For the use of a Registered Medical Practitioner only. Prescribing Information Sitagliptin Phosphate, Metformin Hydrochloride and Glimepiride Tablets GemerSita $\mathbb{R}^{\frac{50}{2}}/\frac{50}{2}/\frac{50}{2}/\frac{50}{2}$



WARNING: LACTIC ACIDOSIS Postmarketing cases of metformin-associated lactic acidosis ware student or death, hypothemia, hypotension, and resistant bradyarthythmias. The onset of metformin associated lactic acidosis is othen subit, accompanied only by nonspecific symptoms such as malaise, myagias, respiratory disfress, somoclence, an aborniata jan. Medformin associated lactic acidosis ware strandardized by devidented blood lactate lace (S monol/Liter), anion gap acidosis (without evidence o ketonuria or ketonemia), an increased lactate/pyruvate ratio, and metformin plasma levels generally-5 mog/mt.
Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such ar topfaramab), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive hear failure), excessive acidoni linkae, and headic impairment.
If melformin-associated lactic acidosis is suspected, immediately discontinue Gemer Sita IR and institute general supportive measures in a hospital setting Prompthemodialysis is recommended.
acticActionsis here have been postmarketing cases of metformin-associated lacic acidosis, including fatal cases. These cases had a subte onset and were accompanied here have been symptoms such as malaise, myagias, abdominal pan, respiratory distress, or increased somnolence, however, hypothemian, hypotension and resista radyarthythmis have occurred with severe acidosis. Metorimin-associated lacic acidosis was haracterized by evented blood lactate concentrations (amoULter), anion gap acidosis (without evidenco of ketoruna or ketoremia), and an increased lactate/privater ratio; metformin planate lacite blood blood acide concentrations (amoULter), anion gap acidosis (without evidenco of ketoruna or ketoremia), and an increased lactate/privater ratio; metformin planate lacite blood blood acide concentrations (angl). Metformin decreases liver uptake of lactate incoale which may increased be in kis facilica cabiosis, especially in patienta a triak.
metformin-associated lactic acidosis is suspected, general supportive measures should be instituted promptly in a hospital setting, along with immedia iscontinuation of Gemer Sita IR. In Gemer Sita IR treated patients with a diagnosis or strong suspicion of factic acidosis, prompt hemodialysis is recommended orreat the acidosis and remove accumulated metformin microfied informin HCI is dialyzable, with a clearance of up to 170 mL/min under good hemodynamic conditions temodialysis has often resulted in reversal of symptoms and recovery.
iducate patients and their families about the symptoms of factic acidosis and if these symptoms occur instruct them to discontinue Gemer Sita IR and report the ymptoms to their physician.
or each of the known and possible risk factors for metformin-associated lactic acidosis, recommendations to reduce the risk of and manage metformin-associate actic acidosis are provided below:
tenal Impairment. The postmarketing metformin-associated lactic acidosis cases primarily occurred in patients with significant renal impairment. The risk of metformin accumulatic nd metformin associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney.
linical recommendations based upon the patient's renal function include.
Before initiating Gemer Sita IR, obtain an estimated glomerular filtration rate (eGFR).
Gemer Sita IR is contraindicated in patients with an eGFR below 30 mL/min/1.73 m ² .
Gemer Sita IR is not recommended in patients with an eGFR between 30 and less than 45 mL/min/1.73 m ² because these patients require a lower dosage sitagliptin than what is available in the fixed combination Gemer Sita IR.
Obtain an eGFR at least annually in all patients taking Gemer Sita IR. In patients at increased risk for the development of renal impairment (e.g., the elderly), ren function should be assessed more frequently.
incenterations he concentrant use of Gener Sita IR with specific drugs may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result grightcant hemodynamic change, interfere with acid-base balance or increase metformin accumulation. Therefore, consider more frequent monitoring of patients.
ge 55 or Greater he risk of melformin-associated lactic acidosis increases with the patient's age bacause elderly patients have a greater likelihood of having hepatic, renal, or cardi patients in younger patients. Assess renaf function more frequently in elderly patients.
<u>iadiological Studies with Contrast</u> diministration of intravascular ionizate contrast agents in metformin-treated patients has led to an acute decrease in renal function and the occurrence of lac disclos. Stop Gemer Stat R at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m ² , alterits with history of hepatic impairment, alcoholism, or heart failure, or in patients with ble administered intra-arterial iodinated contrast. Re-evaluate eGFR cours after the imaging procedure, and restal Gemer Stat R if renal function is table.
urgery and Other Procedures Withholding of food and fluids during surgical or other procedures may increase the risk for volume depletion, hypotension and renal impairment. Gemer Sita houd be temporarily discontinued while patients have restricted flood and fluid intake.
<u>ivpoxe States</u> everal of the postmarketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompani by poperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have bee ssociated with lactic acidosis and may also cause prerenal azotemia. When such events occur, discontinue Gemer Sita IR .
zcessive Alcohol intake licohol potentiates the effect of metformin on lactate metabolism and this may increase the risk of metformin-associated lactic acidosis. Warn patients again nossive alcoholinitate while neckiving Gemer Sta.R.
tepatic Impairment atients with hepatic impairment have developed with cases of metformin-associated lactic acidosis. This may be due to impaired lactate clearance resulting in high

Pancreatitis

There have been postmarkeiing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or neorolizing pancreatitis, in patients taking fixed dose combination (FCC) of stagiliptin and metiromin hydrochichide. After intilation of Geners Stat IR, a patients should be observed carefully for signa and symptoms of pancreatitis, if pancreatitis is suspected, Gener Sita IR, should promptly be discontinued and appropriate management should be initiated. It is unknown whether

Year/Failure An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class. These trials evaluated patients with hpe 2 diabetes mellitus and atherosolencic cardiovascular disease. Consider therrisks an exercised of Gener Stall. R proto inhibiting treatment in patients at risk for heart failure, such as these with a prior history of heart failure and as the impairment, and observe these patients for signs and symptoms of heart failure during therapy. Achies patients of the characteristic symptoms of heart failure and as the interfaced mean failure and as the interfaced mean failure and as the interfaced mean failure and the interfaced mean failure and the interfaced means the interfaced mean failure and the interfaced mean failure and the interfaced mean failure and the interfaced means the

nal function, including acute renal failure, sometimes requiring dialysis. Before initiation of therapy with ion should be assessed. In patients in whom development of renal dysfunction is anticipated, particularly in frequently and **Gemer Sita IR** (siscontinued if evidence of renal impairment is present. **Gemer Sita IR** is

Vitamib_Leticiency in controlled clinications of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B_u levels was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_u absorption from the B_u-intrinsic factor complex, may be associated with anemia to tappears to be radiofly versoible with discontinuation of metformin or vitamin B_u, suprementation. Certain individuals fibres with inadequate vitamin B_u, craciaum intake or absorption) appear to be predisposed to developing subnormal vitamin B_u, levels. Measure hematologic parameters on an annual basis and vitamin B_u measurements al² to 3-year interval in addents on Gemer Staft Raft and manage and boromalies.

Hypoglycania with Concomitant Use with Insulin crimsulin Secretagogues Genere Stat R: may increase the risk of hypoglycenia when combined with insulin and/or an insulin secretagogue (e.g., sulfonylurea). A lower dose of insulin o main insecretagogue may be required to minimize the risk of hypoglycenia when used in combination with Genere Stat R.

actions include anaphylaxis, angloedema, and extollative skin conditions in patients treated with sitaglplin, one of the components of **Gemer Sita IR**. These nactions include anaphylaxis, angloedema, and extollative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 onthis state initiation of treatment with sitagliptin, with some reports occurring after the first does. scontinue Gemer Sita IR, assess for other potential cau

Angioedema has also been reported with other DPP-4 inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with Gemer Sita IR.

were and Disabiling Arthraigia me have been postmarkeling reports of severe and disabiling arthraigia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of ug therapy varied from one duy to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a currence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP4 inhibitors as prosible cause for severe joint pain and

Sultous Pempingia/ Sommarkeling cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of Usiters or encisions while serving Generg Staff, It Judius pemphigoid is supercharge. Generg Staff are Nould be discontinuated and reterral to a dematologist should be considered for serving Generg Staff, It Judius pemphigoid is supercharge. Generg Staff are Nould be discontinuated and reterral to a dematologist should be considered for

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

t be educated to recognize and manage hypoglycaenia. Use caution when initiating and increasing glimepiride doses in patients who may be o hypoglycaemia (e.g., the elderly, patients with renal impairment, patients on other antidiabetic medications). Debilitated or maincurished patients, and Early warning symptoms of hypoglycaemiamay 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 hypoglycaemiabefore the patients aware of the hypoglycaemia.

sensitivity reactions have been postmarketing reports of hypersensitivity reactions in patients treated with glimepiride, including serious reactions such as anaphylaxis, dema, and Stevens-Johnson Syndrome. If a hypersensitivity reaction is suspected, promptly discontinue Gemer Sita IR, assess for other potential causes for

foryfureas can cause hemolytic anemia in patients with glucose 6- phosphate dehydrogenase (G6PD) deficiency. Because glimepiride is a suffonyfurea, use titor in patients with G4PD deficiency and consider the use of a non-sulfonyfurea alternative. There are also postmarketing reports of hemolytic anemia in patients which glimenification deficiency and CBD deficiency.

and Risk of Cardiovascular Mortality with Sulfory/ureas and Risk of Cardiovascular Mortality with Sulfory/ureas diministration of card hypoglycaemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with det alone of plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term, prospective clinical trial designed aluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study aluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study

patients treated for 5 to 8 years with did plus a fixed does of biolutionfield, 1.5 grams per day) had a rate of cardiovascular montality approxim of a patients treated for 5 to 8 years with did plus a fixed does of biolutionfield or the normal montality approximate the and for the treated the fixed the and for the treated the fixed the and the and the and the fixed the and the and the fixed the and the and the and the fixed the and the

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoin ann/u to other oral hyponylurearphic 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 conc

topics anhythese inhibitors frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of se drugs with FDC of sitagliptin and metformin hydrochloride may increase the risk for lactic acidosis. Consider more frequent monitoring of these patients.

Examples: Topiramate, zonisamide, acetazolamide or dichlorphenamide.

Drugs that Reduce Metformin Clearance Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (e.g., organic cationic transporte (2071 // multidue) and toxin extrusion (MATE) inhibitors) could increase systemic exposure to metformin and may increase the risk for factic acidosis.

onsider the benefits and risks of concomitant use with FDC of sitagliptin and metformin hydrochloride. Examples: Ranolazine, vandetanib, dolutegravir, and cimetidine.

Alcohol Alcohol is known to potentiate the effect of metformin on lactate metabolism.

Warn patients against alcohol intake while receiving FDC of sitagliptin and metformin hydrochloride.

Insulin Secretagogues or Insulin Coadministration of FDC of sitagliptin and metformin hydrochloride with an insulin secretagogue (e.g., sulfonylurea)

Patients receiving an insulin secretagogue or insulin may require lower doses of the insulin secretagogue or insulin.

Drugs Affecting Glycemic Control Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control.

When such drugs are administered to a patient receiving FDC of sitagliptin and metformin hydrochloride, observe the patient closely for loss of blood glucose cont When such drugs are withdrawn from a patient receiving FDC of sitagliptin and metformin hydrochloride, observe the patient closely for hydrochloride.

Examples: Thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathornimetics, calcium-channel blockes, and isoniazid.

e following are examples of medications that may increase the glucose-lowering effect of sulfonytureas including glimepiride, increasing the susceptibility to and/or snelly of hypodycaemia: cortal anti-diabetic medications, praminitide acetate, insulin, anglotensin converting enzyme (ACE) inhibitors, th, receptor antagonists rates, proposytheme, pertoxifyline, comatostatin analogis, anabolis storiols and androgens, colydonpshamide, pheryarmidol, guanethidine, fuconazole diffugrizzone, tetracyclines, clarithromycin, disopramilos, quinolosses, and those drugs that are highly protein-bound, such as flucosazole, nonsterioidal and alimantory drugs, salcylulas, sulfarentiase, chicamptenicol, couranters, probenedid and monamine oddase inhibitors. When these medications are iministered to a patient receiving glimepinde, monitor the patient closely for hypoglycaemia. When these medications are withdrawn from a patient receiving mepide, monitor the patient Cosely for verseming glycaemic control.

er following are examples of nedicatore that may reduce the glucose-lowering effect of sufornytuness including glimepiride, leading to exercise gruph of the second second

Beta-blockers, clonidine, and reserpine may lead to either potentiation or weakening of glimepiride's glucose-lowering effect.

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

between oral miconazole and sulfonylureas leading to severe hypoglycaemia has been reported. Whether this interaction also occurs with 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 decreased plasma concentrations of glimepiride which may lead to hypoplycaemia. Rifampin may induce the metabolism of alimepiride, causing decreased plasma concentrations of glimepiride which may lead to worsening glycaemic control.

Concomitant Administration of Colesevelam Colesevelam can reduce the maximum plasma concentration and total exposure of glimepiride when the two are coadministered. However, absorptic when glimepiride as administered 4 hours prior to colesevelam. Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.

4.6. Use in special populations

8. Use the processing of th

Clinical Considerations Diseases-Associated Maternal and/or Entryoy/Fetal Risk Poorly controlled databetes in pregnancy increases the maternal risk for diabetic kebacidosis, preeclampsia, spontaneous abortions, preterm delivery manufacture. Work/orontrivited industrias increases the letal risk for major birth defects, still birth, and macrosoma related motiodly. Lata modula Dublished data from post-marketing studies do not report a clear association with metformin and major brith defocts, miccarriage, or adverse maternal or fetal outcomes when metformin is used during pregnancy. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including mail samples zero and incompation transparator groups.

Animal data Sitagliptin and Metformin No animal reproduction studies were conducted with the coadministration of sitagliptin and metformin.

Stagligin in entrop-teld development studies, stagliptin administered to pregnant rats and rabbits during organogenesis (gestation day 6 to 20) did not adversely affect developmental outcomes at oral doses up to 250 mg/kg (30-times the 100 mg clinical dose) and 125 mg/kg (20-times the 100 mg clinical dose), respectively, based on the statement of the mathematic and statement of t

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 caused no functional or behavioral toxicity in offsprino of rats at doses up to 1000 mm/km

ntal effects when administered to pregnant Sprague Dawley rats and rabbits up to 600 mg/kg/day during the period (of about 2- and 6-times a 2000 mo clinical dose based on body surface area (mg/m²) for rats and rabbits, respectively.

Glimepiride Risk Summary Available data from a small number of published studies and postmarketing experience with glimepiride use in pregnancy over decades have not identified any drur associated risks for major brith defects, miscarnage, or adverse maternal outcomes. However, sulforyturness (including djimepide) cross the placenta and have been associated with montal adverse reactions such as hypolycitamic. Therefore, gjimepide isolated be discontinued at least two veets before respected diffuse following administration of glimepinde to pregnant rats and rabbits at oral doses approximately 4000 times the maximum human dose based on be winfano area, respectively. However, fetoloxicity was observed in rats and rabbits at doses 50 times and 0.1 times the maximum human dose, respectively.

The estimated background risk of major birth defects is 6% to 10% in women with pregestational diabetes with a HbA1c >7% and has been reported to be as high as 20% to 25% in women with a HbA1c >10%. The estimated background risk of miscarriane for the indicated non-utation is unknown.

<u>linical Consistentions</u> Issama-associated maternal and/or embryo-fetal risk boohy controlled diabetes in programcy increases the tetal risk for diabetic ketoacidosis, preedampsia, spontaneous abortions, preterm delivery, and delivery mominications. Pownor controller diabetes increases the tetal risk for major birth defects, still birth, and macrosomia related motifulty.

teornal or treast teorem with gestational diabetes who are treated with sulforylureas during pregnancy may be at increased risk for neonatal intensive care admission ay develop respiratory distress, hypoglycemia, birth injury, and be large for gestational age. Prolonged severe hypoglycemia, alsing 4-10 days, has been and the large of the large of the large of the large of the large for gestational age. The large of a data of the large for gestation and the large for advisor with the large of data of the large for gestation and the large for advisor with the large of data of the large for gestation and the large for gestation and the large for advisor with the

r postpartum period access is nearnates harn to mothers receiving a sulfonylurea at the time of delivery, glimepiride should be d

nano usua a raimai studies, there was no increase in congenital anomalies, but an increase in fetal deaths occurred in rats and rabbits at glimepiride doses 50 times (rats) and 1. filmes (rabbits) the maximum recommended human dose (based on body surface area). This fetotoxicity was observed only at doses inducing maternal novolvevina and a this human that increase tradies do the submanification of glimetring, as tas been similary noted with other submoving vitaes.

etformin Hydrochloride

<u>4</u>
Comation regarding the presence of FDC of situal pipin and metformin hydrochloride in human milk, the effects on the breastfed infant, or the effects
on, Limited published studies report that metformin is present in human milk [see Data]. There are no reports of adverse effects on retermine terroristic infant
in terroristic infantion on the effects of metformin on milk production. Stagliphin is present in human
1a]. The developmental and health benefits of metformin on milk production. Stagliphin is present in hum
1a]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FDC is disaplicit.

nical lactation studies report that metformin is present in human milk, which resulted in infant doses approximately 0.11% to 1% of the maternal weight-age and a milk/plasma ratio ranging between 0.13 and 1. However, the studies were not designed to definitely establish the risk of use of metformin on because of ensultamente eize and limited adverse exercited rate of the risk of the studies of the risk of the results of the risk of the results of the risk o

reasses mans or actaining women using gimepinoe should be monitored for symptoins of hypoglycenia. It is not known whether gimepinois is excreted in hu with and there are not data on the effects of gimepinoe on mit sprouticins. Gimepinois is present in ratin. The developmential and health benefits of breastlee hould be considered along with the mother's clinical need for gimepinoe and any potential adverse effects on the breastled child from gimepinoe or from norkinon matternal contition.

Clinical Considerations Monitoring for adverse react

emia (e.g., iitters, cvanosis, apnea, hypothermia, excessive sleepiness, poor feeding, seizures)

ring prenatal and postnatal studies in rats, significant concentrations of glimepiride were present in breast milk and the serum of the pups. Offspring of rats exposed high levels of glimepiride during pregnarcy and lactation developed skeletal deformities consisting of shortering, thickening, and bending of the humerus during postnatal perior). These skeletal deformations were determined to be the result of rusing form onthers excosed to glimepiride.

Paediatric patients: EDC of sitaglightin pho limepiride tablets is not recommended in paediatric patients.

In general, loss selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Renal function should be assessed more for example in the enterpretent of the enterpreten

ore likely to have renal impairment. In addition, hypoglycemia may be difficult to recognize in of glimepiride in this nation population Glimepiride is substantially excreted by the the elderly. Use caution when initiating glim

Assess renal function prior to initiation of FDC of sitagliptin phosphate, metformin hydrochioride and glimeprinde tablets and periodically thereafter. FDC of sitagliptin phosphate, metformin hydrochioride and glimeprinde tablets is contraindicated in patients with an estimated glomerular filtration rate (eGFR) below 30 nmL/min/1.37 n: FDC of sitagliptin phosphate, metformin hydrochioride and glimeprinde tablets is not recommended in patients with an eGFR between 30 and less than 45

4.7. Effects on ability to drive and use machines There is 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

All sulfonylureas, including glimepiride, can cause severe hypoglycaemia. The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. These impairments may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

 Undesirable effects Sitagliptin Phospha Lactic acidosis Pancreatitis Heart failure Acute renal failure Vitamin B₁₀ deficiency Hypoglycemia with con-Hypersensitivity reaction Severe and disabling art Bullous emerphicid

Sitagliptin and Metformin Coadministration in Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise Table 1 summarizes the most common (> 5% of patients) adverse reactions reported (regardless of investigator assessment of causality) in a 24-week placeb controller factoria turbul nublich statisticin and metformin were controllingter of handlens twith hone 2 diabetes in adenuately controlled on diet and exercise

Patients with Type 2 Diabetes Inadequately Controlled on Diet and Exercise: tor Assessment of Causality) in ≥ 5% of Patients Receiving Combination Therap Number of Patiente (%)

	Placebo	Sitagliptin 100 mg once daily	Metformin HCI 500 mg/ Metformin HCI 1000 mg twice daily†	Sitagliptin 50 mg twice daily + Metformin HCI 500 mg/ Metformin HCI 1000 mg twice daily†	
	N = 176	N = 179	N = 364†	N = 372†	
Diarrhea	7 (4.0)	5 (2.8)	28 (7.7)	28 (7.5)	
Upper Respiratory Tract Infection	9 (5.1)	8 (4.5)	19 (5.2)	23 (6.2)	
Headache	5 (2.8)	2 (1.1)	14 (3.8)	22 (5.9)	

Staglight Add-on Therapy in Patients with Type 2 Diabetes Inadequately Controlled on Metformin Alone In a 24-week placebo-controlled viai of a biolightin 10 mg and ministered once daily added to a twice daily metformin regimen, there were no adverse reactions reported regardless of Investigator assessment of causality in 25% of patients and more commonly than in patients yeen placebo. Discontinuation of therapy due to clinical adverse reactions was similar to the placebo traditmetry roup (slagitplan tan metformin, 15%). Eacebo and metforming, 25%). inal adverse experiences in patients treated with sitagliptin and metformin were similar to those reported for patients

Gastrointestinal Adverse Reactions The incidences of pre-selected gastrointest

Black

GemerSita IR 50+500/1000+1/2 mg Tab - PI (Front/Back) Size: 300 x 400 mm Folding Size: 30 w x 200 mm Market: INDIA-Pharma SPIL/PKGDEV: AA04/Oct/2023-V01, AA05/Oct/2023-V02

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MOC: 30 GSM Bible Paper

				Number of Pat	ients (%)			
	Study of Sitag	Study of Sitagliptin and Metformin in Patients Inadequately Controlled on Diet and Exercise				Study of Sitagliptin Add-on in Patients Inadequately Controlle on Metformin Alone		
	Placebo	Sitagliptin 100 mg once daily	Metformin HCI 500 mg/ Metformin HCI 1000 mg twice daily*	Sitagliptin Metform Metformin	50 mg twice daily + nin HCI 500 mg/ HCI 1000 mg twice daily*	Placebo and Metformin HCl = 1500 mg daily	Sitagliptin 100 mg once daily and Metformin HCI = 1500 mg daily	
	N = 176	N = 179	N = 364		N = 372	N = 237	N = 464	
Narrhea	7 (4.0)	5 (2.8)	28 (7.7)		28 (7.5)	6 (2.5)	11 (2.4)	
lausea	2 (1.1)	2 (1.1)	20 (5.5)		18 (4.8)	2 (0.8)	6 (1.3)	
omiting	1 (0.6)	0 (0.0)	2 (0.5)		8 (2.2)	2 (0.8)	5 (1.1)	
bdominal Pain†	4 (2.3)	6 (3.4)	14 (3.8)		11 (3.0)	9 (3.8)	10 (2.2)	

for Was in Ocupee in the array of the second secon bination with Metformin and Rosigilitazone trolled study of sitagliptin 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on metformin and rosigilitazon I: jacaebo, N=37), the adverse reactions reported regardless of investigator assessment of causatily throuch Week 18 in ≿ 5%, nf natients transm

, N=161; placebo, N=97), the adverse reactions reported regardless of investigator assessment of causality through Week 16 in 25% of patients treated ptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (sitagliptin, 55%; placebo, 52%) and assopharyngita (sitagliptin, 55%; placebo, 52%) and assopharyngita work (sitagliptin, 55%; placebo, 52%) and set work (sitagliptin, 55%; placebo, 62%), nasopharyngita (110%; 93%), amen (38); 52%, placebo, 62%), nasopharyngita (110%; 93%), amen (38); 52%, placebo, face, 4440. ination with Metformin and Insulin abo-controlled study of staglight 100 mg as add-on therapy in patients with type 2 diabetes inadequately controlled on metformin and insulin nicerion NH2731 the only adverse reaction reported regardless of investigator assessment of causality in 25% of patients treated with sitaglight

Judies (N=5) adverse reactions of hypodycemia were based on all reports of symptomatic hypodycemia, a concurrent glucose measurement size output of the symptomatic hypodycemia were accompanied by a blod glucose measurement size of modifications of sitagiptin and as coatministered with a sulforyturea or with insulin, the percentage of patients reporting at least one adverse reaction of hypodycemia was higher than a sub-insulin at the sub-insulina and sitagiptin and a sub-insulina and sitagiptin and a sub-insulina and sitagiptin and sub-insulina and sitagiptin and sub-insulina and sitagiptin and sub-insulina and sub-insulina and sitagiptin and sub-insulina and sub-insulina and sitagiptin and sub-insulina and sitagiptin and sub-insulina and sitagiptin and sub-insulina and s

idence and Rate of Hypoglycemia* (Regardle tion with Metformin Coadministered with Gli	ess of Investigator Assessment of Causality) in Place mepiride or Insulin	bo-Controlled Clinical Studies of Sitagliptir
n to Glimepiride + Metformin (24 weeks)	Sitagliptin 100 mg + Metformin + Glimepiride	Placebo + Metformin + Glimepiride
	N = 116	N = 113
Overall (%)	19 (16.4)	1 (0.9)
Rate (episodes/patient-year)†	0.82	0.02
Severe (%)‡	0 (0.0)	0 (0.0)
-On to Insulin + Metformin (24 weeks)	Sitagliptin 100 mg + Metformin + Insulin	Placebo + Metformin + Insulin
	N = 229	N = 233
Overall (%)	35 (15.3)	19 (8.2)
Rate (episodes/patient-year)†	0.98	0.61
Severe (%)‡	1 (0.4)	1 (0.4)

ts (i.e., a single patient may have had multiple events).

Table 3: In in Combin Add-

tudies, a small increase in white blood cell count (approximately 200 cells/microL difference L) was observed due to a small increase in neutrophils. This change in laboratory paramet

ials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B_c levels, without clinica served in approximately 7% of nationals. Such decrease possibly due to interference with B_c absorption from the B_c intrinsic factor complex

reactions including anaphylaxis, angloedema, rash, urticaria, cutaneous vascuilitis, and exfoliative skin conditions including Stevens-Johaso respiratory tract infection; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatifis function, including acute renal faiture (sometimes requiring dialysis) and tubulointerstillar nephritis; severe and disabiling arthratiga) cut typation; vonting; metadade, myadiga can in extremity; back pain, prunturs, montul unceratoris, stantis; chotestatic: hemotalita. Internalitation and mixee

Glimepiride

inducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to other drug and may not reflect the rates observed in practice.

Adverse events occurred in ≥5% of glimepiride-treated patients and at a greater incidence than with placebo (glimepiride doses ranged from 1-16 mg administerer daily), other than hypoglycaemia, that were reported in 11 pooled placebo-controlled trials, whether or not considered to be possibly or probably related to study

le-blind, placebo-controlled monotherapy trial of 14 weeks duration, patients already on sulfonyturea therapy underwent a 3-week weaks mized to gimepinde 1 mg, 4 mg, 8 mg, or placebo. Patients randomized to gimepinde 4 mg or 8 mg underwent forced-titration from an initi nal doses, as tolerated. The overall incidence of possible hypoglycaemia (defined by the presence of at least one symptom that the investigat out of the overall incidence of possible hypoglycaemia (defined by the presence of at least one symptom that the investigat to hypoglycaemia; a concurrent glucose measurement wa or placebo. All of these events were self-treated.

le-blind, placebo-controlled monotherapy trial of 22 weeks duration, patients received a starting dose of either 1 mg glimepiride or placebo-piride was titrated to a target fasting plasma glucoso of 90-150 mg/dL. Final daily doses of glimepiride wen 1, 2, 3, 4, 6, or 3 mg teee Clinica mail incidence of cossible livocolxceama lis a defined aboro for 14 4-week trial for grimparide v. Raceto was 19, % v. 32, % Al Othes

Weight gain ke all sulfonvlureas, can cause weight gain

n clinical trials, allergic reactions, such as pruntus, erythema, urticaria, and morbillform or maculopapular eruptions, occurred in less than 1% o zatients. These may resolve despite continued treatment with glimepinide. There are postmarketing reports of more serious allergic reactions tension, shock).

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

Ig Experience: g adverse reactions have been identified during postapproval use of glimepiride. Because these reactions are re actions and the second second

tion (SIADH), most often in patients who are on other m

errence of the or on angelinit in rospitate, metorimiting are considered of simplified rates : Stagilging hypotrate, Metorimin Hydrocholoria and Gimepinite ablets (50 mg + 1000 mg + 1 mg) given twice daily (BID) (test) was assessed in administration of Metformin Hydrocholoride 500 mg (2 tablets given BID) and Gimepinide 2 mg tablets given BID (comparator) in patients of type 2

Of total 392 patients, 190 patients were randomized in FDC of Sitagliptin Phosphate, Metformin Hydrochloride and Glimepiride tablets (50 mg + 1000 mg + 1 mg) BID [Test 1] am, of which 181 patients completed the study; and 202 patients were randomized in Co-administration of Metformin Hydrochloride 500 mg (2 tablets BID) and Glimeniride tablets? mn (RID) (Comparation) am of the study; and 202 patients were randomized in Co-administration of Metformin Hydrochloride 500 mg (2 tablets BID) and Glimeniride tablets? mn (RID) (Comparation) am of the study; and an of the study and the study

ring the double blind treatment period, overall 67 TEAEs were reported in 55 (14.0%) patients out of 392 patients; of which 37 TEAEs were reported in 25 (13.2%) tisn's in FDC of Staglighin Phosphate, Metformin Hydrochloride and Gimperiota tablets (50 mg + 1000 mg + 1 mg) BD (Test 1); 38 TEAEs were reported in 30 1.9%) patients in Co-administration of Metformin Hydrochloride 500 mg (2 tablets BID) and Gimepride tablets 2 mg (BID) (Comparator), No SAEs, deaths or life-

ring the open label period, overall 8 TEAEs were reported in 8 (4.4%) patients out of 182 patients in FDC of Sitagliptin Phosphate, Metformin Hydrochloride and mepiride tablels (50 mg + 1000 mg + 1 mg) or (50 mg + 1000 mg + 2 mg) BID (Test 1 or Test 2). No SAEs, deaths or life-threatening TEAEs reported during the study

During the double bind treatment period, a total of 7 propalyasemia events were approximated by 4 (1%) palients, could which 3 (16%) palients (5 event) were from EPG of Staglight motionable. Mediornin Hydrocharkide and Gimenpinis tables (10 mg 10 00 mg + 11 mg 10 T feet 1) and (10 %) palient (2 event) were from administration of Mediornin Hydrocharkide study period.

turing the open label treatment period, 1 hypoglycaemia event was experienced by 1 (0.5%) patient in FDC of Sitagliptin Phosphate, Metformin Hydrochloride and slimepiride tablets (50 mg + 1000 mg + 1 mg) or (50 mg + 1000 mg + 2 mg) BID (Test 1 or Test 2). This event was of Level 1 and the patient did not require

tem Organ Class And Preferred Term – Double blin
 Table 4: I readment Emergent Adverse Events by System Organ Lisss And Preferero 1 erm – Double billind

 System Organ Class Preferred Term
 FDC of Stagglint Prevalents Methomic (90 mg + 100 mg + mg) (Test 1)
 Coastinitiation of Midromin Hydrochloride stabilits (00 mg + 100 mg + mg) (Test 1)
 Coastinitiation of Midromin Hydrochloride stabilits (M+202)
 Overall (N=392)

 Total TEAEs
 25 (13.2%)
 31
 30 (14.9%)
 36
 55 (140%)
 67

 Gastrointestinal disorders
 8 (4.2%)
 9
 20 (9.9%)
 22
 28 (7.1%)
 31

 Adominalgain upper
 1 (0.5%)
 1
 3 (16.9%)
 3
 4 (10%)
 4

 Constraintion
 0
 1 (0.5%)
 1
 1 (0.5%)
 1
 1 (0.5%)
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 1 (0.5%)

Consupation	0		1 (0.5%)	1	1 (0.3%)	1
Diarrhoea	3 (1.6%)	3	5 (2.5%)	6	8 (2.0%)	9
Gastritis	0		2 (1.0%)	2	2 (0.5%)	2
Nausea	0		6 (3.0%)	6	6 (1.5%)	6
Vomiting	4 (2.1%)	5	4 (2.0%)	4	8 (2.0%)	9
General disorders and administration site conditions	3 (1.6%)	3	5 (2.5%)	6	8 (2.0%)	9
Pyrexia	3 (1.6%)	3	5 (2.5%)	6	8 (2.0%)	9
Infections and infestations	1 (0.5%)	1	1 (0.5%)	1	2 (0.5%)	2
Nasopharyngitis	1 (0.5%)	1	1 (0.5%)	1	2 (0.5%)	2
Metabolismand nutritiondisorders	3 (1.6%)	5	1 (0.5%)	2	4 (1.0%)	7
Hypoglycaemia	3 (1.6%)	5	1 (0.5%)	2	4 (1.0%)	7
Musculoskeletaland connective tissue disorders	5 (2.6%)	5	1 (0.5%)	1	6 (1.5%)	6
Arthralgia	1 (0.5%)	1	0		1 (0.3%)	1
Back pain	0		1 (0.5%)	1	1 (0.3%)	1
Myalgia	4 (2.1%)	4	0		4 (1.0%)	4
Nervoussystem disorders	6 (3.2%)	6	3 (1.5%)	3	9 (2.3%)	9
Headache	6 (3.2%)	6	3 (1.5%)	3	9 (2.3%)	9
Respiratory, thoracic and mediastinal disorders	2 (1.1%)	2	1 (0.5%)	1	3 (0.8%)	3
Cough	1 (0.5%)	1	1 (0.5%)	1	2 (0.5%)	2
Phinamhoan	1 /0.6%)	1	0		1 (0.3%)	1

Adverse events are coded into system organ class and pretered term using medurov version 24.00 Percentages are computed using N provided in the Column header. BID: Twice daily; FDC: Fixed dose combination; n: Number of subjects; E: Number of Events.

System Organ Class Preferred Term	FDC of Sitagliptin Phosphate, Metformin Hydrochloride and Glimepiride tablets (Test 1 and T (N=182)			
	Subjects [n (%)]	Events (E)		
Total TEAEs	8 (4.4%)	8		
Gastrointestinal disorders	3 (1.6%)	1		
Abdominal pain upper	1 (0.5%)	1		
Diarrhoea	1 (0.5%)	1		
Vomiting	1 (0.5%)	1		
General disorders and administration site conditions	2 (1.1%)	2		
Pyrexia	2 (1.1%)	2		
Metabolism and nutrition disorders	1 (0.5%)	1		
Hypoglycaemia	1 (0.5%)	1		
Nervous system disorders	1 (0.5%)	1		
Headache	1 (0.5%)	1		
Respiratory, thoracic and mediastinal disorders	1 (0.5%)	1		
Rhinorrhoea	1 (0.5%)	1		

re computed using N provided in the Column header. se combination; n: Number of subjects; E: Number of Events.

In the event of overdose with FDC of stagliptin and metformin hydrochloride, contact the physician. In the event of an overdose, it is reasonable to employ supportive measures, a_a, remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapys included by the gasterist clinical status.

Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3-to 4-hour hemodialysis session. Prolonged hemodia may be considered if clinical yappropriate. It is not known if stagliptin is dialyzable by perinonal dialysis. Overdose of metformin has scouring clinical may also grants. Hypoteneina was reported in approximately (30 of cases, but no causia association with metformin has been established. I acidosis has been reported in approximately (32 of metformin overdose cases. Metformin is dialyzable with a clearance of up to 17 mL/min under acidosis has been reported in approximately (32 of metformin overdose cases. Metformin is dialyzable with a clearance of up to 17 mL/min under anonhumeric confliction. Therefore hemotiquies may be using the creament of acromatide dn with more analiset in whom metformin avaitable in sucreaded is unerotable.

Glimepiride An overdosade of glimepiride, as with other sulfonytureas, can produce severe hypoglycaemia. Mid episodes of hypoglycaemia can be treated with oral glucose Severe hypoglycaemic reactions constitute medical emergencies requiring immediate treatment. Severe hypoglycaemia with coma, seizure, or neurological mgairment can be treated with glucagon or intravenous glucose. Continued observation and additional carbohydrate intake may be necessary because wronkhavenia may reurrater enargent clinical enovery.

Pharmacological properties Sitagliptin Phosphate is a highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme. Metformin Hydrochloride is a biguanide. Glimepiride is a sulfonylurea

5.1. Mechanism of Action Sitagliptin Sitagliptin is a DPP-4 inhibitor, which is belie

The provide the set of the set of

emicagent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasm

Glimepiride Glimepiride privarily lowers blood glucose by stimulating the release of insulin from pancreatic beta cells. Sulfonytureas bind to the sulfonyturea noncontributer and indexes membrane leading to closure of the ATP-sensitive obtassium channel, thereby stimulating the release of insulin. Pharmacodynamic properties Sitagliptin

be 2 diabetes mellitus, administration of straightin led to inhibition of UPP-4 enzyme adtivity for a 24-hour period. After an oral glucose load of a meal, tion resulted in a 2- to 3-loid increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased if insulin release to glucose, resulting in higher C-peptide and insulin concentrations. The rise in insulin with the decrease in glucagon was

In studies with healthy subjects, situaliptin did not lower blood alucose or cause hypoglycemia.

Itagligible and Methomin Coadministration a bracky study by healthy subjects subjects assigning alone increased active GLP-1 concentrations; whereas methormin alone increased active and total GLP-1 oncentrations to similar extents. Coadministration of staglight and methormin had an addive effect on active GLP-1 concentrations; staglight, but not metformin, oncentrations to similar extents. Coadministration of staglight and methormin had an addive effect on active GLP-1 concentrations; staglight, but not metformin, the staglight active and the staglight and methods and the staglight active and the staglight active and the staglight active the staglight active ac

rdiac Electrophysiology a randomized, placebo-controlled crossover study, 79 healthy subjects were administered a single oral dose of sitagliptin 100 mg, sitagliptin 800 mg (8 times the a mmended dose, and placebo. At the recommended dose of 100 mg, there was no effect on the QTc interval obtained at the peak plasma concentration, or at any

In patients with type 2 diabetes mellitus administered sitegliptin 100 mg (N=61) or sitegliptin 200 mg (N=63) daily, there were no meaningful changes in QTc interval based on ECG data obtained at the time of expected peak plasma concentration.

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

ted natemologionin from baseline to the End of veek 15 (mil 1 Fogulation) FDC of Stagleght hospoptate, Meditormin (50 mg + 1060 mg + 1 mg) (Text 1) (50 mg + 1060 mg + 1 mg) (Text 1) (1 = 190) (1 = 190) (1 = 100)

VISITS	Statistic Summary	Actual	Baseline[4]	Actual	Baseline[4]	P value[3]
Visit 1 (Baseline)	n	190		202		
	Mean ± SD	9.18± 0.75		9.14± 0.74		
						0.5716
Week 12	n	187	187	199	199	
	Mean ± SD	8.01± 1.13	-1.18± 1.02	8.03± 1.07	-1.11±0.90	
	P-value[2]		<0.0001		<0.0001	0.5863
Week 16	n	187	187	198	198	
	Mean ± SD	7.39± 1.01	-1.79± 0.98	7.86± 0.97	-1.28± 0.89	
-	P-value[2]		<0.0001		<0.0001	<.0001
[1] BID: Twice daily; Cl	: Confidence interval; FDC:	Fixed dose combination; M	ax: Maximum; Min: Mini	imum; mITT: modified intent	ion to treat; N: Number	of patients; SD:

y copenies of rDL os stagaptuir rosphate, weitorium r/y or controle and stampuroe tawns : IFO Cof Staglingthe Dhosphate, Medinim Hydrocholde and Gimepirote tables (S0 mg + 1 mg) given twice da to Co-administration of Mediornin Hydrocholde 500 mg (2 bables given BID) and Gimepirote 2 mg tables given BID (con this treated with stable total adi) does d Gimepirote 4 mg & Mediornin Hydrocholde = 1500 mg for at least 10 weeks prio

(2) p-value: Paired test (3) p-value: MMRM model is used. The model indudes change in HbA1c as the depent baseline HbA1c as a covariate. Baseline p value is based on Two sample t test. (4) Change from baseline = Post dose values—Baseline values.

Table 7: Mean Change in HbA1 c (%) (Glycosylated Haemoglobin) from Baseline to the End of Week 28 (mITT Population)

FDC of Sitagliptin Phosphate, Metformin Hydrochonde and Glimepiride tablets (Test 1 and Test 2)
(N = 182)
Visits
Statistic Summary
Actual
Change from Baseline[3]

Visit 1 (Screening)	n	182	
	Mean ± SD	9.16± 0.74	
Visit 7 (Week 24)	n	182	182
	Mean ± SD	7.06± 1.01	-2.10± 0.99
	p-value [2]		<.0001
Visit 8 (Week 28)	n	181	181
	Mean ± SD	6.79± 1.03	-2.37± 1.04
	p-value [2]		<.0001
(4) IDID: Tuise della ED	O. Final data combination Ma	Manimum Min Minimum atTT: and different	anti-anti-taken to N. N. where for the starter CD. Observation Deviation

[1] Bit: Twice daily: PLO: Fixed does combination; Max: Maximum; Min: Minimum; mIT: modified intention to treat; N: Numberof patients; SD: S [2] paralaw: Mickicons signed rank: [2] paralaw: Mickons signed rank: [3] Change from baseline = Post dose values = Baseline values. Visit 1 (Screening) data is considered as baseline. The reduction of FBG and PPBG from baseline to end of Week 12 and Week 16 was comparable between test and comparator arm. The prop achieving HbA1 < 7.0% at Week 12 was comparable between two arms. The proportion of participants achieving HbA1 < 7.0% at Week 16 was in FDG of 3tagliptin Phosphate, Metformin Hydrochloride and Gimepride tablets (50 mg/1000 mg/1 mg). (Test 1) arma so comparad to the Metformin Hydrochloride 300 mg and Gimepride tablets 2 mg (comparator) am (rc9.0001). Note of the patients resulted rescue medications of Metformin Hydrochloride 300 mg and Gimepride tablets 2 mg (comparator) am (rc9.0001). Note of the patients resulted rescue medications of Metformin Hydrochloride 300 mg and Gimepride tablets 2 mg (comparator) am (rc9.0001). Note of the patients result of escalar the second comparation the Metformin Hydrochloride 300 mg and Gimepride tablets 2 mg (comparator) at mol (rc9.001). Note of the patients rescuired rescue medications of the second comparation and the second comparation tablets (rc9.001). Note of the patients rescuired rescue medications of the second comparation. The properties of patients achieved tablets (rc9.001). Note of the patients rescuired rescue medications of the second comparation and the second comparation tablets (rc9.001). Note tablets (rc9.001). Note the second comparation and the second comparation at the se

5.3. Pharmacokinetic properties Sitagliptin Phosphate and Metformin Hydrochloride

ten and and a second s

ation of a 100 mg dose to healthy subjects, sitagliptin was rapidly absorbed with peak plasma concentrations (median T___) occurring 1 to 4 hours Effect of Food

high-fat meal with sitagliptin had no effect on the pharmacokinetics of sitagliptin.

The absolute bioavailability of a metformin HCI 500 mg tablet given under fasting conditions is approximately 50-60%. Studies using single oral doses of metformin HCI tables 500 mg to 1,500 mg to 1,500 mg (approximately 1.3 times the maximum recommended data) dosage), indicate that there is a tack of dose supportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination.

Food decreases the extent of and slightly delays the absorption of metitormin, as shown by approximately a 40% lower mean peak plasma concentration (C....), a25% lower area under the plasma concentration evenus time curve (AUC), and a 35-minute protongation of time to peak plasma concentration (T....) following administration of a single 350mg table of metitormin (AUM) thod, compared to the same table tareing administration of a single 350mg table of metitormine of these

I distribution (V/F) of metformin following single oral doses of metformin HCI tablets 850 mg averaged 654 ± 358 L. Metformin is negligibly ns, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of

Elimination: Sitagliptin Approximate mg oral dose

ination of sitagliptin occurs primarily via renal excretion and involves active tubular secretion. Sitagliptin is a substrate for human organic anion transporter-3 AT-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 a substrate of occursoration (Pao), which may also be involved in efficient of and a substrate of occursoration (Pao), which may also be involved in mediation be renal elimination of sitagliptin However, cyclosporine a Pao inhibitor. dd not

Metformin Elimination of metformin occurs primarily via renal excretion. Renal dearance is approximately 3.5 times greater than creatinine dearance, which indicates tha tubular secretion is the major route of metformin elimination.

ately 2-fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal impairment with eGFR of 30 to less than 45 m², and an approximately 4-fold increase was observed in patients with severe renal impairment including patients with end-stage renal disease (ESRD) sis a command to normal hantity control subjects.

ents with Hepatic Impairment alight Phosphate and Metformin Hydrochloride cides characterizing the pharmaccknetics of sitagliptin and metformin after administration FDC of sitagliptin and metformin hydrochloride in patients with hepatir

uguur allents with moderate hepatic impairment (Child-Pugh score 7 to 9), mean AUC and C_{mp} of sitagliptin increased approximately 21% and 13%, respectively, npared to healthy matched controls following administration of a single 100-mg dose of sitagliptin. These differences are not considered to be clinically meaningful.

Wetrommin No pharmacokinetic studies of metformin have been conducted in patients with hepatic impairment Effects of Age. Body Mass Index (BMI), Gender, and Race

pulation pharmacokinetic analysis or a composite analysis of available pharmacokinetic data, BMI, gender, and race do not have a clinically meaningful harmacokinetics of sitagliptin. When the effects of age on renal function are taken into account, age alone did not have a clinically meaningful impacton kinetics of sitagliptin based on a population pharmacokinetic analysis. Elderly subjects (65 to 80 years) had approximately 19% higher plasma

Metformin Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and Cause increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is

Metformin pharmacokinetic parameters did not differ significantly between normal subjects and patients with type 2 diabetes mellitus when analyzed according to gender: Similarly, in controlled clinical studies in patients with type 2 diabetes mellitus, the antihyperglycemic effect of metformin was comparable in males and females.

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type diabates mellitus the antihunerrolycemic effect was comparable in Whites (n=240) Blacks (n=51) and Hispanics (n=24)

vaurusessemenu u urug underacions: tapijolini no tai na timbitori of CYP isozymes CVP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4. Stragliptini is a P-gp substrate but does t inhibit P-gp mediated transport of digoxin. Based on these results, stragliptin is considered unlikely to cause interactions with other drugs that utilize these Sitagliptin is not extensively bound to plasma proteins. Therefore, the propensity of sitagliptin to be involved in clinically meaningful drug by plasma protein binding displacement is very low

In vivo Assessment of Ling interactions: Effects of Staglighting of the other the other of the other Table 8: Effect of Sitagliptin on Systemic Exposure of Coadministered Drugs

Drug	Dose of Coadministered Drug*	Dose of Sitagliptin*	Geometric Mean Ratio (ratio with/without sitagliptin) No Effect = 1.00			
				AUC†	Cmax	
Digoxin	0.25 mg‡ once daily for 10 days	100 mg‡ once daily for 10 days	Digoxin	1.11§	1.18	
Glyburide	1.25 mg	200 mg‡ once daily for 6 days	Glyburide	1.09	1.01	
Simvastatin	20 mg	200 mg‡ once daily for 5 days	Simvastatin	0.85¶	0,80	
			Simvastatin Acid	1.12	1.06	
Rosiglitazone	4 mg	200 mg‡ once daily for 5 days	Rosiglitazone	0.98	0.99	
Warfarin	30 mg single dose on day 5	200 mg‡ once daily for 11 days	S(-) Warfarin	0.95	0.89	
			R(+) Warfarin	0.99	0.89	
Ethinyl estradiol and 2	21 days once daily of 35 µg ethinyl	200 mg‡ once daily for 21 days	Ethinyl estradiol	0.99	0.97	
norethindrone	estradiol with norethindrone 0.5 mg x 7 days, 0.75 mg x 7 days, 1.0 mg x 7 days		Norethindrone	1.03	0.98	
Metformin HCI '	1000 mg‡ twice daily for 14 days	50 mg‡ twice daily for 7 days	Metformin	1.02#	0.97	

Effects of Other Drugs on Sitagliptin

Table 9: Effect of Coadministered Drugs on Systemic Exposure of Sitagliptir

Coadministered Drug	Dose of Coadministered Drug*	Dose of Sitagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effe		Ratio drug) No Effect = 1.0			
				AUC†	Cmax			
Cyclosporine	600 mg once daily	100 mg once daily	Sitagliptin	1.29	1.68			
Metformin HCI	1000 mg‡ twice daily for 14 days	50 mg‡ twice daily for 7 days	Sitagliptin	1.02§	1.05			
*All doses administered as † AUC is reported as AUC ₀ ‡ Multiple dose.	Meteoremin HCL mounding twoice days for 1 k days ounget twice daily for 7 augs Straggiptin 1,028 1.05 Aldoesa administend at single does under softwarks specified. AUC is reported as AUC ₂ , unless otherwise specified.							

oouunnitotorou brug	bose of octaministered brug		No Effect = 1.00		
				AUC†	Cmax
Cimetidine	400 mg	850 mg	Cimetidine	0.95‡	1.01
Glyburide	5 mg	500 mg§	Glyburide	0.78¶	0.63
Furosemide	40 mg	850 mg	Furosemide	0.87¶	0.69
Nifedipine	10 mg	850 mg	Nifedipine	1,10‡	1,08
Propranolo	40 mg	850 mg	Propranolol	1.01‡	0.94
Ibuprofen	400 mg	850 mg	Ibuprofen	0.97#	1.01#

Cl extended-release tablets) 500 mg. netic means, p value of difference <0.0 netic means

Coadministered Drug	Dose of Coadministered Drug*	Dose of Metformin HCI*	Geometric Mean Ratio					
		()	(ratio with/without coadministered drug) No Effe					
				AUC†	Cmax			
Glyburide	5 mg	500 mg‡	Metformin‡	0.98§	0.99§			
Furosemide	40 mg	850 mg	Metformin	1.09§	1.22§			
Nifedipine	10 mg	850 mg	Metformin	1,16	1,21			
Propranolo	40 mg	850 mg	Metformin	0.90	0.94			
Ibuprofen	400 mg	850 mg	Metformin	1.05§	1.07§			
Drugs that are eliminated by renal tubular secretion may increase the accumulation of metformin.								
Cimetidine	400 mg	850 mg	Metformin	1.40	1.61			
Carbonic anhydrase inhi	ibitors may cause metabolic acid	osis.						
Topiramate	100 mg¶	500 mg¶	Metformin	1.25¶	1.17			

Ratio of arithmetic means.
 Steady state 100 mg Topiramate every 12 hr + metform²

Autor purch: Studies with single or al doses of glimepinde in healthy subjects and with multiple or al doses in patients with type 2 diabetes showed peak drug concentrations (C,,,) 2 to 3 hours postdose. When glimepinde was given with meals, the mean C,,,and AUC (area under the curve) were decreased by 8% and 9%, respectively. not accumulate in serum following multiple dosing. The pharmacokinetics of glimepiride does not differ between healthy subjects an earance of glimepiride after oral administration does not change over the 1 mg to 8 mg dose range, indicating linear pharmacokinetic: n healthy subjects, the intraindividual and interindividual variabilities of glimepiride pharmacokinetic parameters were 15%-23% and 24%-29%, respectively,

variable. We have a set of the se

Metabolism: Comparison in monitority of the solution of the so

hen "C-gimppindewas given orally to 3 healthymale subjects, approximately60% of the total radioactivitywas recovered in the unien in 7 days. M1 and M2 acco 80%-90% of the radioactivityrecovered in the unien. The ratio of M1 to M2 in the unine was approximately32 in two subjects and 4:1 in one subject. Approximatel The total radioactivitywas recovered in feos. M1 and M2 accounted/or about 70% (ratio of M1 to M2 was 1:3) of the radioactivityrecovered in the uses. No parent durines in the total radioactivity was recovered in here. M1 and M2 accounted/or about 70% (ratio of M1 to M2 was 1:3) of the radioactivityrecovered in the case. No parent durines in the total radioactivity was recovered in here and the case. No parent durines in the total radioactivity was recovered in here. M1 and M2 accounted/or about 70% (ratio of M1 to M2 was 1:3) of the radioactivity recovered in the case. No parent durines in the total radioactivity was recovered in here. M1 and M2 accounted/or about 70% (ratio of M1 to M2 was 1:3) of the radioactivity recovered in the case. No parent durines in the total radioactivity was recovered in here. M1 and M2 accounted/or about 70% (ratio of M1 to M2 was 1:3) of the radioactivity recovered in the case. No parent durines in the total radioactivity was recovered in here in the case. No parent durine was approximately for the radioactivity was recovered in the case. No parent durine was approximately for the radioactivity was recovered in the case. No parent durine was approximately for the radioactivity was recovered in the case. No parent durine was approximately for the radioactivity was recovered in the case. No parent durine was approximately for the radioactivity was recovered in the case. No parent durine was approximately for the radioactivity was recovered in the case. No parent durine was approximately for the radioactivity was recovered in the case. No parent durine was approximately for the radioactivity for the radioactivity was recovered in the case. No parent durine was approximately

g gimepride pharmacokinetics in patients with type 2 diabetes ≤65 years and those >65 years was evaluated in r laily. There were no significant differences in gimepride pharmacokinetics between the two age groups. The mean AUC zomately 13% lower than that or the younger patients; the mean weight-adjusted clearance for the older patients was unger patients.

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 abetes, the reduction in HbA1C was comparable in Caucasians (n=536), blacks (n=63), and Hispanics (n=63).

imparment single-dose, open-label study, glimepiride 3 mg was administered to patients with mild, moderate and severe renal impairment as estimated by creatinine race (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 0,08,2023 up III consisted of 7 patients with severe renal impairment (CLcr - 20 mL/min). Although glimepiride semm concentration (CLCr - 20 mL/min). Although glimepiride and ALC for ML and an S-fold higher man ALC for ML compared to corresponding at half-life (T_m) for glimepiride did not change, while the half-lives for ML and M2 increased as renal function decreased arentage of loss decreased from 44.4% for Group II or 21% for Group II and 93% for Group III.

sight group, the morbidly obese had lower — and AUC handhose in the section of upmopting in memoradiy obese patients were similar to base in the normal vs. sholly obese patients were S47 ± 21 kng/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 1300 hours ng/mL ss. 3280 hours ng/mL ss. Drug Interactions

usprim 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 if 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.

n and glimepiride resulted in reductions in glimepiride AUC₆₋ and C_{mar} of 18% and 8%, respectively. When glime there was no significant change in glimepiride AUC, ... or C_...... 6% and 3%, respectively.

In a randomized, open-label, 3-way crossover study, healthy subjects received either a single 4 mg dose of gimepiride alone, gimepiride with ranitidine (150 mg twic daily for 4 days; gimepiride was administered on Day 3), or gimepiride with crimetidine (800 mg daily for 4 days; gimepiride alone discussion of gimepiride and a moral descer dispersion discussion for dimension of gimepiride

Propanoiol In a randomized, double-blind, two-period, crossover study, healthy subjects were given either placebo or propranoiol 40 mg three times daily for a total treatment period of 5 days. On Day 4 of each study period, a single 2 mg does of gimepride was administered. The gimepride does were separated by a 14-day washout period. Concomitant administration of prograndio and gimepride significantly increased gimepride doe..., ALC, and T_SM, respectively, and TSM, respectively, and TSM, respectively, and TSM, respectively, and

Warfarian in an open-label, two-way, crossover study, healthy subjects received 4 mg of glimepride daily for 10 days. Single 25 mg doess of warfarin were administered 6 days before starting glimepride and on Day 4 of glimepride administration. The concomitant administration of glimepride din of alter the physica of R and 32 warfarin enationers. No changes were observed in warfarin plasma protein binding. Glimepride resulted in a statistically significant decrease in the pharmacodynamic response to warfarin. The reductions in mean area under the prothrombin time (PT) curve and maximum PT values during glimepride teatment were 3.3% and 39%, respectively, and are unlikely be clinically relevant.

Nonclinical properties

Animal Toxicology or Pharmacology Sitaglintin Phosphate and Metformin Sitagliptin Phosphate and Metformin Hydrochloride No animal studies have been conducted with the FDC of sitagliptin and metformin hydrochloride to evaluate carcinogenesis, mutagenesis o The following of data are based on the findings in studies with sitaglintin and metformin individually.

Stagligin A how-per carcinogenicity study was conducted in male and female rats given oral doses of stagliptin of 50, 150, and 500 mg/kg/day. There was an increases incidence of combined liver aderoma/carcinoma in males and females and of liver carcinoma in females at 500 mg/kg. This dose results in exosures approximately 60 times the human exposure at the maximum recommended daily adult human dose (MRHD) of 100 mg/kg, Data of AUC comparisons. Liver turnors were no observed at 150 mg/kg, approximately 20 times the human exosure at the MRHD. A two-year carcinogenicity study was conducted in male and female mice given and cases of staglingtin of 50, 152, 520, and 550 mg/kg/kg. There was no increases in the incidence of turnos in any organ up to 500 mg/kg, approximately 70 time human exosure at the MRHD. Stagliptin was not mutagenic or classogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a Chines humanser oravic (100) chromosome barenian assay, and mix vito colopencies assay in CHO, an in vitor at the patcher DAN alailone eutons many case and an in vitor observed at 500 mg/kg/garb.

In rat fortill's studies with not garage does of 126, 250, and 1000 mg/kg, makes were treated for 4 weeks prior to maling, during mating, us o scheduled terminate (approximate) & vestes total), and finante were treated a vesks prior to mating through pestation day. The odverse factor in fertility was observed at 125 mg/k (approximate) × 12 times tuman exposure at the MHED of 100 mg/kg based on AUC comparisons). Alt higher does, nondose-related increased resorptions i fermiels were observed (approximate) × 25 and 100 times tuman excousive at the MHED based on AUC comparison.

romosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative. Fertility of male or female rats w affected by metformin when administered at doses as high as 600 ma/ko/day, which is approximately three times the maximum recommended human daily do

Glimepiride Carcinogenesis, Mutagenesis, and Impairment of Fertility: Studies in rats at doses of up to 5000 parts per million (ppm) in complete feed (approximately 34 maximum recommended human dose, based on surface area) for 30 months showed no evidence of carcinogenesis. In mice, administration of glimep months resulted in an increase in benign pancreatic adenoma formation that was dose-related and was thoughit to be the re adenoma formation in mice was observed at a dose of 320 ppm in complete feed, or 46-54 mg/kg body weight/day This recommended dose of 8 mg once daily based on surface area.

Glimepiride was non-mutagenic in a battery of in vitro and in vivo mutagen synthesis, and mouse micronucleus test).

here was no effect of glimepiride on male mouse fertility in animals exposed up to 2500 mg/kg body weight (>1,500 times the mi ased on surface area). Glimepiride had no effect on the fertility of male and female rats administered up to 4000 mg/kg body weight surface area).

Description
The chemical name of sitagliptin phosphate monohydrate is 7-{(37)-3-amino-1-xxx-4-{2,4,5- trifluorophenylbutyl-5,6,7.8-tetrahydro-3-{trifluoromethyl-1,2,4-triazolo(4,3-a)gyrazine phosphate (1:1) monohydrate, metformin hydrochoirde is N.V-dimethylmindoicarbonimic diamide hydrochloride and gimepride is 1-{[]-{2-(3) trifl-4-methyl-2-os-3-oyroriline 1-clanomid) ethylthensibilitolin/3-{trifluor-4-methydrochoirde xu/ruea.

8. Pharmaceutical particulars

8.1. Incompatibilities None known

- 8.2. Shelf-life Refer product label for expiry date. Do not use after expiry date.
- Packaging information Gener Sita IR 50/500/1, Gener Sita IR 50/500/2, Gener Sita IR 50/1000/1 and Gener Sita IR 50/1000/2 is av/

8.4. Storage and handling instructions Store at temperature not exceeding 25°C. K

atient Counselling Information itagliptin Phosphate and Metformin Hydrochloride

LadicAcidosis Explain the risks of lactic acidosis, its symptoms, and conditions that predispose to its development. Advise patients to discontinue promptly notify their physician if unexplained hyperventilation, myalgias, malaise, unusual somnolence or other nonspecific symptic excessive alcohol intake and inform patients about the importance of regular testing of renal function while receiving **Gener Strat** R. T. In the hyperventilation **Comer Strat** R. Toroit on any uncide or relational adjoication produces, as elemporary discontinuation may be required. excessive alcohol intake and inform patients about the i that they are taking **Gemer Sita IR** prior to any surgical

Parcenation inform patients that acute pancmatitis has been reported during postmarketing use of FDC of stagliptin and metformin hydrochloride. Inform patients that persistent severe abdommal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hailmark symptom of acute pancreatilis. Instruct patients to promptly discontinue Genera Stat B, and contact their physical in flemistant severe abdominal pain occurs.

Hearf-Balure Inform patients of the signs and symptoms of heart failure. Before initiating Gemer Sita IR, ask patients about a history of heart failure or other risk factors for heart failure including moderate to severe menal impairment. Instruct patients to contact their physician as soon as possible if they experience symptoms of heart failure, including moderate to severe menal impairment. Instruct patients to contact their physician as soon as possible if they experience symptoms of heart failure, including moderate to severe menal impairment. Instruct patients to contact their physician as soon as possible if they experience symptoms of heart failure, including moderate the severe menal impairment instruct patients of the information of t Vitamin B, Deficiency

reactions (including r Sita IR and seek me

Bullous Pemphigoid

Details of manufacturer sun pharma laboratories ltd.
 Vill: Kokihar, Mirza Palashbari Road, P.O.: Palashbari, Dist: Kamrup, Assam-781128

11. Details of permission or licence number with date Mfg. Lic. No.: 374/DR/Mfg/2013 dated 01.07.2013

. References 1. Adulticenter, Randomized, Comparative, Active-Controlled, Double-Blind, Double-Dummy, Phase 3 Study to Assess Efficacy and Safety of Fixed Dose Combination of Stagliptin Phosphate, Metformin Hydrochloride and Glimepride Tablets in Comparison to Co-administration of Metformin Hydrochloride and Glimepride Tablets in Patients with Twe 2 Diselbers Metitus, Protocol No. ICR/21004, Inclinat study report lated 3⁻¹ July 2023, Son Pharma Laboratories Labora





