ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sitagliptin/Metformin hydrochloride Accord 50 mg/850 mg film-coated tablets
Sitagliptin/Metformin hydrochloride Accord 50 mg/1,000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sitagliptin/Metformin hydrochloride Accord 50 mg/850 mg film-coated tablets
Each tablet contains sitagliptin hydrochloride monohydrate equivalent to 50 mg of sitagliptin and 850 mg of metformin hydrochloride.

Sitagliptin/Metformin hydrochloride Accord 50 mg/1,000 mg film-coated tablets
Each tablet contains sitagliptin hydrochloride 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).

Sitagliptin/Metformin hydrochloride Accord 50 mg/850 mg film-coated tablets
Pink colored, capsule shaped, film coated tablet debossed with 'SM2' on one side and plain on other side. Dimension: 20x10 mm.

Sitagliptin/Metformin hydrochloride Accord 50 mg/1,000 mg film-coated tablets
Red colored, capsule shaped, film coated tablet debossed with 'SM3' on one side and plain on other side. Dimension: Length: 21x10 mm

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For adult patients with type 2 diabetes mellitus:

It 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.

It 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.

It 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.

It 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 sitagliptin/metformin hydrochloride 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, sitagliptin/metformin hydrochloride 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 sitagliptin/metformin hydrochloride 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 sitagliptin/metformin hydrochloride 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, sitagliptin/metformin hydrochloride 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 sitagliptin/metformin hydrochloride is available, individual monocomponents should be used instead of the fixed-dose combination.

GFR mL/min	Metformin	Sitagliptin
60-89	Maximum daily dose is 3,000 mg. Dose reduction may be considered in relation to declining renal function.	Maximum daily dose is 100 mg.
45-59	Maximum daily dose is 2,000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 100 mg.
30-44	Maximum daily dose is 1,000 mg. The starting dose is at most half of the maximum dose.	Maximum daily dose is 50 mg.
< 30	Metformin is contraindicated.	Maximum daily dose is 25 mg.

Hepatic impairment
Sitagliptin/metformin hydrochloride must not be used in patients with hepatic impairment (see section 5.2).

Elderly
As metformin and sitagliptin are excreted by the kidney, sitagliptin/metformin hydrochloride 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
Sitagliptin/Metformin hydrochloride Accord should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy. Currently available data are described in sections 4.8, 5.1, and 5.2. Sitagliptin/Metformin hydrochloride Accord has not been studied in paediatric patients under 10 years of age.

Method of administration

Oral use.
Sitagliptin/metformin hydrochloride should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin.

4.3 Contraindications

Sitagliptin/metformin hydrochloride 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

Sitagliptin/metformin hydrochloride 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, sitagliptin/metformin hydrochloride and other potentially suspect medicinal products should be discontinued; if acute pancreatitis is confirmed, sitagliptin/metformin hydrochloride 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). Sitagliptin/metformin hydrochloride 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 sitagliptin/metformin hydrochloride 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, sitagliptin/metformin hydrochloride 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, sitagliptin/metformin hydrochloride should be discontinued.

Surgery

Sitagliptin/metformin hydrochloride 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. Sitagliptin/metformin hydrochloride should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see sections 4.3 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 sitagliptin/metformin hydrochloride who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, treatment must be stopped immediately and other appropriate corrective measures initiated.

Vitamin B12 Deficiency
Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anaemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

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 sitagliptin/metformin hydrochloride 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
Sitagliptin/metformin hydrochloride must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see sections 4.3 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 medicinal products 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 section 5.3).

Sitagliptin/Metformin hydrochloride Accord 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. Sitagliptin/Metformin hydrochloride Accord 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

Sitagliptin/Metformin hydrochloride Accord 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 sitagliptin/metformin hydrochloride 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 studies conducted with sitagliptin/metformin hydrochloride tablets however bioequivalence of sitagliptin/metformin hydrochloride 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%).

Tabulated list of adverse reactions

Sitagliptin and metformin
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
Vitamin B12 decrease/deficiency[†]	Common
Nervous system disorders	
somnolence	Uncommon
Respiratory, thoracic and mediastinal disorders	
interstitial lung disease*	Frequency not known
Gastrointestinal disorders	
diarrhoea	Uncommon
nausea	Common
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

Adverse reaction	Frequency of adverse reaction
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). Frequency categories are based on information available from metformin Summary of Product Characteristics available in the EU.

Paediatric population

In clinical studies with sitagliptin/metformin hydrochloride in paediatric patients with type 2 diabetes mellitus aged 10 to 17 years, the profile of adverse reactions was generally comparable to that

observed in adults. In paediatric patients on or not on background insulin, sitagliptin was associated with an increased risk of hypoglycaemia.

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 HbA1c 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 studies 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: Medicinal products used in diabetes, combinations of oral blood glucose lowering Medicinal products, ATC code: A10BD07

Sitagliptin/Metformin hydrochloride Accord combines two antihyperglycaemic medicinal products with complementary mechanisms of action to improve glycaemic control in patients with type 2

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

Sitagliptin

Mechanism of action
Sitagliptin 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 adult patients with type 2 diabetes.

In clinical studies, 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)
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 HbA1c 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**		**Hazard Ratio (95% CI)**	**p-value†**
	N (%)	**Incidence rate per 100 patient-years***	**N (%)**	**Incidence rate per 100 patient-years***		
Analysis in the intention-to-treat population						
Number of patients	**7,332**		**7,339**			
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	0.98 (0.89–1.08)	<0.001

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 sitagliptin/metformin hydrochloride in all subsets of the paediatric population in type 2 diabetes mellitus (see section 4.2 for information on paediatric use).

The safety and efficacy of the addition of sitagliptin in paediatric patients aged 10 to 17 years with type 2 diabetes and inadequate glycaemic control on metformin with or without insulin was assessed in two studies over 54 weeks. The addition of sitagliptin (administered as sitagliptin + metformin or sitagliptin + metformin extended release (XR)) was compared to the addition of placebo to metformin or metformin XR.

While superiority of HbA1c reduction was demonstrated for sitagliptin + metformin / sitagliptin + metformin XR over metformin at week 20 in the pooled analysis of these two studies, results from the individual studies were inconsistent. Furthermore, greater efficacy for sitagliptin + metformin / sitagliptin + metformin XR compared to metformin was not observed at week 54. Therefore, sitagliptin/metformin hydrochloride should not be used in paediatric patients aged 10 to 17 years old because of insufficient efficacy (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Sitagliptin/metformin hydrochloride

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

The following statements reflect the pharmacokinetic properties of the individual active substances of sitagliptin/metformin hydrochloride.

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, dose 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 population
The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in paediatric patients (10 to 17 years of age) with type 2 diabetes. In this population, the dose adjusted AUC of sitagliptin in plasma was approximately 18% lower compared to adult patients with type 2 diabetes for a 100 mg dose. No studies with sitagliptin have been performed in paediatric patients < 10 years of age.

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 studies, 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 sitagliptin/metformin hydrochloride.

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 reactions.

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)
calcium hydrogen phosphate
croscarmellose sodium (E468)
magnesium stearate (E470b)
povidone
sodium laurilsulfate

Film coating

poly(vinyl alcohol)
macrogol
talc (E553b)
titanium dioxide (E171)
red iron oxide (E172)
black iron oxide (E172) (For 50/1000 mg only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PVC/PE/PVDC-aluminium blisters and Alu-Alu blisters.
Packs of 10, 28, 30, 56, 84, 168, 196, 200 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n,
Edifici Est, 6ª Planta,
08039, Barcelona,
Spain

8. MARKETING AUTHORISATION NUMBER(S)

Sitagliptin/Metformin hydrochloride Accord 50 mg/850 mg film-coated tablets
EU/1/22/1661/001
EU/1/22/1661/002
EU/1/22/1661/003
EU/1/22/1661/004
EU/1/22/1661/005
EU/1/22/1661/006
EU/1/22/1661/007
EU/1/22/1661/008
EU/1/22/1661/009
EU/1/22/1661/010
EU/1/22/1661/011
EU/1/22/1661/012
EU/1/22/1661/013
EU/1/22/1661/014
EU/1/22/1661/015
EU/1/22/1661/016

Sitagliptin/Metformin hydrochloride Accord 50 mg/1000 mg film-coated tablets
EU/1/22/1661/017
EU/1/22/1661/018
EU/1/22/1661/019
EU/1/22/1661/020
EU/1/22/1661/021
EU/1/22/1661/022
EU/1/22/1661/023
EU/1/22/1661/024
EU/1/22/1661/025
EU/1/22/1661/026
EU/1/22/1661/027
EU/1/22/1661/028
EU/1/22/1661/029
EU/1/22/1661/030
EU/1/22/1661/031
EU/1/22/1661/032

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 July 2022

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

Accord Healthcare Polska Sp. z.o.o.
ul.Lutomierska 50,
95-200, Pabianice, Poland

Pharmadox Healthcare Limited
KW20A Kordin Industrial Park,
Paola PLA 3000, Malta

Accord Healthcare B.V.
Winthontlaan 200,
3526 KV Utrecht, Netherlands

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 (PSURs)**

The requirements for submission of PSURs 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 marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP 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

Sitagliptin/Metformin hydrochloride Accord 50 mg/850 mg film-coated tablets
sitagliptin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

10 tablets
28 tablets
30 tablets
56 tablets
84 tablets
168 tablets
196 tablets
200 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 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

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n,
Edifici Est, 6ª Planta,
08039, Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1661/001 10 tablets (PVC/PE/PVDC/alu)
EU/1/22/1661/002 28 tablets (PVC/PE/PVDC/alu)
EU/1/22/1661/003 30 tablets (PVC/PE/PVDC/alu)
EU/1/22/1661/004 56 tablets (PVC/PE/PVDC/alu)
EU/1/22/1661/005 84 tablets (PVC/PE/PVDC/alu)
EU/1/22/1661/006 168 tablets (PVC/PE/PVDC/alu)
EU/1/22/1661/007 196 tablets (PVC/PE/PVDC/alu)
EU/1/22/1661/008 200 tablets (PVC/PE/PVDC/alu)
EU/1/22/1661/009 10 tablets (alu/alu)
EU/1/22/1661/010 28 tablets (alu/alu)
EU/1/22/1661/011 30 tablets (alu/alu)
EU/1/22/1661/012 56 tablets (alu/alu)
EU/1/22/1661/013 84 tablets (alu/alu)
EU/1/22/1661/014 168 tablets (alu/alu)
EU/1/22/1661/015 196 tablets (alu/alu)
EU/1/22/1661/016 200 tablets (alu/alu)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sitagliptin/Metformin hydrochloride Accord 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

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PVC/PE/PVDC-aluminium BLISTERS
Aluminium- aluminium BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sitagliptin/Metformin hydrochloride Accord 50 mg/850 mg tablets
sitagliptin/metformin hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

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

Sitagliptin/Metformin hydrochloride Accord 50 mg/1000 mg film-coated tablets
sitagliptin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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4. PHARMACEUTICAL FORM AND CONTENTS

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84 tablets
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200 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 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

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n,
Edifici Est, 6ª Planta,
08039, Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1661/017 10 tablets (PVC/PE/PVDC/alu)
EU/1/22/1661/018 28 tablets (PVC/PE/PVDC/alu)
EU/1/22/1661/019 30 tablets (PVC/PE/PVDC/alu)
EU/1/22/1661/020 56 tablets (PVC/PE/PVDC/alu)
EU/1/22/1661/021 84 tablets (PVC/PE/PVDC/alu)
EU/1/22/1661/022 168 tablets (PVC/PE/PVDC/alu)
EU/1/22/1661/023 196 tablets (PVC/PE/PVDC/alu)
EU/1/22/1661/024 200 tablets (PVC/PE/PVDC/alu)
EU/1/22/1661/025 10 tablets (alu/alu)
EU/1/22/1661/026 28 tablets (alu/alu)
EU/1/22/1661/027 30 tablets (alu/alu)
EU/1/22/1661/028 56 tablets (alu/alu)
EU/1/22/1661/029 84 tablets (alu/alu)
EU/1/22/1661/030 168 tablets (alu/alu)
EU/1/22/1661/031 196 tablets (alu/alu)
EU/1/22/1661/032 200 tablets (alu/alu)

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sitagliptin/Metformin hydrochloride Accord 50 mg/1000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PVC/PE/PVDC-aluminium BLISTERS
Aluminium- aluminium BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Sitagliptin/Metformin hydrochloride Accord 50 mg/1000 mg tablets
sitagliptin/metformin hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Sitagliptin/Metformin hydrochloride Accord 50 mg/850 mg film-coated tablets
Sitagliptin/Metformin hydrochloride Accord 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 Sitagliptin/Metformin hydrochloride Accord is and what it is used for

This medicine 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 Sitagliptin/Metformin hydrochloride Accord

Do not take Sitagliptin/Metformin hydrochloride Accord
- 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 this medicine 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 this medicine 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 this medicine.

Warnings and precautions
Cases of inflammation of the pancreas (pancreatitis) have been reported in patients receiving this medicine (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 this medicine.

Risk of lactic acidosis
This medicine 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 this medicine 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 this medicine 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 this medicine:
- 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 this medicine (see section 4)
- if you are taking a sulphonylurea or insulin, diabetes medicines, together with this medicine, 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 this medicine during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with this medicine.

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

During treatment with this medicine, 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 effective in children and adolescents between the ages of 10 and 17 years. It is not known if this medicine is safe and effective when used in children younger than 10 years.

Other medicines and Sitagliptin/Metformin hydrochloride Accord
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 this medicine before or at the time of the injection. Your doctor will decide when you must stop and when to restart your treatment with this medicine.

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 dose of this medicine. 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 this medicine.

Sitagliptin/Metformin hydrochloride Accord with alcohol
Avoid excessive alcohol intake while taking this medicine 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 Do not take this medicine if you are breast-feeding. See section 2, Do not take Sitagliptin/Metformin hydrochloride Accord.

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.

Sitagliptin/Metformin hydrochloride Accord 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 Sitagliptin/Metformin hydrochloride Accord

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 Sitagliptin/Metformin hydrochloride Accord than you should
If you take more than the prescribed dose 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 Sitagliptin/Metformin hydrochloride Accord
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 Sitagliptin/Metformin hydrochloride Accord
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 this medicine, 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 this medicine 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).

This medicine 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 this medicine 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 this medicine) or during post-approval use of this medicine 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, decreased or low vitamin B12 levels in the blood (symptoms may include extreme tiredness (fatigue), a sore and red tongue (glossitis), pins and needles (paraesthesia) or pale or yellow skin). Your doctor may arrange some tests to find out the cause of your symptoms because some of these may also be caused by diabetes or due to other unrelated health problems.
Very rare: 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 Sitagliptin/Metformin hydrochloride Accord

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.

Store below 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 Sitagliptin/Metformin hydrochloride Accord contains

- The active substances are sitagliptin and metformin.

  Sitagliptin/Metformin hydrochloride Accord 50 mg/850 mg film-coated tablets
  Each film-coated tablet (tablet) contains sitagliptin hydrochloride monohydrate equivalent to 50 mg of sitagliptin and 850 mg of metformin hydrochloride.

  Sitagliptin/Metformin hydrochloride Accord 50 mg/1,000 mg film-coated tablets
  Each film-coated tablet (tablet) contains sitagliptin hydrochloride monohydrate equivalent to 50 mg of sitagliptin and 1000 mg of metformin hydrochloride.

- The other ingredients are: In the tablet core: microcrystalline cellulose (E460), calcium hydrogen phosphate, croscarmellose sodium (E468), magnesium stearate (E470b), povidone, sodium laurilsulfate. The tablet film coating contains: poly(vinyl alcohol), macrogol, talc (E553b), titanium dioxide (E171), red iron oxide (E172) and iron oxide black (E172) (For 50/1000 mg only). See section 2 'Sitagliptin/Metformin hydrochloride Accord contains sodium'.

What Sitagliptin/Metformin hydrochloride Accord looks like and contents of the pack

Sitagliptin/Metformin hydrochloride Accord 50 mg/850 mg film-coated tablets
Pink colored, capsule shaped, film coated tablet debossed with 'SM2' on one side and plain on other side. Dimension: 20x10 mm.

Sitagliptin/Metformin hydrochloride Accord 50 mg/1,000 mg film-coated tablets
Red colored, capsule shaped, film coated tablet debossed with 'SM3' on one side and plain on other side. Dimension: 21x10 mm.

PVC/PE/PVDC-aluminium blisters and Alu-Alu blisters. Packs of 10, 28, 30, 56, 84, 168, 196, 200 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est, 6ª Planta,
08039 Barcelona,
Spain

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Paola PLA 3000, Malta

Accord Healthcare B.V.
Winthontlaan 200,
3526 KV Utrecht, Netherlands

This leaflet was last approved in

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