Glumyl®

Glimepiride

FORMS AND PRESENTATION
Glumyl® 1: Tablets. Box of 30.
Glumyl® 2: Tablets. Box of 30.
Glumyl® 3: Tablets. Box of 30.
Glumyl® 4: Tablets. Box of 30.

COMPOSITION
Glumyl® 1: Each tablet contains Glimepiride 1mg.
Glumyl® 2: Each tablet contains Glimepiride 2mg.
Glumyl® 3: Each tablet contains Glimepiride 3mg.
Glumyl® 4: Each tablet contains Glimepiride 4mg.
Excipients: lactose monohydrate, sodium starch glycolate, povidone, magnesium stearate, iron oxide red (Glumyl® 1 & Glumyl® 2), iron oxide yellow (Glumyl® 3).

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Therapeutic class: Oral blood glucose lowering drugs: Sulfonamides, urea derivatives.
ATC code: A10BB12.
Glimepiride is an orally active hypoglycemic 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 depolarisation 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.
Extra-pancreatic activity
The extra-pancreatic 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 cell's 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 in one study.
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. In two studies, the combination achieved the same improvement in metabolic control as insulin alone; however, a lower average dose of insulin was required in combination therapy.
Pharmacokinetic properties
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 approx. 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 C_{max} and AUC (area under the time/concentration curve).
Distribution
Glimepiride has a very low distribution volume (approx. 8.8 liters) which is roughly equal to the albumin distribution space, high protein binding (>99%), and a low clearance (approx. 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 radiolabeled Glimepiride, 58% of the radioactivity was recovered in the urine, and 35% in the feces. 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 feces: 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
Elderly people: Pharmacokinetics were similar in males and females, as well as in young and elderly (above 65 years) patients.
Renal impairment: 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 were similar to those in healthy persons.
Paediatric population: A fed study investigating the pharmacokinetics, safety, and tolerability of a 1 mg single dose of Glimepiride in 30 pediatric patients (4 children aged 10-12 years and 26 children aged 12-17 years) with type 2 diabetes showed mean AUC(0-last), C_{max} and $t_{1/2}$ similar to that previously observed in adults.

INDICATIONS
Glumyl® is indicated for the treatment of type 2 diabetes mellitus, when diet, physical exercise and weight reduction alone are not adequate.

CONTRAINDICATIONS
Glimepiride is contraindicated in patients with the following conditions:
- Hypersensitivity to Glimepiride, other sulfonylureas or sulfonamides or to any of the excipients.
- Diabetes mellitus type 1.
- Diabetic coma.
- Ketoacidosis.
- Severe renal or hepatic function disorders. In case of severe renal or hepatic function disorders, a changeover to insulin is required.

PRECAUTIONS
Glumyl® must be taken shortly before or during a meal. When meals are taken at irregular hours or skipped altogether, treatment with Glumyl® may lead to hypoglycemia. Possible symptoms of hypoglycemia 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 hypoglycemic 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, hypoglycemia may recur.
Severe hypoglycemia or prolonged hypoglycemia, only temporarily controlled by the usual amounts of sugar, requires immediate medical treatment and occasionally hospitalization.
Factors favouring hypoglycemia 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, overdosage with Glumyl®, certain uncompensated disorders of the endocrine system affecting carbohydrate metabolism or counter-regulation of hypoglycemia (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 Glumyl® 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 Glumyl®.
In stress-situations (e.g. accidents, acute operations, infections with fever, etc.) a temporary switch to insulin may be indicated.
Treatment of patients with G6PD-deficiency with sulfonylurea agents can lead to hemolytic anemia. Since Glumyl® belongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.
Glumyl® contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
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 hypoglycemia or hyperglycemia 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 hypoglycemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycemia or have frequent episodes of hypoglycemia. It should be considered whether it is advisable to drive or operate machinery in these circumstances.

PREGNANCY AND LACTATION

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 (hypoglycemia) of Glimepiride.

Consequently, Glumyl® should not be used during the whole pregnancy.

In case of treatment by Glumyl®, 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.

Breast-feeding

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 hypoglycemia in nursing infants, breast-feeding is advised against during treatment with Glumyl®.

DRUG INTERACTIONS

If Glumyl® is taken simultaneously with certain other medicinal products, both undesired increases and decreases in the hypoglycemic 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 an in 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 hypoglycemia 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, disopyramide, fibrates, ACE inhibitors, fluoxetine, MAO-inhibitors, allopurinol, probenecid, sulfinpyrazone, sympatholytics, cyclophosphamide, trophosphamide and iphosphamides, miconazole, 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: estrogens 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 hypoglycemia may be reduced or absent.

Alcohol intake may potentiate or weaken the hypoglycemic 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 4 hours before colesevelam. Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.

ADVERSE EFFECTS

The following adverse reactions from clinical investigations were based on experience with Glimepiride and other sulfonylureas, were listed below by system organ class and in order of decreasing incidence: Very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000) ; very rare (<1/10,000); not known (cannot be estimated from the available data).

Blood and lymphatic system disorders: thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, erythropenia, hemolytic anemia and pancytopenia, which are in general reversible upon discontinuation of medication (rare); severe thrombocytopenia with platelet count less than 10,000/µl and thrombocytopenic purpura (not known).

Immune system disorders: leukocytoclastic vasculitis, mild hypersensitivity reactions that may develop into serious reactions with dyspnea, fall in blood pressure and sometimes shock (very rare); cross-allergenicity with sulfonylureas, sulfonamides or related substances is possible (not known).

Metabolism and nutrition disorders: hypoglycemia (rare).

These hypoglycemic reactions mostly occur immediately, may be severe and are not always easy to correct. The occurrence of such reactions depends, as with other hypoglycemic therapies, on individual factors such as dietary habits and dosage.

Eye disorders: transient visual disturbances may occur especially on initiation of treatment due to changes in blood glucose levels (not known).

Gastrointestinal disorders: dysgeusia (rare); nausea, vomiting, diarrhea, abdominal distension, abdominal discomfort, and abdominal pain, which seldom lead to discontinuation of therapy (very rare).

Hepato-biliary disorders: abnormal hepatic function (e.g. with cholestasis and jaundice), hepatitis and hepatic failure (very rare); increased hepatic enzymes (not known).

Skin and subcutaneous tissue disorders: alopecia (rare); hypersensitivity reactions of the skin may occur as pruritis, rash, urticaria and photosensitivity (not known).

Investigations: weight gain(rare); decreased blood sodium (very rare).

DOSAGE AND ADMINISTRATION

Posology

For oral administration.

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 of Glumyl® 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 glycemic control, in a stepwise manner with an interval of about 1 to 2 weeks between each step, to 2, 3 or 4 mg of Glumyl® per day.

A dosage of more than 4 mg of Glumyl® per day gives better results only in exceptional cases. The maximum recommended dose is 6 mg of Glumyl® per day.

In patients not adequately controlled with the maximum daily dose of Glumyl®, concomitant insulin therapy can be initiated if necessary. While maintaining the Glumyl® 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 Glumyl® 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 hypoglycemic reaction on 1mg of Glumyl® daily, this indicates that they can be controlled by diet alone.

During treatment, as an improvement in control of diabetes is associated with higher insulin sensitivity, Glumyl® requirements may fall. To avoid hypoglycemia 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 lifestyle of the patient, or other factors that increase the risk of hypo-or hyperglycemia.

Switch over from other oral hypoglycemic agents to Glumyl®

A switch over from other oral hypoglycemic agents to Glumyl® can generally be done. For the switch over to Glumyl® 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 minimise the risk of hypoglycemic reactions due to the additive effect.

The recommended starting dose is 1mg of Glumyl® per day. Based on the response the Glumyl® dosage may be increased stepwise, as indicated earlier.

Switch over from Insulin to Glumyl®

In exceptional cases, where type 2 diabetic patients are regulated on insulin, a changeover to Glumyl® may be indicated. The changeover should be undertaken under close medical supervision.

Special population

Paediatric population

There are no data available on the use of Glumyl® in patients under 8 years of age. For children aged 8 to 17 years, there are limited data on Glumyl® as monotherapy.

The available data on safety and efficacy are insufficient in the pediatric population and therefore such use is not recommended.

OVERDOSAGE

After ingestion of an overdosage hypoglycemia 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 hypoglycemia may in general be accompanied by neurological symptoms like restlessness, tremor, visual disturbances, coordination 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 hypoglycemia 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 hyperglycemia. Blood glucose should be closely monitored.

STORAGE CONDITIONS

Store below 25°C.

Keep in original pack in intact conditions.

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Marketing Authorization Holder and Manufacturer:
Benta S.A.L. – Lebanon

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