SUMMARY OF PRODUCT CHARACTERISTICS

1.7 Product Information

1. Name of the medicinal product

Strength : 50/850 mg

INN Name: GLIPINN M 50/850 (Sitagliptin and Metformin Hydrochloride Tablets)

2. Qualitative and quantitative composition

Each film coated tablet contains:
Sitagliptin Phosphate Monohydrate USP
Equivalent to Sitagliptin ……..50 mg
Metformin Hydrochloride BP……850 mg
Excipients ……..q.s

3. Pharmaceutical form :

Dosage Form : Film coated Tablet

Description :

White to off-white oval, biconvex, film-coated tablets, plain on both sides.

4. Clinical Particulars

4.1 Therapeutic indications

For adult patients with type 2 diabetes mellitus:
Sitagliptin and Metformin Hydrochloride Tablet 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.
Sitagliptin and Metformin Hydrochloride Tablet 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.
Sitagliptin and Metformin Hydrochloride Tablet 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. Sitagliptin and Metformin Hydrochloride Tablet 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 and Metformin Hydrochloride Tablet 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 and Metformin Hydrochloride Tablet 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 and Metformin Hydrochloride Tablet is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be required to reduce the risk of hypoglycaemia .

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 and Metformin Hydrochloride Tablet is used in combination with insulin, a lower dose of insulin may be required to reduce the risk of hypoglycaemia .

For the different doses on metformin, Sitagliptin and Metformin Hydrochloride Tablet 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 should be reviewed before considering initiation of metformin in patients with GFR < 60 mL/min.
If no adequate strength of Sitagliptin and Metformin Hydrochloride Tablet 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 and Metformin Hydrochloride Tablet must not be used in patients with hepatic impairment .
Elderly
As metformin and sitagliptin are excreted by the kidney, Sitagliptin and Metformin Hydrochloride Tablet 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.
Paediatric population
Sitagliptin and Metformin Hydrochloride Tablet should not be used in children and adolescents 10 to 17 years of age because of insufficient efficacy. Sitagliptin and Metformin Hydrochloride Tablet has not been studied in paediatric patients under 10 years of age.

4.3 Method of administration

Method of administration

Sitagliptin and Metformin Hydrochloride Tablet should be given twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin.

4.4 Contraindications

Sitagliptin and Metformin Hydrochloride Tablet is contraindicated in patients with:
- hypersensitivity to the active substances or to any of the excipients;
- any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis);
- diabetic pre-coma;
- severe renal failure (GFR< 30 mL/min);
- acute conditions with the potential to alter renal function such as:
  - dehydration,
  - severe infection,
  - shock,
  - intravascular administration of iodinated contrast agents;
- 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.

4.5 Special warning & precautions for use

General

Sitagliptin and Metformin Hydrochloride Tablet 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 and Metformin Hydrochloride Tablet and other potentially suspect medicinal products should be discontinued; if acute pancreatitis is confirmed, Sitagliptin and Metformin Hydrochloride Tablet 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.
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. Sitagliptin and Metformin Hydrochloride Tablet is contraindicated in patients with GFR < 30 mL/min and should be temporarily discontinued during conditions with the potential to alter renal function.
Hypoglycaemia
Patients receiving Sitagliptin and Metformin Hydrochloride Tablet 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.
Surgery
Sitagliptin and Metformin Hydrochloride Tablet 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 and Metformin Hydrochloride Tablet 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.
Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.6 Interaction with other medicinal products and other forms of interactions

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 and Metformin Hydrochloride Tablet 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 and Metformin Hydrochloride Tablet 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 .

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.

4.7 Pregnancy and lactation

Pregnancy
Sitagliptin and Metformin Hydrochloride Tablet 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
Metformin is excreted in human milk in small amounts. It is not known whether sitagliptin is excreted in human milk. Sitagliptin and Metformin Hydrochloride Tablet must therefore not be used in women who are breast-feeding .
Fertility
Human data are lacking.

4.8 Effects on ability to drive and use machine

Sitagliptin and Metformin Hydrochloride Tablet 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 and
Metformin Hydrochloride Tablet is used in combination with a sulphonylurea or with insulin.

4.9 Undesirable effects

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
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.

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.

Paediatric population

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 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.

4.10 Overdose

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
Sitagliptin and Metformin Hydrochloride Tablet 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.

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).

5.2 Pharmacokinetic Properties

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.

Elimination

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.

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.

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 and Metformin Hydrochloride Tablet.

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

Microcrystalline Cellulose USP
Crosscarmellose Sodium USP
Povidone USP
Sodium Lauryl Sulfate USP
Sodium Stearyl fumarate USP
Sheffcoat white 5Y01571 IH
Purified Water USP

Composition of Sheffcoat PVA white (5Y01571)

Ingredient	E#	CI#	CAS#
HPMC 15 CPS	E464	---	9004-65-3
Polyethylene Glycol	E1521	---	25322-68-3
Talc	E553(b)	77019	14807-96-6
Titanium Dioxide	E171	77891	13463-67-7

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

The shelf life of the medicinal product as package for sale

36 Months.

6.4 Special precaution for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

Alu-PVC blister of 10 Tablets.

6.6 Special precautions for disposal and other handling

No special requirement.

7. Marketing Authorization Holder

Pinnacle Life Science Pvt. Ltd.
Mahendra Industrial Estate, Ground Floor
Plot no .109-D, Rd no 29

Sion (East), Mumbai 400 022, INDIA

8. Marketing Authorization Number :

MNB/08/730

9. Manufacturer Name :

Pinnacle Life Science Pvt. Ltd.
Khasra No. 1328-1330, Village Manpura, Tehsil-Baddi,
Distt. Solan, Himachal Pradesh (H.P.) - 174101, India.

10. Date of first authorization/ renewal of the authorization

20-03-2009

11. Date of the revision of the text
