BIOS LAB PRIVATE LIMITED

Certificate of Analysis -COA

QUALITY CONTROL	CERTIFICATE OF ANALYSIS FINISHED PRODUCT	Format No:F/QCGN/022/08

PRODUCT NAME	**: DIEXOMET-G2**		
B.No.	**: D112301E**	**A.R.No.**	**: FPD/210623/03**
B. SIZE	**: 1.0 L**	**MFG. DATE**	**: May-2023**
SAMPLE QTY	**: 100 Tablets**	**EXP. DATE**	**: Apr-20245**
Analysis started on	**: 17.06.2023**	**Date of completion:**	**: 21.06.2023**

S.No	TEST	RESULTS	LIMITS
01.	**Appearance**	Yellow Coloured oval shaped film coated tablets plain on both sides.	Yellow Coloured oval shaped film coated tablets plain on both sides.
02.	**Identification** **By HPLC**	Complies	The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the standard peak in the chromatogram of the standard preparation, as obtained in the assay.
03.	**Average weight**	679.85 mg	696.00 mg ± 5.0 % (661.20 mg to 730.80 mg)
04.	**Uniformity of weight**	+2.23 % to -1.45 %	Individual weight of tablet does not deviate by more than ± 5.0 % from the average weight.
05.	**Dimensions:** Thickness	7.25 mm	7.00 mm to 7.40 mm
06.	**Hardness**	12.46 kg	NLT 4.0 kg
07.	**Dissolution** For Metformin HClby UV I hour III hour X hour For Glimepiride by HPLC	 31.32 % to 38.90 % 63.63 % to 70.63 % 93.98 % to 101.54 % 94.52 % to 101.24 %	 25.0 % to 50.0 % 45.0 % to 75.0 % NLT 85.0 % NLT 75.0 %
08.	**Uniformity of content** For Glimepiride by HPLC	97.03 % to 106.80 %	85.0 % to 115.0 % of the average content.

Analysed by: J.Boyl
Date: 21/06/2023

Checked by:
Date : 21/06/2023

Approved By:
Date: 21/06/2023

Product Mfg . By : SAI PRIMUS LIFE BIOTECH PVT. LTD.

BIOS LAB PRIVATE LIMITED

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09.	**Assay** **Each filmcoated prolonged release bilayered tablet contains:**		
	Glimepiride IP	2.01 mg (100.50 %)	1.80 mg to 2.20 mg (90.0% to 110.0 %)
	Metformin Hydrochloride IP (As Prolonged Release Form)	495.97 mg (99.19 %)	450.0 mg to 550.0 mg (90.0% to 110.0 %)

REMARKS: THE SAMPLE COMPLIES AS PER IP SPECIFICATION.

Analysed by: J.Lay
Date: 21/06/2023

Checked by:
Date : 21/06/2023

Approved By:
Date: 21/06/2023

Product Mfg . By : SAI PRIMUS LIFE BIOTECH PVT. LTD.

BIOS LAB PVT. LTD.

B-8, MILAN COMPLEX, SARKHEJ, AHMEDABAD.

QUALITY CONTROL DEPARTMENT

CERTIFICATE OF ANALYSIS

See Rule 150 E (F) Under The Drugs & Cosmetic Act 1940 and The Rules there under

Report No. : **DT7101A** **Mfg. No.: MNB/06/483**

Sample Name : **DIEXOMET™-G2 TABLETS**

Generic Name : **Glimepiride 2 mg + Metformin HCl PR 500 mg tablets**

Product Name	**DIEXOMET™-G2**	**A.R.No.**	QCFP/D/T/710A/21
Batch No.	DT7101A	**Batch Size**	.50 Lacs Tablets
Mfg. Date	DEC. 2022	**Sample Qty.**	60 Tablets
Exp. Date	NOV. 2024	**Test as per**	Manufacturer Specification
Date of Receipt	28-12-2021	**Date of Release**	30-12-2021

S NO.	TEST	SPECIFICATION	RESULT
1.	Description	Yellow colored, Oval Shaped, biconvex, film coated tablets plain on both sides	Yellow colored, Oval Shaped, biconvex, film coated tablets plain on both sides
2.	Identification	Positive for Metformin Hydrochloride and Glimepiride (by Assay).	Complies
3.	Average Weight	Average weight 635 mg ± 5.0% (Limit -603.3 mg to 666.8 mg)	633.7 mg
4.	Uniformity of Weight	Avg. wt. ± 5.0%	-2.08% to +2.44%
5.	Thickness	6.80 ± 0.2 mm	7.00 mm
6.	Dissolution		
	Metformin HCl Prolonged Release (500 mg) 1st Hour 3rd Hour 10th Hour	 25.0 % to 50.0% 45.0% to 75.0% NLT 80.0%	 35.5% 55.5% 94.6%
	Glimepiride 2 mg	NLT 75.0%	91.1%
7.	Content Uniformity Glimepiride 2 mg	NLT 85.0% & NMT 115.0%	96.1%
8.	ASSAY	Each film coated tablet contains	
	Metformin Hydrochloride IP 500 mg (Prolonged Release)	450.0 mg to 550.0 mg 90.0% to 110.0%	495.1 mg 99.1 %
	Glimepiride IP 2mg	1.8 mg to 2.2 mg 90.0% to 110.0%	2.010 mg 100.5 %

Conclusion: The above product compiles as per IP.

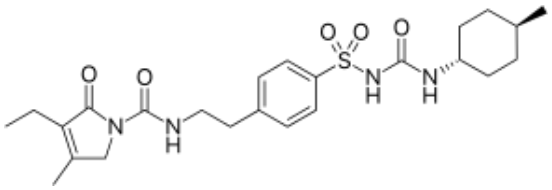
*** Manufactured by:** DAGON PHARMACEUTICALS PVT. LTD. (SOLAN, HP)

DIEXOMET™-G2 TABLETS

Each Tablet Contains
Glimepiride – 2 mg
Metformin HCl – 500 mg (Prolonged Release)

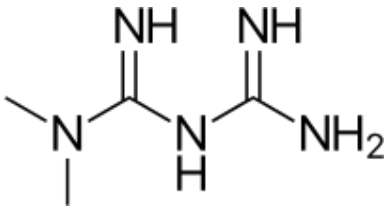
PHARMACEUTICAL DESCRIPTION

GLIMEPIRIDE:
Generic name: Glimepiride
Chemical name: 3-ethyl-4-methyl-2-oxo-N-(2-{4-[({[(1r,4r)-4- methylcyclohexyl]-Chydroxycarbonimidoyl}amino)sulfonyl]phenyl}ethyl)-2,5-dihydro-1H- pyrrole-1carboximidic acid
Molecular mass: 490.617 g/mol
Structural formula:



Empirical formula – $C_{24}H_{34}N_4O_5S$

METFORMIN:
Generic name: Metformin HCl
Chemical name: N, N-Dimethyl imidodi carbonimidic diamide
Molecular mass: 129.16364 g/mol **Structural formula:**



Empirical formula - $C_4H_{11}N_5$ **PHARMACOKINETIC PROPERTIES Glimepiride**

Absorption
The bioavailability of glimepiride after oral administration is complete. Food intake has no relevant influence on absorption, only absorption rate is slightly diminished. Maximum serum concentrations (Cmax) are reached approximately 2.5 hours after oral

intake (mean 0.3 μg/ml during multiple dosing of 4 mg daily) and there is a linear relationship between dose and both Cmax and AUC (area under the time/concentration curve).

Distribution

Glimepiride has a very low distribution volume (approx. 8.8 litres) which is roughly equal to the albumin distribution space, high protein binding (>99%), and a low clearance (approximately 48 ml/min). In animals, glimepiride is excreted in milk. Glimepiride is transferred to the placenta. Passage of the blood brain barrier is low.

Biotransformation and elimination

Mean dominant serum half-life, which is of relevance for the serum concentrations under multiple-dose conditions, is about 5 to 8 hours. After high doses, slightly longer half-lives were noted. After a single dose of radio labeled glimepiride, 58% of the radioactivity was recovered in the urine, and 35% in the faeces. No unchanged substance was detected in the urine. Two metabolites - most probably resulting from hepatic metabolism (major enzyme is CYP2C9) – were identified both in urine and faeces: the hydroxy derivative and the carboxy derivative. After oral administration of glimepiride, the terminal half-lives of these metabolites were 3 to 6 and 5 to 6 hours respectively. Comparison of single and multiple once-daily dosing revealed no significant differences in pharmacokinetics, and the intra-individual variability was very low. There was no relevant accumulation.

Special populations

Pharmacokinetics were similar in males and females, as well as in young and elderly (above 65 years) patients. In patients with low creatinine clearance, there was a tendency for glimepiride clearance to increase and for average serum concentrations to decrease, most probably resulting from a more rapid elimination because of lower protein binding. Renal elimination of the two metabolites was impaired. Overall no additional risk of accumulation is to be assumed in such patients. Pharmacokinetics in five non-diabetic patients after bile duct surgery was similar to those in healthy persons.

Metformin Prolonged-Release

The absolute bioavailability of a metformin 500 mg tablet given under fasting conditions is approximately 50-60%. Following a single oral dose of metformin prolonged-release, C_{max} is achieved within 4-8 hours. Peak plasma levels are approximately 20% lower compared to the same dose of metformin immediate release, however, the extent of absorption (as measured by AUC) is similar to immediate release. Both high and low fat meals had the same effect on the pharmacokinetics of prolonged release. Protein binding of Metformin is Minimal and Metabolism is not done by liver Moreover Biological Half-life is 4-8.7 hours and Excretion us done by Urine (90%).

PHARMACODYNAMIC PROPERTIES & MECHANISM OF ACTION Glimepiride

Glimepiride is an orally active hypoglycaemic substance belonging to the sulfonylurea group. It may be used in non-insulin dependent diabetes mellitus. Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells. As with other sulfonylureas this effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects also postulated for other sulfonylureas.

Insulin release

Sulfonylureas regulate insulin secretion by closing the ATP-sensitive potassium channel in the beta cell membrane. Closing the potassium channel induces depolarization of the beta cell and results - by opening of calcium channels - in an increased influx of calcium into the cell. This leads to insulin release through exocytosis. Glimepiride binds with a high exchange rate to a beta cell membrane protein which is associated with the ATP-sensitive potassium channel but which is different from the usual sulfonylurea binding site.

Extrapancreatic activity

The extrapancreatic effects are for example an improvement of the sensitivity of the peripheral tissue for insulin and a decrease of the insulin uptake by the liver. The uptake of glucose from blood into peripheral muscle and fat tissues occurs via special transport proteins, located in the cells membrane. The transport of glucose in these tissues is the rate limiting step in the use of glucose. Glimepiride increases very rapidly the number of active glucose transport molecules in the plasma membranes of muscle and fat cells, resulting in stimulated glucose uptake.

Glimepiride increases the activity of the glycosyl-phosphatidylinositol-specific phospholipase C which may be correlated with the drug-induced lipogenesis and glycogenesis in isolated fat and muscle cells. Glimepiride inhibits the glucose production in the liver by increasing the intracellular concentration of fructose-2, 6-bisphosphate, which in its turn inhibits the gluconeogenesis.

General

In healthy persons, the minimum effective oral dose is approximately 0.6 mg. The effect of glimepiride is dose-dependent and reproducible. The physiological response to acute physical exercise, reduction of insulin secretion, is still present under glimepiride. There was no significant difference in effect regardless of whether the medicinal product was given 30 minutes or immediately before a meal. In diabetic patients, good metabolic control over 24 hours can be achieved with a single daily dose. Although the hydroxy metabolite of glimepiride caused a small but significant decrease in serum glucose in healthy persons, it accounts for only a minor part of the total drug effect.

Combination therapy with metformin

Improved metabolic control for concomitant glimepiride therapy compared to metformin alone in patients not adequately controlled with the maximum dosage of metformin has been shown.

Combination therapy with insulin

Data for combination therapy with insulin are limited. In patients not adequately controlled with the maximum dosage of glimepiride, concomitant insulin therapy can be initiated. The combination achieved the same improvement in metabolic control as insulin alone; however, a lower average dose of insulin was required in combination therapy.

Children and adolescents

Following glimepiride treatment, there were no new safety concerns noted in children compared to adult patients with type 2 diabetes mellitus. No long-term efficacy and safety data are available in pediatric patients.

Metformin

Metformin improves glucose tolerance in patients with type-2 diabetes (NIDDM), lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

INDICATION Type 2 diabetes mellitus

- As an adjunct to diet and exercise in Non-insulin-dependent (type II) diabetes, whenever blood sugar levels cannot be controlled adequately by diet, physical exercise and weight reduction alone. Glimepiride may also be used in combination with an oral antidiabetic containing metformin or with insulin.
- The drug product should be used only in patients who have not sufficiently responded to either of the following treatments.
  (a) Diet and/or exercise therapy alone
  (b) Use of sulfonylureas in addition to diet and/or exercise therapy (c) Use of thiazolidinediones in addition to diet and/or exercise therapy

CONTRAINDICATIONS Glimepiride

Glimepiride is contraindicated in patients with the following conditions:

- hypersensitivity to glimepiride, other sulfonylureas or sulfonamides or to any of the excipients
- insulin dependent diabetes,
- diabetic coma,
- ketoacidosis,

- Severe renal or hepatic function disorders. In case of severe renal or hepatic function disorders, a changeover to insulin is required.

Metformin

Metformin is contraindicated in people with any condition that could increase the risk of lactic acidosis, including kidney disorders (arbitrarily defined as creatinine levels over 150 µmol/l (1.7 mg/dl), lung disease and liver disease. According to the prescribing information, heart failure (in particular, unstable or acute congestive heart failure) increases the risk of lactic acidosis with metformin.

DOSAGE AND ADMINISTRATION Glimepiride

The basis for successful treatment of diabetes is a good diet, regular physical activity, as well as routine checks of blood and urine. Tablets or insulin cannot compensate if the patient does not keep to the recommended diet. Dosage is determined by the results of blood and urinary glucose determinations.

The starting dose is 1 mg glimepiride per day. If good control is achieved this dosage should be used for maintenance therapy. For the different dosage regimens appropriate strengths are available. If control is unsatisfactory the dosage should be increased, based on the glycaemic control, in a stepwise manner with an interval of about 1 to 2 weeks between each step, to 2, 3 or 4 mg glimepiride per day. A dosage of more than 4 mg glimepiride per day gives better results only in exceptional cases. The maximum recommended dose is 6 mg glimepiride per day.

In patients not adequately controlled with the maximum daily dose of metformin, concomitant glimepiride therapy can be initiated. While maintaining the metformin dose, the glimepiride therapy is started with a low dose, and is then titrated up depending on the desired level of metabolic control up to the maximum daily dose. The combination therapy should be initiated under close medical supervision.

In patients not adequately controlled with the maximum daily dose of glimepiride, concomitant insulin therapy can be initiated if necessary. While maintaining the glimepiride dose, insulin treatment is started at low dose and titrated up depending on the desired level of metabolic control. The combination therapy should be initiated under close medical supervision.

Normally a single daily dose of glimepiride is sufficient. It is recommended that this dose be taken shortly before or during a substantial breakfast or - if none is taken - shortly before or during the first main meal. If a dose is forgotten, this should not be corrected by increasing the next dose. Tablets should be swallowed whole with some liquid.

If a patient has a hypoglycaemic reaction on 1 mg glimepiride daily, this indicates that they can be controlled by diet alone. In the course of treatment, as an improvement in

control of diabetes is associated with higher insulin sensitivity, glimepiride requirements may fall. To avoid hypoglycaemia timely dose reduction or cessation of therapy must therefore be considered. Change in dosage may also be necessary, if there are changes in weight or life style of the patient, or other factors that increase the risk of hypo-or hyperglycaemia.

Switch over from other oral hypoglycaemic agents to glimepiride

A switch over from other oral hypoglycaemic agents to glimepiride can generally be done. For the switch over to glimepiride the strength and the half-life of the previous medicinal product has to be taken into account. In some cases, especially in antidiabetics with a long half-life (e.g. chlorpropamide), a wash out period of a few days is advisable in order to minimize the risk of hypoglycaemic reactions due to the additive effect. The recommended starting dose is 1 mg glimepiride per day. Based on the response the glimepiride dosage may be increased stepwise, as indicated earlier.

Children and adolescents

There are no data available on the use of glimepiride in patients under 8 years of age. For children aged 8 to 17 years, there are limited data on glimepiride as monotherapy. The available data on safety and efficacy are insufficient in the pediatric population and therefore such use is not recommended.

Metformin

The usual adult dosage is 500mg of metformin administered orally once daily. If efficacy isinsufficient, the dose may be increased up to 2550 mg once daily

ADVERSE EFFECTS Glimepiride

The following undesirable effects are based on experience with glimepiride and other sulfonylureas.

Other adverse reactions reported with Glimepiride are:

- **Blood and lymphatic system disorders**

  Rare: thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, erythropenia, haemolytic anaemia and pancytopenia, which are in general reversible upon discontinuation of medication.

  Not known: severe thrombocytopenia with platelet count less than 10,000/µl and thrombocytopenic purpura.

- **Immune system disorders**

  Very rare: leukocytoclastic vasculitis, mild hypersensitivity reactions that may develop into serious reactions with dyspnoea, fall in blood pressure and sometimesshock.

  Not known: Cross-allergenicity with sulfonylureas, sulfonamides or related substances is possible.

- **Metabolism and nutrition disorders** Rare:
  hypoglycaemia.
  These hypoglycaemic reactions mostly occur immediately, may be severe and are not always easy to correct. The occurrence of such reactions depends, as with other hypoglycaemic therapies, on individual factors such as dietary habits and dosage.
- **Eye disorders**
  Not known: Visual disturbances, transient, may occur especially on initiation of treatment, due to changes in blood glucose levels.
- **Gastrointestinal disorders**
  Very rare: nausea, vomiting, diarrhoea, abdominal distension, abdominal discomfort and abdominal pain, which seldom lead to discontinuation of therapy.
- **Hepato-biliary disorders**
  Not known: Hepatic enzymes increased.
  Very rare: hepatic function abnormal (e.g. with cholestasis and jaundice), hepatitis and hepatic failure.
- **Skin and subcutaneous tissue disorders**
  Not known: Hypersensitivity reactions of the skin may occur as pruritus, rash, urticaria and photosensitivity.
- **Investigations**
  Very rare: blood sodium decrease.

Metformin

The most common adverse effect of metformin is gastrointestinal irritation, including diarrhea, cramps, nausea, vomiting, and increased flatulence; metformin is more commonly associated with gastrointestinal side effects than most other antidiabetic drugs.[The most serious potential side effect of metformin use is lactic acidosis; this complication is very rare, and the vast majority of these cases seem to be related to comorbid conditions, such as impaired liver or kidney function, rather than to the metformin itself. Metformin has also been reported to decrease the blood levels of thyroid- stimulating hormone in people with hypothyroidism, the clinical significance of this is stillunknown.

OVERDOSAGE

After ingestion of an overdosage hypoglycaemia may occur, lasting from 12 to 72 hours, and may recur after an initial recovery. Symptoms may not be present for up to 24 hours after ingestion. In general observation in hospital is recommended. Nausea, vomiting and epigastric pain may occur. The hypoglycaemia may in general be accompanied by neurological symptoms like restlessness, tremor, visual disturbances, co-ordination problems, sleepiness, coma and convulsions.

Treatment primarily consists of preventing absorption by inducing vomiting and then drinking water or lemonade with activated charcoal (adsorbent) and sodiumsulphate (laxative). If large quantities have been ingested, gastric lavage is indicated, followed by activated charcoal and sodium-sulphate. In case of (severe) overdosage hospitalization in

an intensive care department is indicated. Start the administration of glucose as soon as possible, if necessary by a bolus intravenous injection of 50 ml of a 50% solution, followed by an infusion of a 10% solution with strict monitoring of blood glucose. Further treatment should be symptomatic.

In, particular when treating hypoglycaemia due to accidental intake of glimepiride in infants and young children, the dose of glucose given must be carefully controlled to avoid the possibility of producing dangerous hyperglycaemia. Blood glucose should be closely monitored.

WARNINGS AND PRECAUTIONS

Glimepiride must be taken shortly before or during a meal. When meals are taken at irregular hours or skipped altogether, treatment with glimepiride may lead to hypoglycaemia. Possible symptoms of hypoglycaemia include: headache, ravenous hunger, nausea, vomiting, lassitude, sleepiness, disordered sleep, restlessness, aggressiveness, impaired concentration, alertness and reaction time, depression, confusion, speech and visual disorders, aphasia, tremor, paresis, sensory disturbances, dizziness, helplessness, loss of self-control, delirium, cerebral convulsions, somnolence and loss of consciousness up to and including coma, shallow respiration and bradycardia. In addition, signs of adrenergic counter-regulation may be present such as sweating, clammy skin, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmias. The clinical picture of a severe hypoglycaemic attack may resemble that of a stroke.

Symptoms can almost always be promptly controlled by immediate intake carbohydrates (sugar). Artificial sweeteners have no effect. It is known from other sulfonylureas that, despite initially successful countermeasures, hypoglycaemia may recur.

Severe hypoglycaemia or prolonged hypoglycaemia, only temporarily controlled by the usual amounts of sugar, requires immediate medical treatment and occasionally hospitalization. Factors favoring hypoglycaemia include:

- unwillingness or (more commonly in older patients) incapacity of the patient to cooperate,
- undernutrition, irregular mealtimes or missed meals or periods of fasting, alterations indiet,
- imbalance between physical exertion and carbohydrate intake,
- consumption of alcohol, especially in combination with skipped meals,
- impaired renal function,
- serious liver dysfunction,
- overdosage with glimepiride,
- certain uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counterregulation of hypoglycaemia (as for example in certain disorders

of thyroid function and in anterior pituitary or adrenocortical insufficiency), - concurrent administration of certain other medicinal products

Treatment with glimepiride requires regular monitoring of glucose levels in blood and urine. In addition determination of the proportion of glycosylated haemoglobin is recommended. Regular hepatic and haematological monitoring (especially leucocytes and thrombocytes) are required during treatment with glimepiride. In stress-situations (e.g. accidents, acute operations, infections with fever, etc.) a temporary switch to insulinmay be indicated.

No experience has been gained concerning the use of Glimepiride in patients with severe impairment of liver function or dialysis patients. In patients with severe impairment of renal or liver function change over to insulin is indicated. Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to hemolytic anaemia. Since glimepiride belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

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glimepiride belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

Special warning on increased risk of cardiovascular mortality
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. The patient should be informed of the potential risks and advantages of glimepiride tablets and of alternative models of therapy. 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.

Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or operate machinery in these circumstances.

DRUG INTERACTIONS Glimepiride

If glimepiride is taken simultaneously with certain other medicinal products, both undesired increases and decreases in the hypoglycaemic action of glimepiride can occur. For this reason, other medicinal products should only be taken with the knowledge (or at the prescription) of the doctor.

Glimepiride is metabolized by cytochrome P450 2C9 (CYP2C9). Its metabolism is known to be influenced by concomitant administration of CYP2C9 inducers (e.g. rifampicin) or inhibitors (e.g. fluconazole). Results from a vivo interaction study reported in literature show that glimepiride AUC is increased approximately 2-fold by fluconazole, one of the most potent CYP2C9 inhibitors. Based on the experience with glimepiride and with other sulfonylureas the following interactions have to be mentioned.

Potentiation of the blood-glucose-lowering effect and, thus, in some instances hypoglycaemia may occur when one of the following medicinal products is taken, for example:

- phenylbutazone, azapropazone and oxyfenbutazone,

- insulin and oral antidiabetic products, such as metformin,
- salicylates and p-amino-salicylic acid,
- anabolic steroids and male sex hormones,
- chloramphenicol, certain long acting sulfonamides, tetracyclines,
- quinolone antibiotics and clarithromycin,
- coumarin anticoagulants,
- fenfluramine,
- fibrates,
- ACE inhibitors,
- fluoxetine, MAO-inhibitors,
- allopurinol, probenecid, sulfinpyrazone,
- sympatholytics,
- cyclophosphamide, trophosphamide and iphosphamides, - miconazol, fluconazole.
- pentoxifylline (high dose parenteral), - tritoqualine.

Weakening of the blood-glucose-lowering effect and, thus raised blood glucose levels may occur when one of the following medicinal products is taken, for example:

- oestrogens and progestogens,
- saluretics, thiazide diuretics,
- thyroid stimulating agents, glucocorticoids,
- phenothiazine derivatives, chlorpromazine,
- adrenaline and sympathicomimetics,
- nicotinic acid (high dosages) and nicotinic acid derivatives,
- laxatives (long term use),
- phenytoin, diazoxide,
- glucagon, barbiturates and rifampicin,
- acetazolamide

- H2 antagonists, betablockers, clonidine and reserpine may lead to either potentiation or weakening of the blood glucose lowering effect. Under the influence of sympatholytic medicinal products such as betablockers, clonidine, guanethidine and reserpine, the signs of adrenergic counterregulation to hypoglycaemia may be reduced or absent.
- Alcohol intake may potentiate or weaken the hypoglycaemic action of glimepiride in an unpredictable fashion. Glimepiride may either potentiate or weaken the effects of coumarin derivatives.
- Colesevelam binds to glimepiride and reduces glimepiride absorption from the gastro-intestinal tract. No interaction was observed when glimepiride was taken at least for 4 hours before colesevelam. Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.

Metformin

The H_2-receptor antagonist cimetidine causes an increase in the plasma concentration of metformin, by reducing clearance of metformin by the kidneys; both metformin and cimetidine are cleared from the body by tubular secretion, and both, particularly the cation (positively charged) form of cimetidine, may compete for the same transport mechanism. A small double-blind, randomized study found the antibiotic cephalexin to also increase metformin concentrations by a similar mechanism; theoretically, other cationic medications may produce the same effect.

SPECIAL POPULATIONS:

Glimepiride

Pregnancy

Risk related to the diabetes

Abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities and perinatal mortality. So the blood glucose level must be closely monitored during pregnancy in order to avoid the teratogenic risk. The use of insulin is required under such circumstances. Patients who consider pregnancy should inform their physician.

Risk related to glimepiride

There are no adequate data from the use of glimepiride in pregnant women. Animal studies have shown reproductive toxicity which likely was related to the pharmacologic action (hypoglycaemia) of glimepiride. Consequently, glimepiride should not be used during the whole pregnancy. In case of treatment by glimepiride, if the patient plans to become pregnant or if a pregnancy is discovered, the treatment should be switched as soon as possible to insulin therapy.

Lactation

The excretion in human milk is unknown. Glimepiride is excreted in rat milk. As other sulfonylureas are excreted in human milk and because there is a risk of hypoglycaemia in nursing infants, breast-feeding is advised against during treatment with glimepiride.

Metformin Patients with Type 2 Diabetes

- In the presence of normal renal function, there are no differences between single- or multiple- dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects, nor is there any accumulation of metformin in either group at usual clinical doses.
- The pharmacokinetics of metformin hydrochloride extended-release tablets in patients with type 2 diabetes is comparable to those in healthy normal adults.

Renal Insufficiency

- In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Hepatic Insufficiency

- No pharmacokinetic studies of metformin have been conducted in patients withhepatic insufficiency.

Geriatrics

- Limited data from controlled pharmacokinetic studies of metformin hydrochloride tablets in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function. Metformin hydrochloride extended release tablets treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

STORAGE CONDITION- Store below 30°C in dry place. Keep out of reach of children.

PRESENTATION- Glimepiride 2 mg + Metformin HCl Prolonged Release 500 mg tablets

PACKING- 1*10 TAB

BIOS LAB PVT. LTD.

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