

**For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory Only.**

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**AZULIX SM IR**

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**1. Generic Name**

Sitagliptin Phosphate, Metformin Hydrochloride & Glimepiride Tablets (50+1000+1/2 mg)

Sitagliptin Phosphate, Metformin Hydrochloride & Glimepiride Tablets (50+500+1/2 mg)

**2. Qualitative and quantitative Composition:**

**AZULIX SM IR (50+1000+1/2 mg)**

Each film coated tablet contains:

Sitagliptin Phosphate Monohydrate I.P.

equivalent to Sitagliptin.....50 mg

Metformin Hydrochloride I.P.....1000 mg

Glimepiride I.P.....1/2mg

Excipients.....q.s.

Colours: Ferric oxide Red USP-NF, Ferric oxide Yellow USP-NF & Titanium Dioxide I.P.

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Glimepiride I.P.....1/2 mg

Excipients.....q.s.

Colours: Ferric oxide Red USP-NF, Ferric oxide Yellow USP-NF & Titanium Dioxide I.P.

The Excipients used are Colloidal Silicone Dioxide, Microcrystalline Cellulose, Mannitol, Providone K, Metformin Hydrochloride, Croscarmellose Sodium, Magnesium Stearate and Instacoate Aqua.

**3. Dosage form and strength**

**Dosage form:** Film coated tablet

**Strength:** Sitagliptin 50 mg Metformin Hydrochloride 1000 mg and Glimepiride 1/2 mg,  
Sitagliptin 50 mg, metformin hydrochloride 500 mg and Glimepiride 1/2 mg

**4. Clinical particulars**

**4.1 Therapeutic indication**

It is indicated for the treatment of as an adjunct to diet an exercise to improve Glycemic control in adults with type 2 diabetes mellitus

## 4.2 Posology and method of administration

### Posology

Dose: As directed by the Physician.

The recommended dose is one tablet daily. Each film coated tablet contains a fixed dose of Sitagliptin Phosphate, Metformin Hydrochloride & Glimepiride.

### Method of administration

AZULIX SM should be given orally and can be taken with or without food. Tablets are to be swallowed whole.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

### *Sitagliptin/ Metformin*

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.

### *Glimepiride*

Glimepiride tablet is contraindicated in patients with a history of a hypersensitivity reaction to Glimepiride or any of the product's ingredients

Sulfonamide derivatives: Patients who have developed an allergic reaction to sulfonamide derivatives may develop an allergic reaction to glimepiride. Do not use glimepiride in patients who have a history of an allergic reaction to sulfonamide derivatives.

## 4.4 Special warnings and precautions for use

### *Sitagliptin*

#### General

Sitagliptin should not be used in patients with type 1 diabetes or 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 other potentially suspect medicinal products should be discontinued; if acute pancreatitis is confirmed, Sitagliptin should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

### Hypoglycaemia when used in combination with other anti-hyperglycaemic medicinal products

In clinical trials of Sitagliptin as monotherapy and as part of combination therapy with medicinal products not known to cause hypoglycaemia (i.e. metformin and/or a PPAR $\gamma$  agonist), rates of hypoglycaemia reported with sitagliptin were similar to rates in patients taking placebo. Hypoglycaemia has been observed when sitagliptin was used in combination with insulin or a sulphonylurea. Therefore, to reduce the risk of hypoglycaemia, a lower dose of sulphonylurea or insulin may be considered.

### Renal impairment

Sitagliptin is renally excreted. To achieve plasma concentrations of sitagliptin similar to those in patients with normal renal function, lower dosages are recommended in patients with GFR < 45 mL/min, as well as in ESRD patients requiring haemodialysis or peritoneal dialysis.

When considering the use of sitagliptin in combination with another anti-diabetic medicinal product, its conditions for use in patients with renal impairment should be checked.

### 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 should be discontinued, other potential causes of the event should be assessed, and alternative treatment for diabetes should be instituted.

### 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 should be discontinued.

## ***Metformin***

### Lactic acidosis:

Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever 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 condition 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 muscle cramps, abdominal pain, 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. Metformin is contraindicated in patients with GFR <30 ml / min and should be temporarily discontinued in presence of conditions that alter renal function..

#### Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with chronic stable heart failure, metformin may be used with regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, metformin is contraindicated.

#### Administration of iodinated contrast media:

Intravascular administration of iodinated contrast agents may lead to contrast-induced nephropathy resulting in metformin accumulation and increased risk of lactate acidosis. Metformin should be discontinued before or at the time of imaging procedure and should not be reinstated until at least 48 hours after, provided that renal function has been evaluated and demonstrated to be stable.

#### Surgery:

Metformin 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 reevaluated and found to be stable.

#### Paediatric population:

The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin is initiated. No effect of metformin on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of metformin on these parameters in metformin-treated children, especially prepubescent children, is recommended.

#### Children aged between 10 and 12 years:

Only 15 subjects aged between 10 and 12 years were included in the controlled clinical studies conducted in children and adolescents. Although efficacy and safety of metformin in these children did not differ from efficacy and safety in older children and adolescents, particular caution is recommended when prescribing to children aged between 10 and 12 years.

#### Other precautions:

All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.

The usual laboratory tests for diabetes monitoring should be performed regularly.

Metformin alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulfonylureas or meglitinides).

### ***Glimepiride***

## Hypoglycemia

All sulfonylureas, including glimepiride, can cause severe hypoglycemia. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. These impairments may present a risk in situations where these abilities are especially important, such as driving or operating other machinery. Severe hypoglycemia can lead to unconsciousness or convulsions and may result in temporary or permanent impairment of brain function or death.

Patients must be educated to recognize and manage hypoglycemia. Use caution when initiating and increasing glimepiride doses in patients who may be predisposed to hypoglycemia (e.g., the elderly, patients with renal impairment, patients on other anti-diabetic medications). Debilitated or malnourished patients, and those with adrenal, pituitary, or hepatic impairment are particularly susceptible to the hypoglycemic action of glucose-lowering medications. Hypoglycemia is also more likely to occur when caloric intake is deficient, after severe or prolonged exercise, or when alcohol is ingested. Early warning symptoms of hypoglycemia may be different or less pronounced in patients with autonomic neuropathy, the elderly, and in patients who are taking beta-adrenergic blocking medications or other sympatholytic agents. These situations may result in severe hypoglycemia before the patient is aware of the hypoglycemia.

## Hypersensitivity Reactions

There have been postmarketing reports of hypersensitivity reactions in patients treated with glimepiride, including serious reactions such as anaphylaxis, angioedema, and Stevens-Johnson Syndrome. If a hypersensitivity reaction is suspected, promptly discontinue glimepiride, assess for other potential causes for the reaction, and institute alternative treatment for diabetes.

## Hemolytic Anemia

Sulfonylureas can cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. Because glimepiride is a sulfonylurea, use caution in patients with G6PD deficiency and consider the use of a non-sulfonylurea alternative. There are also postmarketing reports of haemolytic anemia in patients receiving glimepiride who did not have known G6PD deficiency.

## Increased Risk of Cardiovascular Mortality with Sulfonylureas

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups.

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2 and a half times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality.

Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of glimepiride and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical

structure.

### Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with glimepiride or any other anti-diabetic drug.

## **4.5 Drugs interactions**

### ***Sitagliptin***

#### *Effects of other medicinal products on sitagliptin*

Clinical data described below suggest that the risk for clinically meaningful interactions by co-administered medicinal products is low.

In reported *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 effect of potent CYP3A4 inhibitors in the setting of renal impairment has not been assessed in a clinical study. In reported *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*.

*Metformin:* Co-administration of multiple twice-daily doses of 1,000 mg metformin with 50 mg sitagliptin did not meaningfully alter the pharmacokinetics of sitagliptin in patients with type 2 diabetes.

*Cyclosporin:* A study was conducted to assess the effect of cyclosporin, 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 cyclosporin increased the AUC and C<sub>max</sub> 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<sub>max</sub> 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 reported *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*.

### ***Metformin***

*Concomitant use not recommended:*

Alcohol:

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

Iodinated contrast agents

Metformin must be discontinued prior to, or at the time of the test and not be 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.

Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics):

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of metformin with

- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

***Glimepiride***

Drugs Affecting Glucose Metabolism

A number of medications affect glucose metabolism and may require glimepiride dose adjustment and particularly close monitoring for hypoglycemia or worsening glycemic control. The following are examples of medications that may increase the glucose-lowering effect of sulfonylureas including glimepiride, increasing the susceptibility to and/or intensity of hypoglycemia: oral anti-diabetic medications, pramlintide acetate, insulin, angiotensin converting enzyme (ACE) inhibitors, H<sub>2</sub> receptor antagonists, fibrates, propoxyphene, pentoxifylline, somatostatin analogs, anabolic steroids and androgens, cyclophosphamide, phenylramidol, guanethidine, fluconazole, sulfapyrazone, tetracyclines, clarithromycin,

disopyramide, quinolones, and those drugs that are highly protein-bound, such as fluoxetine, nonsteroidal anti-inflammatory drugs, salicylates, sulfonamides, chloramphenicol, coumarins, probenecid and monoamine oxidase inhibitors.

When these medications are administered to a patient receiving glimepiride, monitor the patient closely for hypoglycemia. When these medications are withdrawn from a patient receiving glimepiride, monitor the patient closely for worsening glycemic control.

The following are examples of medications that may reduce the glucose-lowering effect of sulfonylureas including glimepiride, leading to worsening glycemic control: danazol, glucagon, somatropin, protease inhibitors, atypical antipsychotic medications (e.g., olanzapine and clozapine), barbiturates, diazoxide, laxatives, rifampin, thiazides and other diuretics, corticosteroids, phenothiazines, thyroid hormones, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics (e.g., epinephrine, albuterol, terbutaline), and isoniazid.

When these medications are administered to a patient receiving glimepiride, monitor the patient closely for worsening glycemic control. When these medications are withdrawn from a patient receiving glimepiride, monitor the patient closely for hypoglycemia. Beta-blockers, clonidine, and reserpine may lead to either potentiation or weakening of glimepiride's glucose-lowering effect. Both acute and chronic alcohol intake may potentiate or weaken the glucose-lowering action of glimepiride in an unpredictable fashion.

The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

#### Miconazole

A potential interaction between oral miconazole and sulfonylureas leading to severe hypoglycemia has been reported. Whether this interaction also occurs with other dosage forms of miconazole is not known.

#### Cytochrome P450 2C9 Interactions

There may be an interaction between glimepiride and inhibitors (e.g., fluconazole) and inducers (e.g., rifampin) of cytochrome P450 2C9. Fluconazole may inhibit the metabolism of glimepiride, causing increased plasma concentrations of glimepiride which may lead to hypoglycemia. Rifampin may induce the metabolism of glimepiride, causing decreased plasma concentrations of glimepiride which may lead to worsening glycemic control.

#### Concomitant Administration of Colesevelam

Colesevelam can reduce the maximum plasma concentration and total exposure of glimepiride when the two are coadministered. However, absorption is not reduced when glimepiride is administered 4 hours prior to colesevelam. Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.

### **4.6 Use in special populations (pregnant women, lactating women, paediatric patients, geriatric patients etc)**

#### **Pregnancy**

##### ***Sitagliptin***

There are no reported adequate data from the use of sitagliptin in pregnant women. The reported studies in animals have shown reproductive toxicity at high doses. The potential risk for humans is unknown. Due to lack of human data, sitagliptin should not be used during pregnancy.



### ***Metformin***

A limited amount of data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. Animal studies do not indicate harmful effects with respect to pregnancy, embryonic or fetal development, parturition or postnatal development.

When the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with metformin but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the fetus.

### ***Glimepiride***

Available data from a small number of published studies and postmarketing experience with glimepiride use in pregnancy over decades have not identified any drug associated risks for major birth defects, miscarriage, or adverse maternal outcomes. However, sulfonylureas (including glimepiride) cross the placenta and have been associated with neonatal adverse reactions such as hypoglycemia. Therefore, glimepiride should be discontinued at least two weeks before expected delivery. Poorly controlled diabetes in pregnancy is also associated with risks to the mother and Fetus.

### **Breast-feeding**

#### ***Sitagliptin***

It is unknown whether sitagliptin is excreted in human breast milk. Animal studies have shown excretion of sitagliptin in breast milk. Sitagliptin should not be used during breast-feeding.

#### ***Metformin***

Metformin is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breastfeeding is not recommended during metformin treatment. A decision on whether to discontinue breast-feeding should be made, taking into account the benefit of breastfeeding and the potential risk to adverse effects on the child.

#### ***Glimepiride***

Breastfed infants of lactating women using glimepiride should be monitored for symptoms of hypoglycemia (see Clinical Considerations). It is not known whether glimepiride is excreted in human milk and there are no data on the effects of glimepiride on milk production. Glimepiride is present in rat milk [see Data]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for glimepiride and any potential adverse effects on the breastfed child from glimepiride or from the underlying maternal condition.

### **Fertility**

#### ***Sitagliptin***

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

#### ***Metformin***

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

#### ***Glimepiride***

No data available

#### 4.7 **Effects on ability to drive and use machines**

*Sitagliptin* 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.

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

*Metformin* monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.

However, patients should be alerted to the risk of hypoglycaemia when metformin is used in combination with other antidiabetic agents (e.g. sulfonylureas, insulin or meglitinides).

*Glimepiride* can cause severe hypoglycemia the patient's ability to concentrate and react may be impaired as a result of hypoglycemia. These impairments may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

#### 4.8 **Undesirable effects**

##### *Sitagliptin*

##### *Tabulated list of adverse reactions*

Adverse reactions are listed below (Table 1) by system organ class and frequency. Frequencies are defined as: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ) and not known (cannot be estimated from the available data).

**The frequency of adverse reactions identified from reported placebo-controlled clinical studies of Sitagliptin monotherapy and post-marketing experience**

<b>Adverse reaction</b>	<b>Frequency of adverse reaction</b>
<b>Blood and lymphatic system disorders</b>	
thrombocytopenia	Rare
<b>Immune system disorders</b>	
hypersensitivity reactions including anaphylactic responses	Frequency not known
<b>Metabolism and nutrition disorders</b>	
hypoglycaemia	Common
<b>Nervous system disorders</b>	
headache	Common
dizziness	Uncommon
<b>Respiratory, thoracic and mediastinal disorders</b>	
interstitial lung disease	Frequency not known
<b>Gastrointestinal disorders</b>	
constipation	Uncommon
vomiting	Frequency not known
acute pancreatitis	Frequency not known
fatal and non-fatal haemorrhagic and necrotizing pancreatitis	Frequency not known

<b>Skin and subcutaneous tissue disorders</b>	
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
<b>Musculoskeletal and connective tissue disorders</b>	
arthralgia	Frequency not known
myalgia	Frequency not known
pain in extremity	Frequency not known
back pain	Frequency not known
arthropathy	Frequency not known
<b>Renal and urinary disorders</b>	
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:

In addition to the drug-related adverse experiences described above, adverse experiences reported regardless of causal relationship to medication and occurring in at least 5 % and more commonly in patients treated with sitagliptin included upper respiratory tract infection and nasopharyngitis. Additional adverse experiences reported regardless of causal relationship to medication that occurred more frequently in patients treated with sitagliptin (not reaching the 5 % level, but occurring with an incidence of > 0.5 % higher with sitagliptin than that in the control group) included osteoarthritis and pain in extremity.

Some adverse reactions were observed more frequently in studies of combination use of sitagliptin with other anti-diabetic medicinal products than in studies of sitagliptin monotherapy. These included hypoglycaemia (frequency very common with the combination of sulphonylurea and metformin), influenza (common with insulin (with or without metformin)), nausea and vomiting (common with metformin), flatulence (common with metformin or pioglitazone), constipation (common with the combination of sulphonylurea and metformin), peripheral oedema (common with pioglitazone or the combination of pioglitazone and metformin), somnolence and diarrhoea (uncommon with metformin), and dry mouth (uncommon with insulin (with or without metformin)).

Paediatric population

In clinical trials with sitagliptin in paediatric patients with type 2 diabetes mellitus aged 10 to 17 years, the profile of adverse reactions was comparable to that observed in adults.

*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  $\geq 30$  and  $< 50$

mL/min/1.73 m<sup>2</sup>), 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.

### ***Metformin***

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take metformin in 2 or 3 daily doses and to increase slowly the doses.

The following adverse reactions may occur under treatment with metformin. Frequencies are defined as follows

very common:  $\geq 1/10$ ; common  $\geq 1/100$ ,  $< 1/10$ ; uncommon  $\geq 1/1,000$ ,  $< 1/100$ ; rare  $\geq 1/10,000$ ,  $< 1/1,000$ ; very rare  $< 1/10,000$ .

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

#### *Metabolism and nutrition disorders:*

Very rare:

Lactic acidosis.

Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.

#### *Nervous system disorders:*

Common: Taste disturbance

#### *Gastrointestinal disorders:*

Very common: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

#### *Hepatobiliary disorders:*

Very rare: Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorders:

Very rare: Skin reactions such as erythema, pruritus, urticaria

#### *Paediatric population*

In published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year, adverse event reporting was similar in nature

and severity to that reported in adults.

**Glimepiride**

Hypoglycemia

Hemolytic anemia

**Clinical Trials Experience**

Approximately 2,800 patients with type 2 diabetes have been treated with Glimepiride in the controlled clinical trials. In these trials, approximately 1,700 patients were treated with Glimepiride for at least 1 year.

Table 1 summarizes adverse events, other than hypoglycemia, that were reported in 11 pooled placebo-controlled trials, whether or not considered to be possibly or probably related to study medication. Treatment duration ranged from 13 weeks to 12 months. Terms that are reported represent those that occurred at an incidence of  $\geq 5\%$  among Glimepiride-treated patients and more commonly than in patients who received placebo.

<b>Table 1: Eleven Pooled Placebo-Controlled Trials ranging from 13 weeks to 12 months : Adverse Events (excluding hypoglycemia) Occurring in <math>\geq 5\%</math> of glimepiride-treated Patients and at a Greater Incidence than with Placebo*</b>		
	<b>Glimepiride N=745 %</b>	<b>Placebo N=294 %</b>
Headache	8.2	7.8
Accidental Injury	5.8	3.4
Flu Syndrome	5.4	4.4
Nausea	5.0	3.4
Dizziness	5.0	2.4

\* Glimepiride doses ranged from 1 to 16 mg administered daily †Insufficient information to determine whether any of the accidental injury events were associated with hypoglycemia.

In a randomized, double-blind, placebo-controlled monotherapy trial of 14 weeks duration, patients already on sulfonylurea therapy underwent a 3-week washout period then were randomized to glimepiride 1 mg, 4 mg, 8 mg or placebo. Patients randomized to glimepiride 4 mg or 8 mg underwent forced-titration from an initial dose of 1 mg to these final doses, as tolerated. The overall incidence of possible hypoglycemia (defined by the presence of at least one symptom that the investigator believed might be related to hypoglycemia; a concurrent glucose measurement was not required) was 4% for glimepiride 1 mg, 17% for glimepiride 4 mg, 16% for glimepiride 8 mg and 0% for placebo. All of these events were self-treated.

In a randomized, double-blind, placebo-controlled monotherapy trial of 22 weeks duration, patients received a starting dose of either 1 mg glimepiride or placebo daily. The dose of glimepiride was titrated to a target fasting plasma glucose of 90 to 150 mg/dL. Final daily doses of glimepiride were 1, 2, 3, 4, 6, or 8 mg. The overall incidence of possible hypoglycemia (as defined above for the 14-week trial) for glimepiride vs. placebo was 19.7% vs. 3.2%. All of these events were self-treated.

Weight gain: glimepiride, like all sulfonylureas, can cause weight gain.

Allergic Reactions: In clinical trials, allergic reactions, such as pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions, occurred in less than 1% of glimepiride-treated patients. These may resolve despite continued treatment with glimepiride. There are postmarketing reports of more serious allergic reactions (e.g., dyspnea, hypotension, shock).

#### Laboratory Tests

Elevated serum alanine aminotransferase (ALT): In 11 pooled placebo-controlled trials of glimepiride, 1.9% of glimepiride-treated patients and 0.8% of placebo-treated patients developed serum ALT greater than 2 times the upper limit of the reference range.

Postmarketing Experience the following adverse reactions have been identified during post-approval use of Glimepiride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Serious hypersensitivity reactions, including anaphylaxis, angioedema, and Stevens - Johnson syndrome
- Hemolytic anemia in patients with and without G6PD deficiency
- Impairment of liver function (e.g. with cholestasis and jaundice), as well as hepatitis, which may progress to liver failure.
- Porphyria cutanea tarda, photosensitivity reactions and allergic vasculitis
- Leukopenia, agranulocytosis, aplastic anemia, and pancytopenia
- Thrombocytopenia (including severe cases with platelet count less than 10,000/ $\mu$ L) and thrombocytopenic purpura
- Hepatic porphyria reactions and disulfiram-like reactions
- Hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH), most often in patients who are on other medications or who have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone
- Dysgeusia
- Alopecia

#### 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 requested to report any suspected adverse reactions via any point of contact of Torrent Pharma available at: [http://www.torrentpharma.com/index.php/site/info/adverse\\_event\\_reporting](http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting).

By reporting side effects, you can help provide more information on the safety of this medicine.

## 4.9 Overdose

### *Sitagliptin*

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

observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.

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.

Sitagliptin is modestly dialysable. 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.

### ***Metformin***

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

### ***Glimepiride***

An overdosage of glimepiride, as with other sulfonylureas, can produce severe hypoglycemia. Mild episodes of hypoglycemia can be treated with oral glucose. Severe hypoglycemic reactions constitute medical emergencies requiring immediate treatment. Severe hypoglycemia with coma, seizure, or neurological impairment can be treated with glucagon or intravenous glucose. Continued observation and additional carbohydrate intake may be necessary because hypoglycemia may recur after apparent clinical recovery.

## **5. Pharmacological properties**

### **5.1 Mechanism of Action**

#### ***Sitagliptin***

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 insulintropic 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 (PPAR $\gamma$ ) agonists, alpha-glucosidase inhibitors, and amylin analogues.

In a reported 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.

#### ***Metformin***

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce

hypoglycaemia.

Metformin may act via 3 mechanisms:

- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization.
- and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.

### ***Glimepiride***

Glimepiride primarily lowers blood glucose by stimulating the release of insulin from pancreatic beta cells. Sulfonylureas bind to the sulfonylurea receptor in the pancreatic beta- cell plasma membrane, leading to closure of the ATP-sensitive potassium channel, thereby stimulating the release of insulin.

## **5.2 Pharmacodynamic properties**

### ***Sitagliptin***

#### *Clinical efficacy and safety*

Overall, sitagliptin improved glycaemic control when used as monotherapy or in combination treatment in adult patients with type 2 diabetes.

Two studies were conducted to evaluate the efficacy and safety of sitagliptin monotherapy. Treatment with sitagliptin at 100 mg once daily as monotherapy provided significant improvements in HbA1c, fasting plasma glucose (FPG), and 2-hour post-prandial glucose (2-hour PPG), compared to placebo in two studies, one of 18- and one of 24-weeks duration. Improvement of surrogate markers of beta cell function, including HOMA- $\beta$  (Homeostasis Model Assessment- $\beta$ ), proinsulin to insulin ratio, and measures of beta cell responsiveness from the frequently-sampled meal tolerance test were observed. The observed incidence of hypoglycaemia in patients treated with sitagliptin was similar to placebo. Body weight did not increase from baseline with sitagliptin therapy in either study, compared to a small reduction in patients given placebo.

Sitagliptin 100 mg once daily provided significant improvements in glycaemic parameters compared with placebo in two 24-week studies of sitagliptin as add-on therapy, one in combination with metformin and one in combination with pioglitazone. Change from baseline in body weight was similar for patients treated with sitagliptin relative to placebo. In these studies there was a similar incidence of hypoglycaemia reported for patients treated with sitagliptin or placebo.

A 24-week placebo-controlled reported study was designed to evaluate the efficacy and safety of sitagliptin (100 mg once daily) added to glimepiride alone or glimepiride in combination with metformin. The addition of sitagliptin to either glimepiride alone or to glimepiride and metformin provided significant improvements in glycaemic parameters. Patients treated with sitagliptin had a modest increase in body weight compared to those given placebo.

A 26-week placebo-controlled reported 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.



A 24-week placebo-controlled reported 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. 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.

In a 24-week placebo-controlled reported 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.

A 24-week active (metformin)-controlled reported study was designed to evaluate the efficacy and safety of sitagliptin 100 mg once daily (N=528) compared to metformin (N=522) in patients with inadequate glycaemic control on diet and exercise and who were not on anti-hyperglycaemic therapy (off therapy for at least 4 months). The mean dose of metformin was approximately 1,900 mg per day. The reduction in HbA1c from mean baseline values of 7.2 % was -0.43 % for sitagliptin and -0.57 % for metformin (Per Protocol Analysis). The overall incidence of gastrointestinal adverse reactions considered as drug-related in patients treated with sitagliptin was 2.7 % compared with 12.6 % in patients treated with metformin. The incidence of hypoglycaemia was not significantly different between the treatment groups (sitagliptin, 1.3 %; metformin, 1.9 %). Body weight decreased from baseline in both groups (sitagliptin, -0.6 kg; metformin -1.9 kg).

In a reported 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 HbA1c. The mean glipizide dose used in the comparator group was 10 mg per day with approximately 40 % of patients requiring a glipizide dose of  $\leq 5$  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 compared to a significant weight gain in patients administered glipizide (-1.5 vs. +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 reported 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. Baseline HbA1c was 8.74 % and baseline insulin dose was 37 IU/day. Patients were instructed to titrate their insulin glargine dose based on fingerstick fasting glucose values. 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 in patients treated with sitagliptin and insulin (with or without metformin) was -1.31 % compared to -0.87 % in patients treated with placebo and insulin (with or without metformin), a difference of -0.45 % [95 % CI: -0.60, -0.29]. The incidence of hypoglycaemia was 25.2 % in patients treated with sitagliptin and insulin (with or without metformin) and 36.8 % in patients treated with placebo and insulin (with or without metformin). The difference was mainly due to a higher percentage of patients in the placebo group experiencing 3 or more episodes of hypoglycaemia (9.4 vs. 19.1 %). There was no difference in the incidence of severe hypoglycaemia.

A reported study comparing sitagliptin at 25 or 50 mg once daily to glipizide at 2.5 to 20 mg/day was conducted in patients with moderate to severe renal impairment. This study involved 423 patients with chronic renal impairment (estimated glomerular filtration rate < 50 mL/min). After 54 weeks, the mean reduction from baseline in HbA1c was -0.76 % with sitagliptin and -0.64 % with glipizide (Per-Protocol Analysis). In this study, the efficacy and safety profile of sitagliptin at 25 or 50 mg once daily was generally similar to that observed in other monotherapy studies in patients with normal renal function. The incidence of hypoglycaemia in the sitagliptin group (6.2 %) was significantly lower than that in the glipizide group (17.0 %). There was also a significant difference between groups with respect to change from baseline body weight (sitagliptin -0.6 kg; glipizide +1.2 kg).

Another reported study comparing sitagliptin at 25 mg once daily to glipizide at 2.5 to 20 mg/day was conducted in 129 patients with ESRD who were on dialysis. After 54 weeks, the mean reduction from baseline in HbA1c was -0.72 % with sitagliptin and -0.87 % with glipizide. In this study, the efficacy and safety profile of sitagliptin at 25 mg once daily was generally similar to that observed in other monotherapy studies in patients with normal renal function. The incidence of hypoglycaemia was not significantly different between the treatment groups (sitagliptin, 6.3 %; glipizide, 10.8 %).

In another reported study involving 91 patients with type 2 diabetes and chronic renal impairment (creatinine clearance < 50 mL/min), the safety and tolerability of treatment with sitagliptin at 25 or 50 mg once daily were generally similar to placebo. In addition, after 12 weeks, the mean reductions in HbA1c (sitagliptin -0.59 %; placebo -0.18 %) and FPG (sitagliptin -25.5 mg/dL; placebo -3.0 mg/dL) were generally similar to those observed in other monotherapy studies in patients with normal renal function.

The TECOS was a randomised study in 14,671 patients in the intention-to-treat population with an HbA1c of  $\geq 6.5$  to 8.0 % with established CV disease who received sitagliptin (7,332) 100 mg daily (or 50 mg daily if the baseline eGFR was  $\geq 30$  and < 50 mL/min/1.73 m<sup>2</sup>) or placebo (7,339) added to usual care targeting regional standards for HbA1c and CV risk factors. Patients with an eGFR < 30 mL/min/1.73 m<sup>2</sup> were not to be enrolled in the study. The study population included 2,004 patients  $\geq 75$  years of age and 3,324 patients with renal impairment (eGFR < 60 mL/min/1.73 m<sup>2</sup>).

Over the course of the study, the overall estimated mean (SD) difference in HbA1c 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.

#### Paediatric population

A 54-week, double-blind reported study was conducted to evaluate the efficacy and safety of sitagliptin 100 mg once daily in paediatric patients (10 to 17 years of age) with type 2 diabetes who were not on anti hyperglycaemic therapy for at least 12 weeks (with HbA1c 6.5% to 10%) or were on a stable dose of insulin for at least 12 weeks (with HbA1c 7% to 10%). Patients were randomised to sitagliptin 100 mg once daily or placebo for 20 weeks.

Mean baseline HbA1c was 7.5%. Treatment with sitagliptin 100 mg did not provide significant

improvement in HbA1c at 20 weeks. The reduction in HbA1c in patients treated with sitagliptin (N=95) was 0.0% compared to 0.2% in patients treated with placebo (N=95), a difference of -0.2% (95% CI: -0.7, 0.3).

### ***Metformin***

In clinical studies, use of metformin was associated with either a stable body weight or modest weight loss.

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

### ***Glimepiride***

In healthy subjects, the time to reach maximal effect (minimum blood glucose concentrations) was approximately 2 to 3 hours after single oral doses of glimepiride. The effects of glimepiride on HbA1c, fasting plasma glucose, and postprandial glucose have been assessed in clinical trials.

## **5.3 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 Mm.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 reported *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  $t_{1/2}$  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 (IC<sub>50</sub>=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**

#### *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  $\geq$  60 to  $<$  90 mL/min) and patients with moderate renal impairment (GFR  $\geq$  45 to  $<$  60 mL/min), respectively. Because increases of this magnitude are not clinically relevant, dosage adjustment in these patients is not necessary.

Plasma AUC of sitagliptin was increased approximately 2-fold in patients with moderate renal impairment (GFR  $\geq$  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  $\leq$  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.

Pharmacokinetics and pharmacodynamics (glucosuria) in children with type 2 diabetes mellitus aged 10-17 years were similar to those observed in adults with type 2 diabetes mellitus.

#### *Other patient characteristics with sitagliptin*

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 reported composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

### ***Metformin***

#### *Absorption:*

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear.

At the recommended metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 microgram/ml. In controlled clinical trials, maximum metformin plasma levels (C<sub>max</sub>) did not exceed 5 microgram/ml, even at maximum doses.

#### *Distribution:*

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (V<sub>d</sub>) ranged between 63-276 l.

#### *Metabolism:*

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

#### *Elimination:*

Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

#### Characteristics in specific group of patients

##### *Renal impairment*

The available data in persons with moderate renal insufficiency are sparse and no reliable estimation of systemic metformin exposure in this subgroup could be made compared to persons with normal renal function. Therefore, dose adjustment should be based on clinical efficacy / tolerability.

##### *Paediatric population*

Single dose study: After single doses of metformin hydrochloride 500 mg paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults. Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg twice daily for 7 days in pediatric patients the peak plasma concentration (C<sub>max</sub>) and systemic exposure (AUC<sub>0-t</sub>) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses

of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

## ***Glimepiride***

### *Absorption*

Studies with single oral doses of glimepiride in healthy subjects and with multiple oral doses in patients with type 2 diabetes showed peak drug concentrations (C<sub>max</sub>) 2 to 3 hours postdose. When glimepiride was given with meals, the mean C<sub>max</sub> and AUC (area under the curve) were decreased by 8% and 9%, respectively.

Glimepiride does not accumulate in serum following multiple dosing. The pharmacokinetics of glimepiride does not differ between healthy subjects and patients with type 2 diabetes. Clearance of glimepiride after oral administration does not change over the 1 mg to 8 mg dose range, indicating linear pharmacokinetics.

In healthy subjects, the intraindividual and interindividual variabilities of glimepiride pharmacokinetic parameters were 15% to 23% and 24% to 29%, respectively.

### *Distribution*

After intravenous dosing in healthy subjects, the volume of distribution (V<sub>d</sub>) was 8.8 L (113 mL/kg), and the total body clearance (CL) was 47.8 mL/min. Protein binding was greater than 99.5%.

### *Metabolism*

Glimepiride is completely metabolized by oxidative biotransformation after either an intravenous or oral dose. The major metabolites are the cyclohexyl hydroxy methyl derivative (M1) and the carboxyl derivative (M2). Cytochrome P450 2C9 is involved in the biotransformation of glimepiride to M1. M1 is further metabolized to M2 by one or several cytosolic enzymes. M2 is inactive. In animals, M1 possesses about one-third of the pharmacological activity of glimepiride, but it is unclear whether M1 results in clinically meaningful effects on blood glucose in humans.

### *Excretion*

When <sup>14</sup>C-glimepiride was given orally to 3 healthy male subjects, approximately 60% of the total radioactivity was recovered in the urine in 7 days. M1 and M2 accounted for 80% to 90% of the radioactivity recovered in the urine. The ratio of M1 to M2 in the urine was approximately 3:2 in two subjects and 4:1 in one subject. Approximately 40% of the total radioactivity was recovered in feces. M1 and M2 accounted for about 70% (ratio of M1 to M2 was 1:3) of the radioactivity recovered in feces. No parent drug was recovered from urine or feces. After intravenous dosing in patients, no significant biliary excretion of glimepiride or its M1 metabolite was observed.

## **Specific Populations**

### *Geriatric patients*

A comparison of glimepiride pharmacokinetics in patients with type 2 diabetes ≤65 years and those >65 years was evaluated in a multiple-dose study using glimepiride 6 mg daily. There were no significant differences in glimepiride pharmacokinetics between the two age groups. The mean AUC at steady state for the older patients was approximately 13% lower than that for the younger patients; the mean weight adjusted clearance for the older patients was approximately 11% higher than that for the younger patients.

### *Gender*

There were no differences between males and females in the pharmacokinetics of glimepiride when adjustment was made for differences in body weight.

#### *Race*

No studies have been conducted to assess the effects of race on glimepiride pharmacokinetics but in placebo-controlled trials of glimepiride in patients with type 2 diabetes, the reduction in HbA1C was comparable in Caucasians (n = 536), blacks (n = 63), and Hispanics (n = 63).

#### *Renal impairment*

In a single-dose, open-label study glimepiride 3 mg was administered to patients with mild, moderate and severe renal impairment as estimated by creatinine clearance (CLcr): Group I consisted of 5 patients with mild renal impairment (CLcr > 50 mL/min), Group II consisted of 3 patients with moderate renal impairment (CLcr = 20 to 50 mL/min) and Group III consisted of 7 patients with severe renal impairment (CLcr < 20 mL/min). Although glimepiride serum concentrations decreased max with decreasing renal function, Group III had a 2.3-fold higher mean AUC for M1 and an 8.6-fold higher mean AUC for M2 compared to corresponding mean AUCs in Group I. The apparent terminal half-life (T) for glimepiride did not change, while the half-lives for M1 and M2 increased as renal function decreased. Mean urinary excretion of M1 plus M2 as a percentage of dose decreased from 44.4% for Group I to 21.9% for Group II and 9.3% for Group III.

#### *Hepatic impairment*

It is unknown whether there is an effect of hepatic impairment on glimepiride pharmacokinetics because the pharmacokinetics of glimepiride has not been adequately evaluated in patients with hepatic impairment.

#### *Obese patients*

The pharmacokinetics of glimepiride and its metabolites were measured in a single-dose study involving 28 patients with type 2 diabetes who either had normal body weight or were morbidly obese. While the t, clearance and volume of distribution of glimepiride in the morbidly obese patients were similar to those in the normal weight group, the morbidly obese had lower C and AUC than those of normal body weight. The mean C, AUC, AUC values of glimepiride in normal vs. morbidly obese patients were 547 ± 218 ng/mL vs. 410 ± 124 ng/mL, 3210 ± 1030 hours•ng/mL vs. 2820 ± 1110 hours•ng/mL and 4000 ± 1320 hours•ng/mL vs. 3280 ± 1360 hours•ng/mL, respectively.

#### *Drug Interactions*

##### *Aspirin*

In a randomized, double-blind, two-period, crossover study, healthy subjects were given either placebo or aspirin 1 gram three times daily for a total treatment period of 5 days. On Day 4 of each study period, a single 1 mg dose of glimepiride was administered. The glimepiride doses were separated by a 14-day washout period. Coadministration of aspirin and glimepiride resulted in a 34% decrease in the mean glimepiride AUC and a 4% decrease in the mean glimepiride C.

##### *Colesevelam*

Concomitant administration of colesevelam and glimepiride resulted in reductions in glimepiride AUC and C of 18% and 8%, respectively. When glimepiride was administered 4 hours prior to colesevelam, there was no significant change in glimepiride AUC or C, -6% and 3%, respectively

### *Cimetidine and ranitidine*

In a randomized, open-label, 3-way crossover study, healthy subjects received either a single 4 mg dose of glimepiride alone, glimepiride with ranitidine (150 mg twice daily for 4 days; glimepiride was administered on Day 3), or glimepiride with cimetidine (800 mg daily for 4 days; glimepiride was administered on Day 3). Co-administration of cimetidine or ranitidine with a single 4 mg oral dose of glimepiride did not significantly alter the absorption and disposition of glimepiride.

### *Propranolol*

In a randomized, double-blind, two-period, crossover study, healthy subjects were given either placebo or propranolol 40 mg three times daily for a total treatment period of 5 days. On Day 4 of each study period, a single 2 mg dose of glimepiride was administered.

The glimepiride doses were separated by a 14-day washout period. Concomitant administration of propranolol and glimepiride significantly increased glimepiride C<sub>max</sub>, AUC, and T<sub>1/2</sub> by 23%, 22%, and 15%, respectively, and decreased glimepiride CL/f by 18%. The recovery of M1 and M2 from urine was not changed.

### *Warfarin*

In an open-label, two-way, crossover study, healthy subjects received 4 mg of glimepiride daily for 10 days. Single 25 mg doses of warfarin were administered 6 days before starting glimepiride and on Day 4 of glimepiride administration. The concomitant administration of glimepiride did not alter the pharmacokinetics of R- and S-warfarin enantiomers. No changes were observed in warfarin plasma protein binding. Glimepiride resulted in a statistically significant decrease in the pharmacodynamics response to warfarin. The reductions in mean area under the prothrombin time (PT) curve and maximum PT values during glimepiride treatment were 3.3% and 9.9%, respectively, and are unlikely to be clinically relevant.

## **6. Nonclinical properties**

### **6.1 Animal Toxicology or Pharmacology**

#### *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 reveal no special hazard for humans based on conventional studies on safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

### ***Glimepiride***

Carcinogenesis, Mutagenesis , and Impairment of Fertility

Studies in rats at doses of up to 5000 parts per million (ppm) in complete feed (approximately 340 times the maximum recommended human dose, based on surface area) for 30 months showed no evidence of carcinogenesis. In mice, administration of glimepiride for 24 months resulted in an increase in benign pancreatic adenoma formation that was dose-related and was thought to be the result of chronic pancreatic stimulation.

No adenoma formation in mice was observed at a dose of 320 ppm in complete feed, or 46 to 54 mg/kg body weight/day. This is at least 28 times the maximum human recommended dose of 8 mg once daily based on surface area.

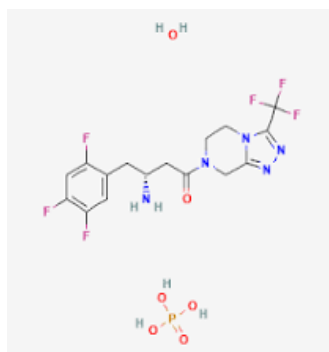
Glimepiride was non-mutagenic in a battery of in vitro and in vivo mutagenicity studies (Ames test, somatic cell mutation, chromosomal aberration, unscheduled DNA synthesis, and mouse micronucleus test).

There was no effect of glimepiride on male mouse fertility in animals exposed up to 2500 mg/kg body weight (>1,500 times the maximum recommended human dose based on surface area). Glimepiride had no effect on the fertility of male and female rats administered up to 4000 mg/kg body weight (approximately 4,000 times the maximum recommended human dose based on surface area).

## **7. Description**

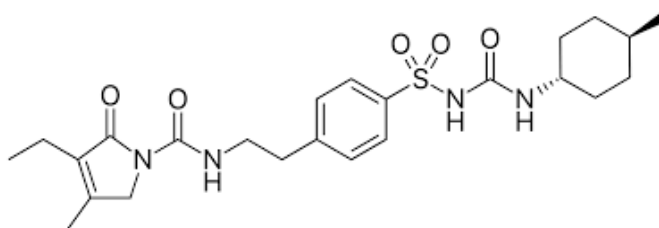
### **Sitagliptin Phosphate Monohydrate:**

Sitagliptin Phosphate is (3R)-3-amino-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3- $\alpha$ ]pyrazine-7(8H)-yl]-4-(2,4,5-trifluorophenyl)butan-1-one phosphate monohydrate. The empirical formula is  $C_{16}H_{18}F_6N_5O_5P \cdot H_2O$  and the molecular weight is 523.3 g/mol. The structural formula is:



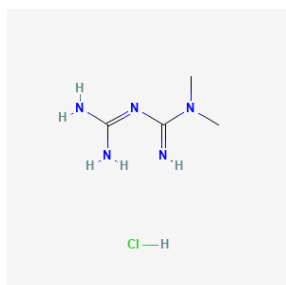
### **Glimepiride:**

Glimepiride is 1-[[4-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulphonyl]-3-trans-(4-methylcyclohexyl)urea. The empirical formula is  $C_{24}H_{34}N_4O_5S$  and the molecular weight is 490.6 g/mol. The structural formula is:



### **Metformin Hydrochloride:**

Metformin Hydrochloride is 1,1-dimethylbiguanide hydrochloride. The empirical formula is  $C_4H_{11}N_5, HCl$  and the molecular weight is 165.6 g/mol. The structural formula is:



### **AZULIX SM IR (50+1000+1/2 mg)**

Sitagliptin Phosphate, Metformin Hydrochloride & Glimepiride Tablets are Beige colored, capsule shape, biconvex, film coated tablets, plain on both sides. The Excipients used are Colloidal Silicone Dioxide, Microcrystalline Cellulose, Mannitol, Providone K, Croscarmellose Sodium, Magnesium Stearate and Instacoate Aqua.

### **AZULIX SM IR (50+500+1/2 mg)**

Sitagliptin, Glimepiride & Metformin Hydrochloride Tablets are peach colored, oval shaped, biconvex, film coated tablets, plain on both sides. The Excipients used are Colloidal Silicone Dioxide, Microcrystalline Cellulose, Mannitol, Providone K 30, Croscarmellose Sodium, Magnesium Stearate and Instacoate Aqua.

## **8. Pharmaceutical particulars**

### **8.1 Incompatibilities**

Not applicable

## 8.2 Shelf-life

Do not use later than date of expiry.

## 8.3 Packaging information

AZULIX SM IR is available in pack of 10 Tablet.

## 8.4 Storage and handing instructions

Store below 30<sup>o</sup> C.

Keep out of reach of Children.

It is dangerous to take this preparation except under medical supervision

## 9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

## 10. Details of manufacturer

Exemed Pharmaceuticals,

Plot No. 133/1 & 133/2, G.I.D.C.,

Selvas Road, Vapi-396 195,

Dist.: Valsad, State: Gujarat, India.

## 11. Details of permission or licence number with date

Mfg. Licence No: G/25/2011 Issued on: 03.11.2023

## 12. Date of revision

NA

## MARKETED BY



TORRENT PHARMACEUTICALS LTD.

**IN/AZULIX SM IR (50+1000+1/2 mg)(50+500+1/2 mg)/Dec-23/01/PI**