BIOS LAB PVT. LTD.

B-8, MILAN COMPLEX, SARKHEJ, AHMEDABAD.

QUALITY CONTROL DEPARTMENT

CERTIFICATE OF ANALYSIS

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

Report No. :	**FT-21/1070721**	**Mfg. No.:**	**14/UA/LL/2014**
Sample Name :	**BIOMET™ - G2P TABLETS**		
Generic Name :	**Glimepiride 2 mg, Metformin Hydrochloride (Sustained Release) 500 mg and Pioglitazone 15 mg Tablets**		

Product Name	**BIOMET™ - G2P**	**A.R.No.**	RFT-21/1070721
Batch No.	RT-1070721	**Batch Size**	0.51 Lacs
Mfg. Date	JUL. 2021	**Sample Qty.**	60 Tablets
Exp. Date	JUN. 2023	**Test as per**	Manufacturer Specification
Date of Receipt	25-07-2021	**Date of Release**	27-07-2021

S NO.	TEST	RESULT	SPECIFICATION
1.	Description	Orange and white coloured, elongated biconvex, bilayered uncoated tablet having a breakline on one side & plain on other side.	Orange and white coloured, elongated biconvex, bilayered uncoated tablet having a breakline on one side & plain on other side.
2.	Identification	Complies	Should be complies in assay
3.	Average weight	1007.4 mg	1000 mg ± 5.0%
4.	Uniformity of weight	Complies	± 5.0% of average weight
5.	Friability	0.31%	NMT: 1.0%
6.	Dissolution		
	Metformin Hydrochloride (SR) 0.1 M HCl for 10 hrs.		
	(a) 1st hours	38.94%	25% to 50%
	(b) 3rd hours	66.08%	45% to 75%
	(c) 10th hours	91.96%	NLT - 80%
7.	ASSAY	Each Uncoated bilayered tablet contains:	

Contents	Claim	Limit		Obtained
		Lower	Upper	
Glimepiride IP	2.0 mg	1.8 mg	2.20 mg	1.96 mg
Metformin Hydrochloride IP (As sustained release)	500.0 mg	450.0 mg	550.0 mg	494.86 mg
Pioglitazone Hydrochloride IP Eqv. To Pioglitazone	15.0 mg	13.5 mg	16.5 mg	14.91 mg

Conclusion: The above sample is complies as per I.H Specification.

* Manufactured by: RENOWED LIFE SCIENCES (HARIDWAR)

BIOMET™- G2P TABLETS

Each Tablet Contains

Glimepiride – 2 mg
Metformin HCl – 500 mg (Sustain Release)
Pioglitazone - 15 mg

For Pioglitazone:

1. THE DRUG SHOULD BE USED AT FIRST LINE OF THERAPY FOR DIABETES.
2. **ADVICE FOR HEALTHCARE PROFESSIONALS**
   - Patients with active bladder cancer or with a history of bladder cancer and those with uninvestigated haematuria should not receive pioglitazone.
   - Prescribers should review the safety and efficacy of pioglitazone in individuals after 3-6 month of treatment to ensure that only patients who are deriving benefit continue to be treated. Pioglitazone should be stopped in patients who do not respond adequately to treatment (e.g. reduction in Glycosylated hemoglobin HbA1C).
   - Before starting pioglitazone, the following known risk factors for development of bladder cancer should be assessed in individuals: age, current or past history of smoking, exposure to some occupational or chemotherapy agents such as cyclophosphamide, or previous irradiation of the pelvic region.
   - Use in elderly patients should be considered carefully before and during treatment because the risk of bladder cancer increases with age. Elderly patients should start on the lowest possible dose and be regularly monitored because of the risks of bladder cancer and heart failure associated with pioglitazone.

PHARMACEUTICAL DESCRIPTION

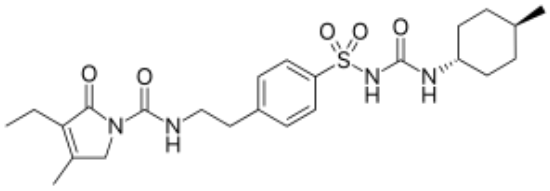
GLIMEPIRIDE:

Generic name: Glimepiride

Chemical name: 3-ethyl-4-methyl-2-oxo-N-(2-{4-[({[(1r,4r)-4-methylcyclohexyl]-C-hydroxycarbonimidoyl}amino)sulfonyl]phenyl}ethyl)-2,5-dihydro-1H-pyrrole-1-carboximidic acid

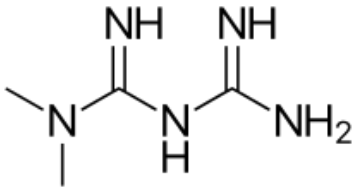
Molecular mass: 490.617 g/mol

Structural formula:



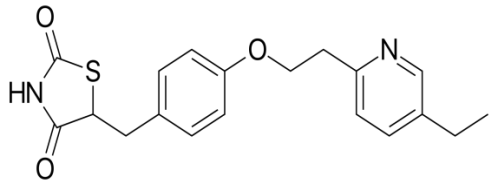
Empirical formula – $C_{24}H_{34}N_4O_5S$

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



Empirical formula - $C_4H_{11}N_5$

PIOGLITAZONE:
Generic name: Pioglitazone
Chemical name: 5-[[4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione
Molecular mass: 356.44 g/mol
Structural formula:



Empirical formula – $C_{19}H_{20}N_2O_3S$

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 (C_{max}) are reached approximately 2.5 hours after oral intake (mean 0.3µg/ml during multiple dosing of 4mg daily) and there is a linear relationship between dose and both C_{max} 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 Sustain-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 sustain-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 sustain 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%).

Pioglitazone

Serum concentrations of total pioglitazone (pioglitazone plus active metabolites) remain elevated 24 hours after once daily dosing. Steady-state serum concentrations of both pioglitazone and total pioglitazone are achieved within 7 days. At steady state, two of the pharmacologically active metabolites of pioglitazone, Metabolites III (M-III) and IV (M-IV), reach serum concentrations equal to or greater than pioglitazone. In both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations and 20% to 25% of the total area under the serum concentration-time curve (AUC).

Maximum serum concentration (C_{max}), AUC, and trough serum concentrations (C_{min}) for both pioglitazone and total pioglitazone increase proportionally at doses of 15 mg and 30 mg per day. There is a slightly less than proportional increase for pioglitazone and total pioglitazone at a dose of 60 mg per day.

Absorption

Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption.

Distribution
The mean apparent volume of distribution (V_d/F) of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean ± SD) L/kg of body weight. Pioglitazone is extensively protein bound (>99%) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. Metabolites M-III and M-IV also are extensively bound (>98%) to serum albumin.

Metabolism
Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-II and M-IV (hydroxy derivatives of pioglitazone) and M-III (keto derivative of pioglitazone) are pharmacologically active in animal models of type 2 diabetes. In addition to pioglitazone, M-III and M-IV are the principal drug-related species found in human serum following multiple dosing. At steady state, in both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the total peak serum concentrations and 20% to 25% of the total AUC.

Pioglitazone incubated with expressed human P450 or human liver microsomes results in the formation of M-IV and to a much lesser degree, M-II. The major cytochrome P450 isoforms involved in the hepatic metabolism of pioglitazone are CYP2C8 and CYP3A4 with contributions from a variety of other isoforms including the mainly extra hepatic CYP1A1. Ketoconazole inhibited up to 85% of hepatic pioglitazone metabolism in vitro at a concentration equal molar to pioglitazone. Pioglitazone did not inhibit P450 activity when incubated with human P450 liver microsomes. In vivo human studies have not been performed to investigate any induction of CYP3A4 by pioglitazone.

Excretion
Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.

The mean serum half-life of pioglitazone and total pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F, calculated to be 5 to 7 L/hr.

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 extra pancreatic 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.

Pioglitazone

Pioglitazone enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal and improves hepatic sensitivity to insulin. In patients with type 2 diabetes, the decreased insulin resistance produced by pioglitazone results in lower plasma glucose concentrations, lower plasma insulin concentrations, and lower HbA1c values. Additionally, patients treated with pioglitazone had mean decreases in serum triglycerides, mean increases in HDL cholesterol, and no consistent mean changes in LDL and total cholesterol.

Pioglitazone selectively stimulates the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) and to a lesser extent PPAR-γ. It modulates the transcription of the insulin-sensitive genes involved in the control of glucose and lipid metabolism in the muscle, adipose tissue, and the liver. As a result, pioglitazone reduces insulin resistance in the liver and peripheral tissues; increases the expense of insulin-dependent glucose; decreases withdrawal of glucose from the liver; reduces quantity of glucose, insulin and glycated hemoglobin in the bloodstream.

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, pioglitazone 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.

Pioglitazone

Initiation of Pioglitazone in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated. Use in patients with known hypersensitivity to pioglitazone, metformin or any other component of Brand.

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 dose is 2 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 2 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 2 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 is insufficient, the dose may be increased up to 2550 mg once daily.

Pioglitazone
The usual adult dosage is 15-30 mg of Pioglitazone administered orally once daily with meal. Initially may increase dose by 15 mg with careful monitoring to 45 mg once daily maximum.

Type 2 Diabetes Mellitus
- Indicated as monotherapy or with insulin or insulin secretagogues
- 15-30 mg orally with meal every daily initially; may increase dose by 15 mg with careful monitoring to 45 mg each day

- Monitor ALT at start of treatment, each month for 12 months, then every 3 months thereafter.

Dosage Modification:

- Co-administration with insulin secretagogue (sulfonylurea): Decrease insulin secretagogue dose
- Co-administration with insulin: Decrease insulin dose by 10-25%
- Co-administration with strong CYP2C8 inhibitors (gemfibrozil): Limit maximum pioglitazone dose to 15 mg daily.

Not recommended for pediatric use

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 sometimes shock.
  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 co-morbid 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 still unknown.

Pioglitazone

The most Common adverse effects include headaches, muscle pains, inflammation of the throat, and swelling. Serious side effects may include bladder cancer, low blood sugar, heart failure, and osteoporosis. Use in not recommended in pregnancy or breastfeeding. It is in the thiazolidinedione (TZD) class and works by improving sensitivity of tissues to insulin.

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 sodium-sulphate (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,
- under nutrition, irregular mealtimes or missed meals or periods of fasting, alterations in diet,
- imbalance between physical exertion and carbohydrate intake,
- consumption of alcohol, especially in combination with skipped meals,
- impaired renal function,
- serious liver dysfunction,
- over dosage with glimepiride,
- certain uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counter regulation 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 hemoglobin is recommended. Regular hepatic and hematological 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 insulin may 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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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
- H_2 antagonists, beta blockers, 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 beta blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter regulation 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.

Pioglitazone

Combination of Pioglitazone with sulfonylureas or insulin reciprocally exponentiate risk of hypoglycemia. Therapy with pioglitazone will increases the chance of pregnancy in individuals taking oral contraception.

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 with hepatic 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.

Pioglitazone

Renal Insufficiency: The serum elimination half-life of pioglitazone, M-III, and M-IV remains unchanged in patients with moderate (creatinine clearance 30 to 60 mL/min) to severe (creatinine clearance < 30 mL/min) renal impairment when compared to normal subjects. No dose adjustment in patients with renal dysfunction. Hepatic Insufficiency: Compared with normal controls, subjects with impaired hepatic function

(Child-Pugh Grade B/C) have an approximate 45% reduction in pioglitazone and total pioglitazone mean peak concentrations but no change in the mean AUC values. It should not be initiated if the patient exhibits clinical evidence of active liver disease or serum transaminase levels (ALT) exceeds 2.5 times the upper limit of normal.

Elderly: In healthy elderly subjects, peak serum concentrations of pioglitazone and total pioglitazone are not significantly different, but AUC values are slightly higher and the terminal half-life values slightly longer than for younger subjects. These changes were not of a magnitude that would be considered clinically relevant.

Pediatrics: Pharmacokinetic data in the pediatric population are not available.

Gender: The mean C_{max} and AUC values were increased 20% to 60% in females. Monotherapy and in combination with sulfonylurea, metformin, or insulin and improved glycemic control in both males and females. Hemoglobin A1C (HbA_{1c}) decreases from baseline were generally greater for females than for males (average mean difference in HbA_{1c} 0.5%). Since therapy should be individualized for each patient to achieve glycemic control, no dose adjustment is recommended based on gender alone.

Ethnicity: Pharmacokinetic data among various ethnic groups are not available.

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

PRESENTATION- Glimepiride 2mg + Metformin HCl Sustain Release 500mg + Pioglitazone 15mg tablets

PACKING- 1*10 TAB

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