have been reported. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, Ristfor should be discontinued, other potential causes of the event should be assessed, and alternative treatment for diabetes should be instituted (see section 4.8).

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

Surgery
Ristfor must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. 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.

Administration of iodinated contrast agent
Intravascular administration of iodinated contrast agents may lead to contrast-induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Ristfor 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 4.3 and 4.5).

Change in clinical status of patients with previously controlled type 2 diabetes
A patient with type 2 diabetes previously well controlled on Ristfor 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, treatment must be stopped immediately and other appropriate corrective measures initiated.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of multiple doses of sitagliptin (50 mg twice daily) and metformin (1,000 mg twice daily) did not meaningfully alter the pharmacokinetics of either sitagliptin or metformin in patients with type 2 diabetes.

Pharmacokinetic drug interaction studies with Ristfor have not been performed; however, such studies have been conducted with the individual active substances, sitagliptin and metformin.

Concomitant use not recommended

Alcohol
Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in cases of fasting, malnutrition or hepatic impairment.

Iodinated contrast agents
Ristfor 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 4.3 and 4.4).

Combinations 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, 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.

Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporter-2 [OCT2] / multidrug and toxin extrusion [MATE] inhibitors such as ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Consider the benefits and risks of concomitant use. Close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when such products are co-administered.

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 performed, 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.

ACE-inhibitors may decrease the blood glucose levels. If necessary, the dose of the anti-hyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.

Effects of other medicinal products on sitagliptin
In vitro and clinical data described below suggest that the risk for clinically meaningful interactions following co-administration of other medicinal products is low.

In vitro studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin is CYP3A4, with contribution from CYP2C8. In patients with normal renal function, metabolism, including via CYP3A4, plays only a small role in the clearance of sitagliptin. Metabolism may play a more significant role in the elimination of sitagliptin in the setting of severe renal impairment or end-stage renal disease (ESRD). For this reason, it is possible that potent CYP3A4 inhibitors (i.e., ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the pharmacokinetics of sitagliptin in patients with severe renal impairment or ESRD. The effects of potent CYP3A4 inhibitors in the setting of renal impairment have not been assessed in a clinical study.

In vitro transport studies showed that sitagliptin is a substrate for p-glycoprotein and organic anion transporter-3 (OAT3). OAT3 mediated transport of sitagliptin was inhibited *in vitro* by probenecid, although the risk of clinically meaningful interactions is considered to be low. Concomitant administration of OAT3 inhibitors has not been evaluated *in vivo*.

Ciclosporin: A study was conducted to assess the effect of ciclosporin, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Co-administration of a single 100 mg oral dose of sitagliptin and a single 600 mg oral dose of ciclosporin increased the AUC and C_{max} of sitagliptin by approximately 29 % and 68 %, respectively. These changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors.

Effects of sitagliptin on other medicinal products
Digoxin: Sitagliptin had a small effect on plasma digoxin concentrations. Following administration of 0.25 mg digoxin concomitantly with 100 mg of sitagliptin daily for 10 days, the plasma AUC of digoxin was increased on average by 11 %, and the plasma C_{max} on average by 18 %. No dose adjustment of digoxin is recommended. However, patients at risk of digoxin toxicity should be monitored for this when sitagliptin and digoxin are administered concomitantly.

In vitro data suggest that sitagliptin does not inhibit nor induce CYP450 isoenzymes. In clinical studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing *in vivo* evidence of a low propensity for causing interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT). Sitagliptin may be a mild inhibitor of p-glycoprotein *in vivo*.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of sitagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses of sitagliptin (see section 5.3).

A limited amount of data suggests 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 also section 5.3).

Ristfor should not be used during pregnancy. If a patient wishes to become pregnant or if a pregnancy occurs, treatment should be discontinued and the patient switched to insulin treatment as soon as possible.

Breast-feeding
No studies in lactating animals have been conducted with the combined active substances of this medicinal product. In studies performed with the individual active substances, both sitagliptin and metformin are excreted in the milk of lactating rats. Metformin is excreted in human milk in small

amounts. It is not known whether sitagliptin is excreted in human milk. Ristfor must therefore not be used in women who are breast-feeding (see section 4.3).

Fertility
Animal data do not suggest an effect of treatment with sitagliptin on male and female fertility. Human data are lacking.

4.7 Effects on ability to drive and use machines

Ristfor has no or negligible influence on the ability to drive and use machines. However, when driving or using machines, it should be taken into account that dizziness and somnolence have been reported with sitagliptin.

In addition, patients should be alerted to the risk of hypoglycaemia when Ristfor is used in combination with a sulphonylurea or with insulin.

4.8 Undesirable effects

Summary of the safety profile
There have been no therapeutic clinical trials conducted with Ristfor tablets however bioequivalence of Ristfor with co-administered sitagliptin and metformin has been demonstrated (see section 5.2). Serious adverse reactions including pancreatitis and hypersensitivity reactions have been reported. Hypoglycaemia has been reported in combination with sulphonylurea (13.8%) and insulin (10.9%).

Sitagliptin and metformin
Tabulated list of adverse reactions
Adverse reactions are listed below as MedDRA preferred term by system organ class and absolute frequency (Table 1). 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) and not known (cannot be estimated from the available data).

Table 1: The frequency of adverse reactions identified from placebo-controlled clinical studies of sitagliptin and metformin alone, and post-marketing experience

Adverse reaction	**Frequency of adverse reaction**
Blood and lymphatic system disorders	
thrombocytopenia	Rare
Immune system disorders	
hypersensitivity reactions including anaphylactic responses[*,†]	Frequency not known
Metabolism and nutrition disorders	
hypoglycaemia[†]	Common
Nervous system disorders	
somnolence	Uncommon
Respiratory, thoracic and mediastinal disorders	
interstitial lung disease[*]	Frequency not known
Gastrointestinal disorders	
diarrhoea	Uncommon
nausea	Common

Adverse reaction	Frequency of adverse reaction
flatulence	Common
constipation	Uncommon
upper abdominal pain	Uncommon
vomiting	Common
acute pancreatitis[*,†,‡]	Frequency not known
fatal and non-fatal haemorrhagic and necrotizing pancreatitis[*,†]	Frequency not known
Skin and subcutaneous tissue disorders	
pruritus[*]	Uncommon
angioedema[*,†]	Frequency not known
rash[*,†]	Frequency not known
urticaria[*,†]	Frequency not known
cutaneous vasculitis[*,†]	Frequency not known
exfoliative skin conditions including Stevens-Johnson syndrome[*,†]	Frequency not known
bullous pemphigoid[*]	Frequency not known
Musculoskeletal and connective tissue disorders	
arthralgia[*]	Frequency not known
myalgia[*]	Frequency not known
pain in extremity[*]	Frequency not known
back pain[*]	Frequency not known
arthropathy[*]	Frequency not known
Renal and urinary disorders	
impaired renal function[*]	Frequency not known
acute renal failure[*]	Frequency not known

[*] Adverse reactions were identified through post-marketing surveillance.
[†] **See section 4.4.**
[‡] See *TECOS Cardiovascular Safety Study* below.

Description of selected adverse reactions
Some adverse reactions were observed more frequently in studies of combination use of sitagliptin and metformin with other anti-diabetic medicinal products than in studies of sitagliptin and metformin alone. These included hypoglycaemia (frequency very common with sulphonylurea or insulin), constipation (common with sulphonylurea), peripheral oedema (common with pioglitazone), and headache and dry mouth (uncommon with insulin).

Sitagliptin
In monotherapy studies of sitagliptin 100 mg once daily alone compared to placebo, adverse reactions reported were headache, hypoglycaemia, constipation, and dizziness.

Among these patients, adverse events reported regardless of causal relationship to medicinal product occurring in at least 5 % included upper respiratory tract infection and nasopharyngitis. In addition, osteoarthritis and pain in extremity were reported with frequency uncommon (> 0.5 % higher among sitagliptin users than that in the control group).

Metformin
Gastrointestinal symptoms were reported very commonly in clinical studies and post-marketing use of metformin. 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. Additional adverse reactions associated with metformin include metallic taste (common); lactic acidosis, liver function disorders, hepatitis, urticaria, erythema, and pruritus (very rare). 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). Frequency categories are based on information available from metformin Summary of Product Characteristics available in the EU.

TECOS Cardiovascular Safety Study
The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) included 7,332 patients treated with sitagliptin, 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 mL/min/1.73 m^2), and 7,339 patients treated with placebo in the intention-to-treat population. Both treatments were added to usual care targeting regional standards for HbA_{1c} and CV risk factors. The overall incidence of serious adverse events in patients receiving sitagliptin was similar to that in patients receiving placebo.

In the intention-to-treat population, among patients who were using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 2.7 % in sitagliptin-treated patients and 2.5 % in placebo-treated patients; among patients who were not using insulin and/or a sulfonylurea at baseline, the incidence of severe hypoglycaemia was 1.0 % in sitagliptin-treated patients and 0.7 % in placebo-treated patients. The incidence of adjudication-confirmed pancreatitis events was 0.3 % in sitagliptin-treated patients and 0.2 % in placebo-treated patients.

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 national reporting system listed in Appendix V.

4.9 Overdose

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

A large overdose of metformin (or co-existing risks of lactic acidosis) may lead to lactic acidosis which is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

In clinical studies, approximately 13.5 % of the dose was removed over a 3- to 4-hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialysable by peritoneal dialysis.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose lowering drugs, ATC code: A10BD07

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

Sitagliptin

Mechanism of action

Sitagliptin phosphate is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes. The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP--4 enzyme, sitagliptin increases the levels of two known active incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production. When blood glucose levels are low, insulin release is not enhanced and glucagon secretion is not suppressed. Sitagliptin is a potent and highly selective inhibitor of the enzyme DPP-4 and does not inhibit the closely-related enzymes DPP-8 or DPP-9 at therapeutic concentrations. Sitagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulphonylureas or meglitinides, biguanides, peroxisome proliferator-activated receptor gamma (PPARγ) agonists, alpha-glucosidase inhibitors, and amylin analogues.

In a two-day study in healthy subjects, sitagliptin alone increased active GLP-1 concentrations, whereas metformin alone increased active and total GLP-1 concentrations to similar extents. Co-administration of sitagliptin and metformin had an additive effect on active GLP-1 concentrations. Sitagliptin, but not metformin, increased active GIP concentrations.

Clinical efficacy and safety

Overall, sitagliptin improved glycaemic control when used as monotherapy or in combination treatment.

In clinical trials, sitagliptin as monotherapy improved glycaemic control with significant reductions in haemoglobin A_{1c} (HbA_{1c}) and fasting and postprandial glucose. Reduction in fasting plasma glucose (FPG) was observed at 3 weeks, the first time point at which FPG was measured. The observed incidence of hypoglycaemia in patients treated with sitagliptin was similar to placebo. Body weight did not increase from baseline with sitagliptin therapy. Improvements in surrogate markers of beta cell function, including HOMA-β (Homeostasis Model Assessment-β), proinsulin to insulin ratio, and measures of beta cell responsiveness from the frequently-sampled meal tolerance test were observed.

Studies of sitagliptin in combination with metformin

In a 24-week, placebo-controlled clinical study to evaluate the efficacy and safety of the addition of sitagliptin 100 mg once daily to ongoing metformin, sitagliptin provided significant improvements in glycaemic parameters compared with placebo. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo. In this study there was a similar incidence of hypoglycaemia reported for patients treated with sitagliptin or placebo.

In a 24-week placebo-controlled factorial study of initial therapy, sitagliptin 50 mg twice daily in combination with metformin (500 mg or 1,000 mg twice daily) provided significant improvements in glycaemic parameters compared with either monotherapy. The decrease in body weight with the combination of sitagliptin and metformin was similar to that observed with metformin alone or placebo; there was no change from baseline for patients on sitagliptin alone. The incidence of hypoglycaemia was similar across treatment groups.

Study of sitagliptin in combination with metformin and a sulphonylurea

A 24-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to glimepiride (alone or in combination with metformin). The addition of

sitagliptin to glimepiride and metformin provided significant improvements in glycaemic parameters. Patients treated with sitagliptin had a modest increase in body weight (+1.1 kg) compared to those given placebo.

Study of sitagliptin in combination with metformin and a PPARγ agonist
A 26-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to the combination of pioglitazone and metformin. The addition of sitagliptin to pioglitazone and metformin provided significant improvements in glycaemic parameters. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo. The incidence of hypoglycaemia was also similar in patients treated with sitagliptin or placebo.

Study of sitagliptin in combination with metformin and insulin
A 24-week placebo-controlled study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to insulin (at a stable dose for at least 10 weeks) with or without metformin (at least 1,500 mg). In patients taking pre-mixed insulin, the mean daily dose was 70.9 U/day. In patients taking non-pre-mixed (intermediate/long-acting) insulin, the mean daily dose was 44.3 U/day. Data from the 73 % of patients who were taking metformin are presented in Table 2. The addition of sitagliptin to insulin provided significant improvements in glycaemic parameters. There was no meaningful change from baseline in body weight in either group.

Table 2: HbA_{1c} results in placebo-controlled combination therapy studies of sitagliptin and metformin*

Study	Mean baseline HbA_{1c} (%)	Mean change from baseline HbA_{1c} (%)	Placebo-corrected mean change in HbA_{1c} (%) (95 % CI)
Sitagliptin 100 mg once daily added to ongoing metformin therapy‖ (N=453)	8.0	-0.7†	-0.7†,‡ (-0.8, -0.5)
Sitagliptin 100 mg once daily added to ongoing glimepiride + metformin therapy‖ (N=115)	8.3	-0.6†	-0.9†,‡ (-1.1, -0.7)
Sitagliptin 100 mg once daily added to ongoing pioglitazone + metformin therapy¶ (N=152)	8.8	-1.2†	-0.7†,‡ (-1.0, -0.5)
Sitagliptin 100 mg once daily added to ongoing insulin + metformin therapy ‖ (N=223)	8.7	-0.7§	-0.5§,‡ (-0.7, -0.4)
Initial Therapy (twice daily)‖: Sitagliptin 50 mg + metformin 500 mg (N=183)	8.8	-1.4†	-1.6†,‡ (-1.8, -1.3)

Study	Mean baseline HbA_{1c} (%)	Mean change from baseline HbA_{1c} (%)	Placebo-corrected mean change in HbA_{1c} (%) (95 % CI)
Initial Therapy (twice daily)[‖]: Sitagliptin 50 mg + metformin 1,000 mg (N=178)	8.8	-1.9[†]	-2.1[†,‡] (-2.3, -1.8)

* All Patients Treated Population (an intention-to-treat analysis).
[†] Least squares means adjusted for prior antihyperglycaemic therapy status and baseline value.
[‡] $p< 0.001$ compared to placebo or placebo + combination treatment.
[‖] HbA_{1c} (%) at week 24.
[¶] HbA_{1c} (%) at week 26.
[§] Least squares mean adjusted for insulin use at Visit 1 (pre-mixed vs. non-pre-mixed [intermediate- or long-acting]), and baseline value.

In a 52-week study, comparing the efficacy and safety of the addition of sitagliptin 100 mg once daily or glipizide (a sulphonylurea) in patients with inadequate glycaemic control on metformin monotherapy, sitagliptin was similar to glipizide in reducing HbA_{1c} (-0.7 % mean change from baselines at week 52, with baseline HbA_{1c} of approximately 7.5 % in both groups). The mean glipizide dose used in the comparator group was 10 mg per day with approximately 40 % of patients requiring a glipizide dose of ≤ 5 mg/day throughout the study. However, more patients in the sitagliptin group discontinued due to lack of efficacy than in the glipizide group. Patients treated with sitagliptin exhibited a significant mean decrease from baseline in body weight (-1.5 kg) compared to a significant weight gain in patients administered glipizide (+1.1 kg). In this study, the proinsulin to insulin ratio, a marker of efficiency of insulin synthesis and release, improved with sitagliptin and deteriorated with glipizide treatment. The incidence of hypoglycaemia in the sitagliptin group (4.9 %) was significantly lower than that in the glipizide group (32.0 %).

A 24-week placebo-controlled study involving 660 patients was designed to evaluate the insulin-sparing efficacy and safety of sitagliptin (100 mg once daily) added to insulin glargine with or without metformin (at least 1,500 mg) during intensification of insulin therapy. Among patients taking metformin, baseline HbA_{1c} was 8.70 % and baseline insulin dose was 37 IU/day. Patients were instructed to titrate their insulin glargine dose based on fingerstick fasting glucose values. Among patients taking metformin, at Week 24, the increase in daily insulin dose was 19 IU/day in patients treated with sitagliptin and 24 IU/day in patients treated with placebo. The reduction in HbA_{1c} for patients treated with sitagliptin, metformin, and insulin was -1.35 % compared to -0.90 % for patients treated with placebo, metformin, and insulin, a difference of -0.45 % [95 % CI: -0.62, -0.29]. The incidence of hypoglycaemia was 24.9 % for patients treated with sitagliptin, metformin, and insulin and 37.8 % for patients treated with placebo, metformin, and insulin. The difference was mainly due to a higher percentage of patients in the placebo group experiencing 3 or more episodes of hypoglycaemia (9.1 vs. 19.8 %). There was no difference in the incidence of severe hypoglycaemia.

Metformin

Mechanism of action

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).

Clinical efficacy and safety
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.

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).

The TECOS was a randomised study in 14,671 patients in the intention-to-treat population with an HbA_{1c} of ≥ 6.5 to 8.0 % with established CV disease who received sitagliptin (7,332) 100 mg daily (or 50 mg daily if the baseline eGFR was ≥ 30 and < 50 mL/min/1.73 m^2) or placebo (7,339) added to usual care targeting regional standards for HbA_{1c} and CV risk factors. Patients with an eGFR < 30 mL/min/1.73 m^2 were not to be enrolled in the study. The study population included 2,004 patients ≥ 75 years of age and 3,324 patients with renal impairment (eGFR < 60 mL/min/1.73 m^2).

Over the course of the study, the overall estimated mean (SD) difference in HbA_{1c} between the sitagliptin and placebo groups was 0.29 % (0.01), 95 % CI (-0.32, -0.27); p < 0.001.

The primary cardiovascular endpoint was a composite of the first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for unstable angina. Secondary cardiovascular endpoints included the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; first occurrence of the individual components of the primary composite; all-cause mortality; and hospital admissions for congestive heart failure.

After a median follow up of 3 years, sitagliptin, when added to usual care, did not increase the risk of major adverse cardiovascular events or the risk of hospitalisation for heart failure compared to usual care without sitagliptin in patients with type 2 diabetes (Table 3).

Table 3: Rates of Composite Cardiovascular Outcomes and Key Secondary Outcomes

	Sitagliptin 100 mg		**Placebo**			
	N (%)	**Incidence rate per 100 patient-years***	**N (%)**	**Incidence rate per 100 patient-years***	**Hazard Ratio (95% CI)**	**p-value†**
Analysis in the Intention-to-Treat Population						
Number of patients	**7,332**		**7,339**		0.98 (0.89–1.08)	<0.001

	Sitagliptin 100 mg		Placebo		Hazard Ratio (95% CI)	p-value[†]
	N (%)	Incidence rate per 100 patient-years*	N (%)	Incidence rate per 100 patient-years*		
Primary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalisation for unstable angina)	839 (11.4)	4.1	851 (11.6)	4.2		
Secondary Composite Endpoint (Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke)	745 (10.2)	3.6	746 (10.2)	3.6	0.99 (0.89–1.10)	<0.001
Secondary Outcome						
Cardiovascular death	380 (5.2)	1.7	366 (5.0)	1.7	1.03 (0.89-1.19)	0.711
All myocardial infarction (fatal and non-fatal)	300 (4.1)	1.4	316 (4.3)	1.5	0.95 (0.81–1.11)	0.487
All stroke (fatal and non-fatal)	178 (2.4)	0.8	183 (2.5)	0.9	0.97 (0.79–1.19)	0.760
Hospitalisation for unstable angina	116 (1.6)	0.5	129 (1.8)	0.6	0.90 (0.70–1.16)	0.419
Death from any cause	547 (7.5)	2.5	537 (7.3)	2.5	1.01 (0.90–1.14)	0.875
Hospitalisation for heart failure[‡]	228 (3.1)	1.1	229 (3.1)	1.1	1.00 (0.83–1.20)	0.983

***** Incidence rate per 100 patient-years is calculated as 100 × (total number of patients with ≥ 1 event during eligible exposure period per total patient-years of follow-up).

[†] Based on a Cox model stratified by region. For composite endpoints, the p-values correspond to a test of non-inferiority seeking to show that the hazard ratio is less than 1.3. For all other endpoints, the p-values correspond to a test of differences in hazard rates.

[‡] The analysis of hospitalisation for heart failure was adjusted for a history of heart failure at baseline.

Paediatric population

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

5.2 Pharmacokinetic properties

Ristfor

A bioequivalence study in healthy subjects demonstrated that the Ristfor (sitagliptin/metformin hydrochloride) combination tablets are bioequivalent to co-administration of sitagliptin phosphate and metformin hydrochloride as individual tablets.

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

Sitagliptin

Absorption

Following oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8.52 μM•hr, C_{max} was 950 nM. The absolute bioavailability of sitagliptin is approximately 87 %. Since co-administration of a high-fat meal with sitagliptin had no effect on the pharmacokinetics, sitagliptin may be administered with or without food.

Plasma AUC of sitagliptin increased in a dose-proportional manner. Dose-proportionality was not established for C_{max} and C_{24hr} (C_{max} increased in a greater than dose-proportional manner and C_{24hr} increased in a less than dose-proportional manner).

Distribution
The mean volume of distribution at steady state following a single 100-mg intravenous dose of sitagliptin to healthy subjects is approximately 198 litres. The fraction of sitagliptin reversibly bound to plasma proteins is low (38 %).

Biotransformation
Sitagliptin is primarily eliminated unchanged in urine, and metabolism is a minor pathway. Approximately 79 % of sitagliptin is excreted unchanged in the urine.

Following a [^{14}C]sitagliptin oral dose, approximately 16 % of the radioactivity was excreted as metabolites of sitagliptin. Six metabolites were detected at trace levels and are not expected to contribute to the plasma DPP-4 inhibitory activity of sitagliptin. *In vitro* studies indicated that the primary enzyme responsible for the limited metabolism of sitagliptin was CYP3A4, with contribution from CYP2C8.

In vitro data showed that sitagliptin is not an inhibitor of CYP isoenzymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4 and CYP1A2.

Elimination
Following administration of an oral [^{14}C]sitagliptin dose to healthy subjects, approximately 100 % of the administered radioactivity was eliminated in faeces (13 %) or urine (87 %) within one week of dosing. The apparent terminal $t_{½}$ following a 100-mg oral dose of sitagliptin was approximately 12.4 hours. Sitagliptin accumulates only minimally with multiple doses. The renal clearance was approximately 350 mL/min.

Elimination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 (hOAT-3), which may be involved in the renal elimination of sitagliptin. The clinical relevance of hOAT-3 in sitagliptin transport has not been established. Sitagliptin is also a substrate of p-glycoprotein, which may also be involved in mediating the renal elimination of sitagliptin. However, ciclosporin, a p-glycoprotein inhibitor, did not reduce the renal clearance of sitagliptin. Sitagliptin is not a substrate for OCT2 or OAT1 or PEPT1/2 transporters. *In vitro*, sitagliptin did not inhibit OAT3 (IC50=160 μM) or p-glycoprotein (up to 250 μM) mediated transport at therapeutically relevant plasma concentrations. In a clinical study sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of p-glycoprotein.

Characteristics in patients
The pharmacokinetics of sitagliptin were generally similar in healthy subjects and in patients with type 2 diabetes.

Renal impairment
A single-dose, open-label study was conducted to evaluate the pharmacokinetics of a reduced dose of sitagliptin (50 mg) in patients with varying degrees of chronic renal impairment compared to normal healthy control subjects. The study included patients with mild, moderate, and severe renal impairment, as well as patients with ESRD on haemodialysis. In addition, the effects of renal impairment on sitagliptin pharmacokinetics in patients with type 2 diabetes and mild, moderate, or severe renal impairment (including ESRD) were assessed using population pharmacokinetic analyses.

Compared to normal healthy control subjects, plasma AUC of sitagliptin was increased by approximately 1.2-fold and 1.6-fold in patients with mild renal impairment (GFR ≥ 60 to < 90 mL/min) and patients with moderate renal impairment (GFR ≥ 45 to < 60 mL/min), respectively.

Because increases of this magnitude are not clinically relevant, dosage adjustment in these patients is not necessary.

Plasma AUC of sitagliptin was increased approximately 2-fold in patients with moderate renal impairment (GFR ≥ 30 to < 45 mL/min), and approximately 4-fold in patients with severe renal impairment (GFR < 30 mL/min), including patients with ESRD on haemodialysis. Sitagliptin was modestly removed by haemodialysis (13.5 % over a 3- to 4-hour haemodialysis session starting 4 hours post-dose).

Hepatic impairment
No dose adjustment for sitagliptin is necessary for patients with mild or moderate hepatic impairment (Child-Pugh score ≤ 9). There is no clinical experience in patients with severe hepatic impairment (Child-Pugh score > 9). However, because sitagliptin is primarily renally eliminated, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin.

Elderly
No dose adjustment is required based on age. Age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 years) had approximately 19 % higher plasma concentrations of sitagliptin compared to younger subjects.

Paediatric
No studies with sitagliptin have been performed in paediatric patients.

Other patient characteristics
No dose adjustment is necessary based on gender, race, or body mass index (BMI). These characteristics had no clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

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 5 μg/mL, even at maximum doses.

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 Vd ranged between 63 – 276 L.

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

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

5.3 Preclinical safety data

No animal studies have been conducted with Ristfor.

In 16-week studies in which dogs were treated with either metformin alone or a combination of metformin and sitagliptin, no additional toxicity was observed from the combination. The NOEL in these studies was observed at exposures to sitagliptin of approximately 6 times the human exposure and to metformin of approximately 2.5 times the human exposure.

The following data are findings in studies performed with sitagliptin or metformin individually.

Sitagliptin
Renal and liver toxicity were observed in rodents at systemic exposure values 58 times the human exposure level, while the no-effect level was found at 19 times the human exposure level. Incisor teeth abnormalities were observed in rats at exposure levels 67 times the clinical exposure level; the no-effect level for this finding was 58-fold based on the 14-week rat study. The relevance of these findings for humans is unknown. Transient treatment-related physical signs, some of which suggest neural toxicity, such as open-mouth breathing, salivation, white foamy emesis, ataxia, trembling, decreased activity, and/or hunched posture were observed in dogs at exposure levels approximately 23 times the clinical exposure level. In addition, very slight to slight skeletal muscle degeneration was also observed histologically at doses resulting in systemic exposure levels of approximately 23 times the human exposure level. A no-effect level for these findings was found at an exposure 6-fold the clinical exposure level.

Sitagliptin has not been demonstrated to be genotoxic in preclinical studies. Sitagliptin was not carcinogenic in mice. In rats, there was an increased incidence of hepatic adenomas and carcinomas at systemic exposure levels 58 times the human exposure level. Since hepatotoxicity has been shown to correlate with induction of hepatic neoplasia in rats, this increased incidence of hepatic tumours in rats was likely secondary to chronic hepatic toxicity at this high dose. Because of the high safety margin (19-fold at this no-effect level), these neoplastic changes are not considered relevant for the situation in humans.

No treatment related effects on fertility were observed in male and female rats given sitagliptin prior to and throughout mating.

In a pre-/post-natal development study performed in rats sitagliptin showed no adverse effects.

Reproductive toxicity studies showed a slight treatment-related increased incidence of foetal rib malformations (absent, hypoplastic and wavy ribs) in the offspring of rats at systemic exposure levels more than 29 times the human exposure levels. Maternal toxicity was seen in rabbits at more than 29 times the human exposure levels. Because of the high safety margins, these findings do not suggest a relevant risk for human reproduction. Sitagliptin is secreted in considerable amounts into the milk of lactating rats (milk/plasma ratio: 4:1).

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
microcrystalline cellulose (E460)
povidone K29/32 (E1201)
sodium lauril sulfate
sodium stearyl fumarate

Film coating
poly(vinyl alcohol)
macrogol 3350
talc (E553b)
titanium dioxide (E171)
iron oxide red (E172)
iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Opaque blisters (PVC/PE/PVDC and aluminium).
Packs of 14, 28, 56, 60, 112, 168, 180, 196 film-coated tablets, multi-packs containing 196 (2 packs of 98) and 168 (2 packs of 84) film-coated tablets. Pack of 50 x 1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/620/009
EU/1/10/620/010
EU/1/10/620/011
EU/1/10/620/012
EU/1/10/620/013
EU/1/10/620/014
EU/1/10/620/015
EU/1/10/620/016
EU/1/10/620/018
EU/1/10/620/021
EU/1/10/620/022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 March 2010
Date of latest renewal: 16 December 2014

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

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

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

BIOTON S.A.
Macierzysz, ul. Poznańska 12
05-850 Ożarów Mazowiecki
Poland

Merck Sharp & Dohme Ltd.
Shotton Lane, Cramlington
Northumberland NE23 3JU
United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

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

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ristfor 50 mg/850 mg film-coated tablets
sitagliptin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains sitagliptin phosphate monohydrate equivalent to 50 mg of sitagliptin and 850 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
56 film-coated tablets
60 film-coated tablets
112 film-coated tablets
168 film-coated tablets
180 film-coated tablets
196 film-coated tablets
50 x 1 film-coated tablets
Multi-pack containing 196 (2 packs of 98) film-coated tablets
Multi-pack containing 168 (2 packs of 84) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/620/001 14 film-coated tablets
EU/1/10/620/002 28 film-coated tablets
EU/1/10/620/003 56 film-coated tablets
EU/1/10/620/019 60 film-coated tablets
EU/1/10/620/004 112 film-coated tablets
EU/1/10/620/005 168 film-coated tablets
EU/1/10/620/020 180 film-coated tablets
EU/1/10/620/006 196 film-coated tablets
EU/1/10/620/007 50 x 1 film-coated tablets
EU/1/10/620/008 196 (2 x 98) film-coated tablets
EU/1/10/620/017 168 (2 x 84) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ristfor
50 mg
850 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON for Multi-packs 2 packs – without blue box - 50 mg/850 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Ristfor 50 mg/850 mg film-coated tablets
sitagliptin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains sitagliptin phosphate monohydrate equivalent to 50 mg of sitagliptin and 850 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

98 film-coated tablets. Component of a multi-pack, can't be sold separately.
84 film-coated tablets. Component of a multi-pack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/620/008
EU/1/10/620/017

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Ristfor 50 mg/850 mg tablets
sitagliptin/metformin HCl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

MSD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ristfor 50 mg/1,000 mg film-coated tablets
sitagliptin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains sitagliptin phosphate monohydrate equivalent to 50 mg of sitagliptin and 1,000 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
56 film-coated tablets
60 film-coated tablets
112 film-coated tablets
168 film-coated tablets
180 film-coated tablets
196 film-coated tablets
50 x 1 film-coated tablets
Multi-pack containing 196 (2 packs of 98) film-coated tablets
Multi-pack containing 168 (2 packs of 84) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/620/009 14 film-coated tablets
EU/1/10/620/010 28 film-coated tablets
EU/1/10/620/011 56 film-coated tablets
EU/1/10/620/021 60 film-coated tablets
EU/1/10/620/012 112 film-coated tablets
EU/1/10/620/013 168 film-coated tablets
EU/1/10/620/022 180 film-coated tablets
EU/1/10/620/014 196 film-coated tablets
EU/1/10/620/015 50 x 1 film-coated tablets
EU/1/10/620/016 196 (2 x 98) film-coated tablets
EU/1/10/620/018 168 (2 x 84) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ristfor
50 mg
1,000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON for Multi-packs 2 packs – without blue box - 50 mg/1,000 mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

Ristfor 50 mg/1,000 mg film-coated tablets
sitagliptin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains sitagliptin phosphate monohydrate equivalent to 50 mg of sitagliptin and 1,000 mg of metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

98 film-coated tablets. Component of a multi-pack, can't be sold separately.
84 film-coated tablets. Component of a multi-pack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/620/016
EU/1/10/620/018

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Ristfor 50 mg/1,000 mg tablets
sitagliptin/metformin HCl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

MSD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ristfor 50 mg/850 mg film-coated tablets
sitagliptin/metformin hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ristfor is and what it is used for

Ristfor contains two different medicines called sitagliptin and metformin.
- sitagliptin belongs to a class of medicines called DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors)
- metformin belongs to a class of medicines called biguanides.

They work together to control blood sugar levels in adult patients with a form of diabetes called 'type 2 diabetes mellitus'. This medicine helps to increase the levels of insulin produced after a meal and lowers the amount of sugar made by your body.

Along with diet and exercise, this medicine helps lower your blood sugar. This medicine can be used alone or with certain other medicines for diabetes (insulin, sulphonylureas, or glitazones).

What is type 2 diabetes?
Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems like heart disease, kidney disease, blindness, and amputation.

2. What you need to know before you take Ristfor

Do not take Ristfor:
- if you are allergic to sitagliptin or metformin or any of the other ingredients of this medicine (listed in section 6)
- if you have severely reduced kidney function
- if you have uncontrolled diabetes, with e.g. severe hyperglycaemia (high blood glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis (see "Risk of lactic acidosis" below) or ketoacidosis. Ketoacidosis is a condition in which substances called 'ketone bodies' accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual fruity smell.

- if you have a severe infection or are dehydrated
- if you are going to have an X-ray where you will be injected with a dye. You will need to stop taking Ristfor at the time of the X-ray and for 2 or more days after as directed by your doctor, depending on how your kidneys are working
- if you have recently had a heart attack or have severe circulatory problems, such as 'shock' or breathing difficulties
- if you have liver problems
- if you drink alcohol to excess (either every day or only from time to time)
- if you are breast-feeding.

Do not take Ristfor if any of the above apply to you and talk with your doctor about other ways of managing your diabetes. If you are not sure, talk to your doctor, pharmacist or nurse before taking Ristfor.

Warnings and precautions
Cases of inflammation of the pancreas (pancreatitis) have been reported in patients receiving Ristfor (see section 4).

If you encounter blistering of the skin it may be a sign for a condition called bullous pemphigoid. Your doctor may ask you to stop Ristfor.

Risk of lactic acidosis
Ristfor may cause a very rare, but very serious side effect called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration (see further information below), liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease).
If any of the above apply to you, talk to your doctor for further instructions.

Stop taking Ristfor for a short time if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instructions.

Stop taking Ristfor and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma.
Symptoms of lactic acidosis include:
- vomiting
- stomach ache (abdominal pain)
- muscle cramps
- a general feeling of not being well with severe tiredness
- difficulty in breathing
- reduced body temperature and heartbeat

Lactic acidosis is a medical emergency and must be treated in a hospital.

Talk to your doctor or pharmacist before taking Ristfor:
- if you have or have had a disease of the pancreas (such as pancreatitis)
- if you have or have had gallstones, alcohol dependence or very high levels of triglycerides (a form of fat) in your blood. These medical conditions can increase your chance of getting pancreatitis (see section 4).
- if you have type 1 diabetes. This is sometimes called insulin-dependent diabetes
- if you have or have had an allergic reaction to sitagliptin, metformin, or Ristfor (see section 4)
- if you are taking a sulphonylurea or insulin, diabetes medicines, together with Ristfor, as you may experience low blood sugar levels (hypoglycaemia). Your doctor may reduce the dose of your sulphonylurea or insulin

If you need to have major surgery you must stop taking Ristfor during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with Ristfor.

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

During treatment with Ristfor, your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or if you have worsening kidney function.

Children and adolescents
Children and adolescents below 18 years should not use this medicine. It is not known if this medicine is safe and effective when used in children and adolescents under 18 years of age.

Other medicines and Ristfor
If you need to have an injection of a contrast medium that contains iodine into your bloodstream, for example, in the context of an X-ray or scan, you must stop taking Ristfor before or at the time of the injection. Your doctor will decide when you must stop and when to restart your treatment with Ristfor.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. You may need more frequent blood glucose and kidney function tests, or your doctor may need to adjust the dosage of Ristfor. It is especially important to mention the following:

- medicines (taken by mouth, inhalation, or injection) used to treat diseases that involve inflammation, like asthma and arthritis (corticosteroids)
- medicines which increase urine production (diuretics)
- medicines used to treat pain and inflammation (NSAID and COX-2-inhibitors, such as ibuprofen and celecoxib)
- certain medicines for the treatment of high blood pressure (ACE inhibitors and angiotensin II receptor antagonists)
- specific medicines for the treatment of bronchial asthma (β-sympathomimetics)
- iodinated contrast agents or alcohol-containing medicines
- certain medicines used to treat stomach problems such as cimetidine
- ranolazine, a medicine used to treat angina
- dolutegravir, a medicine used to treat HIV infection
- vandetanib, a medicine used to treat a specific type of thyroid cancer (medullary thyroid cancer)
- digoxin (to treat irregular heart beat and other heart problems). The level of digoxin in your blood may need to be checked if taking with Ristfor.

Ristfor with alcohol
Avoid excessive alcohol intake while taking Ristfor since this may increase the risk of lactic acidosis (see section “Warnings and precautions”).

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. You should not take this medicine during pregnancy or if you are breast-feeding. See section 2, **Do not take Ristfor**.

Driving and using machines
This medicine has no or negligible influence on the ability to drive and use machines. However, dizziness and drowsiness have been reported with sitagliptin, which may affect your ability to drive or use machines.

Taking this medicine in combination with medicines called sulphonylureas or with insulin can cause hypoglycaemia, which may affect your ability to drive and use machines or work without safe foothold.

Ristfor contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Ristfor

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

- Take one tablet:
  - twice daily by mouth
  - with meals to lower your chance of an upset stomach.

- Your doctor may need to increase your dose to control your blood sugar.

- If you have reduced kidney function, your doctor may prescribe a lower dose.

You should continue the diet recommended by your doctor during treatment with this medicine and take care that your carbohydrate intake is equally distributed over the day.

This medicine alone is unlikely to cause abnormally low blood sugar (hypoglycaemia). When this medicine is used with a sulphonylurea medicine or with insulin, low blood sugar can occur and your doctor may reduce the dose of your sulphonylurea or insulin.

If you take more Ristfor than you should
If you take more than the prescribed dosage of this medicine, contact your doctor immediately. Go to the hospital if you have symptoms of lactic acidosis such as feeling cold or uncomfortable, severe nausea or vomiting, stomach ache, unexplained weight loss, muscular cramps, or rapid breathing (see section "Warnings and precautions").

If you forget to take Ristfor
If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take a double dose of this medicine.

If you stop taking Ristfor
Continue to take this medicine as long as your doctor prescribes it so you can continue to help control your blood sugar. You should not stop taking this medicine without talking to your doctor first. If you stop taking Ristfor, your blood sugar may rise again.

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

4. Possible side effects

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

STOP taking Ristfor and contact a doctor immediately if you notice any of the following serious side effects:

- Severe and persistent pain in the abdomen (stomach area) which might reach through to your back with or without nausea and vomiting, as these could be signs of an inflamed pancreas (pancreatitis).

Ristfor may cause a very rare (may affect up to 1 in 10,000 people), but very serious side effect called lactic acidosis (see section "Warnings and precautions"). If this happens, you must **stop taking Ristfor and contact a doctor or the nearest hospital immediately**, as lactic acidosis may lead to coma.

If you have a serious allergic reaction (frequency not known), including rash, hives, blisters on the skin/peeling skin and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing, stop taking this medicine and call your doctor right away. Your doctor may prescribe a medicine to treat your allergic reaction and a different medicine for your diabetes.

Some patients taking metformin have experienced the following side effects after starting sitagliptin:
Common (may affect up to 1 in 10 people): low blood sugar, nausea, flatulence, vomiting
Uncommon (may affect up to 1 in 100 people): stomach ache, diarrhoea, constipation, drowsiness

Some patients have experienced diarrhoea, nausea, flatulence, constipation, stomach ache or vomiting when starting the combination of sitagliptin and metformin together (frequency is common).

Some patients have experienced the following side effects while taking this medicine with a sulphonylurea such as glimepiride:
Very common (may affect more than 1 in 10 people): low blood sugar
Common: constipation

Some patients have experienced the following side effects while taking this medicine in combination with pioglitazone:
Common: swelling of the hands or legs

Some patients have experienced the following side effects while taking this medicine in combination with insulin:
Very common: low blood sugar
Uncommon: dry mouth, headache

Some patients have experienced the following side effects during clinical studies while taking sitagliptin alone (one of the medicines in Ristfor) or during post-approval use of Ristfor or sitagliptin alone or with other diabetes medicines:
Common: low blood sugar, headache, upper respiratory infection, stuffy or runny nose and sore throat, osteoarthritis, arm or leg pain
Uncommon: dizziness, constipation, itching
Rare: reduced number of platelets
Frequency not known: kidney problems (sometimes requiring dialysis), vomiting, joint pain, muscle pain, back pain, interstitial lung disease, bullous pemphigoid (a type of skin blister)

Some patients have experienced the following side effects while taking metformin alone:
Very common: nausea, vomiting, diarrhoea, stomach ache and loss of appetite. These symptoms may happen when you start taking metformin and usually go away
Common: a metallic taste
Very rare: decreased vitamin B12 levels, hepatitis (a problem with your liver), hives, redness of the skin (rash) or itching

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ristfor

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

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

Do not store above 30°C.

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

6. Contents of the pack and other information

What Ristfor contains

- The active substances are sitagliptin and metformin. Each film-coated tablet (tablet) contains sitagliptin phosphate monohydrate equivalent to 50 mg of sitagliptin and 850 mg of metformin hydrochloride.

- The other ingredients are: In the tablet core: microcrystalline cellulose (E460), povidone K 29/32 (E1201), sodium lauril sulfate, and sodium stearyl fumarate. In addition, the film coating contains: poly(vinyl alcohol), macrogol 3350, talc (E553b), titanium dioxide (E171), iron oxide red (E172), and iron oxide black (E172).

What Ristfor looks like and contents of the pack

Capsule-shaped, pink film-coated tablet with “515” debossed on one side.

Opaque blisters (PVC/PE/PVDC and aluminium). Packs of 14, 28, 56, 60, 112, 168, 180, 196 film-coated tablets, multi-packs containing 196 (2 packs of 98) and 168 (2 packs of 84) film-coated tablets. Pack of 50 x 1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed.

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

Package leaflet: Information for the patient

Ristfor 50 mg/1,000 mg film-coated tablets
sitagliptin/metformin hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ristfor is and what it is used for

Ristfor contains two different medicines called sitagliptin and metformin.
- sitagliptin belongs to a class of medicines called DPP-4 inhibitors (dipeptidyl peptidase-4 inhibitors)
- metformin belongs to a class of medicines called biguanides.

They work together to control blood sugar levels in adult patients with a form of diabetes called 'type 2 diabetes mellitus'. This medicine helps to increase the levels of insulin produced after a meal and lowers the amount of sugar made by your body.

Along with diet and exercise, this medicine helps lower your blood sugar. This medicine can be used alone or with certain other medicines for diabetes (insulin, sulphonylureas, or glitazones).

What is type 2 diabetes?
Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems like heart disease, kidney disease, blindness, and amputation.

2. What you need to know before you take Ristfor

Do not take Ristfor:
- if you are allergic to sitagliptin or metformin or any of the other ingredients of this medicine (listed in section 6)
- if you have severely reduced kidney function
- if you have uncontrolled diabetes, with e.g. severe hyperglycaemia (high blood glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis (see "Risk of lactic acidosis" below) or ketoacidosis. Ketoacidosis is a condition in which substances called 'ketone bodies' accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual fruity smell.

- if you have a severe infection or are dehydrated
- if you are going to have an X-ray where you will be injected with a dye. You will need to stop taking Ristfor at the time of the X-ray and for 2 or more days after as directed by your doctor, depending on how your kidneys are working
- if you have recently had a heart attack or have severe circulatory problems, such as 'shock' or breathing difficulties
- if you have liver problems
- if you drink alcohol to excess (either every day or only from time to time)
- if you are breast-feeding.

Do not take Ristfor if any of the above apply to you and talk with your doctor about other ways of managing your diabetes. If you are not sure, talk to your doctor, pharmacist or nurse before taking Ristfor.

Warnings and precautions
Cases of inflammation of the pancreas (pancreatitis) have been reported in patients receiving Ristfor (see section 4).

If you encounter blistering of the skin it may be a sign for a condition called bullous pemphigoid. Your doctor may ask you to stop Ristfor.

Risk of lactic acidosis
Ristfor may cause a very rare, but very serious side effect called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration (see further information below), liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease).
If any of the above apply to you, talk to your doctor for further instructions.

Stop taking Ristfor for a short time if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instructions.

Stop taking Ristfor and contact a doctor or the nearest hospital immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma.
Symptoms of lactic acidosis include:
- vomiting
- stomach ache (abdominal pain)
- muscle cramps
- a general feeling of not being well with severe tiredness
- difficulty in breathing
- reduced body temperature and heartbeat

Lactic acidosis is a medical emergency and must be treated in a hospital.

Talk to your doctor or pharmacist before taking Ristfor:
- if you have or have had a disease of the pancreas (such as pancreatitis)
- if you have or have had gallstones, alcohol dependence or very high levels of triglycerides (a form of fat) in your blood. These medical conditions can increase your chance of getting pancreatitis (see section 4).
- if you have type 1 diabetes. This is sometimes called insulin-dependent diabetes
- if you have or have had an allergic reaction to sitagliptin, metformin, or Ristfor (see section 4)
- if you are taking a sulphonylurea or insulin, diabetes medicines, together with Ristfor, as you may experience low blood sugar levels (hypoglycaemia). Your doctor may reduce the dose of your sulphonylurea or insulin

If you need to have major surgery you must stop taking Ristfor during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with Ristfor.

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

During treatment with Ristfor, your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or if you have worsening kidney function.

Children and adolescents
Children and adolescents below 18 years should not use this medicine. It is not known if this medicine is safe and effective when used in children and adolescents under 18 years of age.

Other medicines and Ristfor
If you need to have an injection of a contrast medium that contains iodine into your bloodstream, for example, in the context of an X-ray or scan, you must stop taking Ristfor before or at the time of the injection. Your doctor will decide when you must stop and when to restart your treatment with Ristfor.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. You may need more frequent blood glucose and kidney function tests, or your doctor may need to adjust the dosage of Ristfor. It is especially important to mention the following:

- medicines (taken by mouth, inhalation, or injection) used to treat diseases that involve inflammation, like asthma and arthritis (corticosteroids)
- medicines which increase urine production (diuretics)
- medicines used to treat pain and inflammation (NSAID and COX-2-inhibitors, such as ibuprofen and celecoxib)
- certain medicines for the treatment of high blood pressure (ACE inhibitors and angiotensin II receptor antagonists)
- specific medicines for the treatment of bronchial asthma (β-sympathomimetics)
- iodinated contrast agents or alcohol-containing medicines
- certain medicines used to treat stomach problems such as cimetidine
- ranolazine, a medicine used to treat angina
- dolutegravir, a medicine used to treat HIV infection
- vandetanib, a medicine used to treat a specific type of thyroid cancer (medullary thyroid cancer)
- digoxin (to treat irregular heart beat and other heart problems). The level of digoxin in your blood may need to be checked if taking with Ristfor.

Ristfor with alcohol
Avoid excessive alcohol intake while taking Ristfor since this may increase the risk of lactic acidosis (see section “Warnings and precautions”).

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are plan ning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. You should not take this medicine during pregnancy or if you are breast-feeding. See section 2, **Do not take Ristfor**.

Driving and using machines
This medicine has no or negligible influence on the ability to drive and use machines. However, dizziness and drowsiness have been reported with sitagliptin, which may affect your ability to drive or use machines.

Taking this medicine in combination with medicines called sulphonylureas or with insulin can cause hypoglycaemia, which may affect your ability to drive and use machines or work without safe foothold.

Ristfor contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Ristfor

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

- Take one tablet:
  - twice daily by mouth
  - with meals to lower your chance of an upset stomach.

- Your doctor may need to increase your dose to control your blood sugar.

- If you have reduced kidney function, your doctor may prescribe a lower dose.

You should continue the diet recommended by your doctor during treatment with this medicine and take care that your carbohydrate intake is equally distributed over the day.

This medicine alone is unlikely to cause abnormally low blood sugar (hypoglycaemia). When this medicine is used with a sulphonylurea medicine or with insulin, low blood sugar can occur and your doctor may reduce the dose of your sulphonylurea or insulin.

If you take more Ristfor than you should
If you take more than the prescribed dosage of this medicine, contact your doctor immediately. Go to the hospital if you have symptoms of lactic acidosis such as feeling cold or uncomfortable, severe nausea or vomiting, stomach ache, unexplained weight loss, muscular cramps, or rapid breathing (see section "Warnings and precautions").

If you forget to take Ristfor
If you miss a dose, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule. Do not take a double dose of this medicine.

If you stop taking Ristfor
Continue to take this medicine as long as your doctor prescribes it so you can continue to help control your blood sugar. You should not stop taking this medicine without talking to your doctor first. If you stop taking Ristfor, your blood sugar may rise again.

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

4. Possible side effects

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

STOP taking Ristfor and contact a doctor immediately if you notice any of the following serious side effects:

- Severe and persistent pain in the abdomen (stomach area) which might reach through to your back with or without nausea and vomiting, as these could be signs of an inflamed pancreas (pancreatitis).

Ristfor may cause a very rare (may affect up to 1 in 10,000 people), but very serious side effect called lactic acidosis (see section "Warnings and precautions"). If this happens, you must **stop taking Ristfor and contact a doctor or the nearest hospital immediately**, as lactic acidosis may lead to coma.

If you have a serious allergic reaction (frequency not known), including rash, hives, blisters on the skin/peeling skin and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing, stop taking this medicine and call your doctor right away. Your doctor may prescribe a medicine to treat your allergic reaction and a different medicine for your diabetes.

Some patients taking metformin have experienced the following side effects after starting sitagliptin:
Common (may affect up to 1 in 10 people): low blood sugar, nausea, flatulence, vomiting
Uncommon (may affect up to 1 in 100 people): stomach ache, diarrhoea, constipation, drowsiness

Some patients have experienced diarrhoea, nausea, flatulence, constipation, stomach ache or vomiting when starting the combination of sitagliptin and metformin together (frequency is common).

Some patients have experienced the following side effects while taking this medicine with a sulphonylurea such as glimepiride:
Very common (may affect more than 1 in 10 people): low blood sugar
Common: constipation

Some patients have experienced the following side effects while taking this medicine in combination with pioglitazone:
Common: swelling of the hands or legs

Some patients have experienced the following side effects while taking this medicine in combination with insulin:
Very common: low blood sugar
Uncommon: dry mouth, headache

Some patients have experienced the following side effects during clinical studies while taking sitagliptin alone (one of the medicines in Ristfor) or during post-approval use of Ristfor or sitagliptin alone or with other diabetes medicines:
Common: low blood sugar, headache, upper respiratory infection, stuffy or runny nose and sore throat, osteoarthritis, arm or leg pain
Uncommon: dizziness, constipation, itching
Rare: reduced number of platelets
Frequency not known: kidney problems (sometimes requiring dialysis), vomiting, joint pain, muscle pain, back pain, interstitial lung disease, bullous pemphigoid (a type of skin blister)

Some patients have experienced the following side effects while taking metformin alone:
Very common: nausea, vomiting, diarrhoea, stomach ache and loss of appetite. These symptoms may happen when you start taking metformin and usually go away
Common: a metallic taste
Very rare: decreased vitamin B12 levels, hepatitis (a problem with your liver), hives, redness of the skin (rash) or itching

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ristfor

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

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

Do not store above 30°C.

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

6. Contents of the pack and other information

What Ristfor contains

- The active substances are sitagliptin and metformin. Each film-coated tablet (tablet) contains sitagliptin phosphate monohydrate equivalent to 50 mg of sitagliptin and 1,000 mg of metformin hydrochloride.

- The other ingredients are: In the tablet core: microcrystalline cellulose (E460), povidone K 29/32 (E1201), sodium lauril sulfate, and sodium stearyl fumarate. In addition, the film coating contains the following inactive ingredients: poly(vinyl alcohol), macrogol 3350, talc (E553b), titanium dioxide (E171), iron oxide red (E172), and iron oxide black (E172).

What Ristfor looks like and contents of the pack

Capsule-shaped, red film-coated tablet with “577” debossed on one side.

Opaque blisters (PVC/PE/PVDC and aluminium). Packs of 14, 28, 56, 60, 112, 168, 180, 196 film-coated tablets, multi-packs containing 196 (2 packs of 98) and 168 (2 packs of 84) film-coated tablets. Pack of 50 x 1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed.

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