4

clinical trials, maximum metformin plasma levels (Cmax) did not exceed 5 µg/mL, even at maximum doses.
Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40 % lower plasma peak concentration, a 25 % decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.
Distribution
Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Vd ranged between 63 – 276 L.
Biotransformation
Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.
Elimination
Renal clearance of metformin is > 400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

DRUG 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 Glipmevia 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
Glipmevia 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.
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.

Overdosage:
During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were administered. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin. There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for periods of up to 28 days.
A large overdose of metformin (or co-existing risks of lactic acidosis) may lead to lactic acidosis which is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.
In 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.

Pharmaceutical Information:
Storage conditions:
Store below 30°C. Protect from direct sunlight, heat & moisture.
Keep out of reach and sight of children.

Pack size: 3 x 10 tablets

SPLEF1202

Manufactured by:
FREDUN PHARMACEUTICALS LTD.
14, 15, 16, Zorabian Industrial Complex,
Vevoor, Palghar (E) - 401 404. INDIA

Manufactured for :
Galaxy Pharmaceuticals
B. No. : 36, Gala No. 2,3,4A, Bhiwandi, Thane (Mumbai) M.S. India

1

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

GLIPMEVIA

(Sitagliptin Phosphate 50 mg and Metformin Hydrochloride 500/850/1000 mg Tablets)

COMPOSITION:
GLIPMEVIA 50/500
Each film coated tablet contains:

Sitagliptin Phosphate Monohydrate	BP	64.25 mg
Equivalent to Sitagliptin		50 mg
Metformin Hydrochloride	BP	500 mg

Excipients: q.s.
Colour: Iron Oxide Red, Iron Oxide Black, Titanium Dioxide BP

GLIPMEVIA 50/850
Each film coated tablet contains:

Sitagliptin Phosphate Monohydrate	BP	64.25 mg
Equivalent to Sitagliptin		50 mg
Metformin Hydrochloride	BP	850 mg

Excipients: q.s.
Colour: Iron Oxide Red, Iron Oxide Black

GLIPMEVIA 50/1000
Each film coated tablet contains:

Sitagliptin Phosphate Monohydrate	BP	64.25 mg
Equivalent to Sitagliptin		50 mg
Metformin Hydrochloride	BP	1000 mg

Excipients: q.s.
Colour: Iron Oxide Red, Titanium Dioxide BP

THERAPEUTIC CATEGORY:
For adult patients with type 2 diabetes mellitus:
Glipmevia 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.
Glipmevia 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.
Glipmevia 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.
Glipmevia 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.

POSOLOGY AND METHOD OF ADMINISTRATION:
The dose of antihyperglycaemic therapy with Glipmevia 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, Glipmevia 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 Glipmevia 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 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 Glipmevia 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, Glipmevia 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.
Hepatic impairment:
Glipmevia must not be used in patients with hepatic impairment.
Elderly:
As metformin and sitagliptin are excreted by the kidney, Glipmevia should be used

2

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

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

PHARMACODYNAMICS:
Pharmacotherapeutic group: Drugs used in diabetes, Combinations of oral blood glucose lowering drugs.
Glipmevia 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).
Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Glipmevia in all subsets of the paediatric population in type 2 diabetes mellitus.

CONTRAINDICATIONS:
Glipmevia 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
acute or chronic disease which may cause tissue hypoxia such as:
- hepatic impairment;
- acute alcohol intoxication, alcoholism;
- breast-feeding.

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

3

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).
WARNING & PRECAUTIONS:
Do not store above 30°C.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PREGNANCY AND LACTATION:
Pregnancy
There are no adequate data from the use of sitagliptin in pregnant women. Studies in animals have shown reproductive toxicity at high doses of sitagliptin.
A limited amount of data suggests the use of metformin in pregnant women is not associated with an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition or postnatal development.
Glipmevia should not be used during pregnancy. If a patient wishes to become pregnant or if a pregnancy occurs, treatment should be discontinued and the patient switched to insulin treatment as soon as possible.
Breast-feeding
No studies in lactating animals have been conducted with the combined active substances of this medicinal product. In studies performed with the individual active substances, both sitagliptin and metformin are excreted in the milk of lactating rats. Metformin is excreted in human milk in small amounts. It is not known whether sitagliptin is excreted in human milk. Glipmevia must therefore not be used in women who are breast-feeding.
Fertility
Animal data do not suggest an effect of treatment with sitagliptin on male and female fertility. Human data are lacking.

PHARMACOKINETICS PROFILE:
A bioequivalence study in healthy subjects demonstrated that the Glipmevia (sitagliptin/metformin hydrochloride) combination tablets are bioequivalent to co-administration of sitagliptin phosphate and metformin hydrochloride as individual tablets.
The following statements reflect the pharmacokinetic properties of the individual active substances of Glipmevia.
Sitagliptin
Absorption
Following oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median Tmax) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8.52 µMhr, Cmax 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 Cmax and C24hr (Cmax increased in a greater than dose-proportional manner and C24hrincreased 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 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.
Elimination
Following administration of an oral 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 t½ 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.
Metformin
Absorption
After an oral dose of metformin, Tmax is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60 % in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30 %.
After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 µg/mL. In controlled

BUYER & COUNTRY	**GALAXY PHARMA-RWANDA**	COLOUR SHADE	C:0 M:0 Y:0 K:100
BRAND	**GLIPMEVIA 50/500, 50/850, 50/1000**	PAPER & GRAMMAGE	54 GSM
GENERIC	SITAGLIPTIN PHOSPHATE AND METFORMIN HYDROCHLORIDE TABLETS	PRODUCT CODE	SPLEF1202
LIC. NO.	KD-135	REGISTRATION NO.	NA
PACK SIZE	3 x 10 TABLETS	NAME OF ARTIST	Rao :)
SIZE OF LEAFLET	140 (L) X 180 (H) mm	APPROVED BY	