- serious liver dysfunction,
- overdose with Gvardens,
- 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 Gvardens 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 Gvardens.

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 Gvardens 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.

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.

Presentation:

Gvardens 1, 2, 3 or 4 : 3x10 alu alu blister in carton-box, with instruction for use.

Storage:

Keep in dry place, protected from light at a temperature below 25°C. Keep out of reach of children.

Shelf life:

Labeled. Do not use after expiry date.

Distribution Condition:

Prescribed medicine.

Manufactured for:
BELINDA Laboratories
London, United Kingdom
Manufactured by:
Akums Drugs & Pharmaceuticals Ltd.
19, 20, 21, Sector-6A, I.I.E., SIDCUL,
Ranipur, Haridwar-249403, INDIA

GVARDENS

Instructions for the medicinal product

Trade name: Gvardens.
International nonproprietary name: Glimepiride.
Dosage form: Uncoated tablets.
Composition:
Gvardens 1 : Each uncoated tablet contains:
Glimepiride USP 1 mg;
Gvardens 2 : Each uncoated tablet contains:
Glimepiride USP 2 mg;
Gvardens 3 : Each uncoated tablet contains:
Glimepiride USP 3 mg;
Gvardens 4 : Each uncoated tablet contains:
Glimepiride USP 4 mg;
Pharmacotherapeutic group: Blood glucose lowering drugs, excl. insulins: Sulfonamides, urea derivatives.
ATC Classification: A10BB12.
Pharmacologic property:
Pharmacodynamics:
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 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.
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.
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.
Special populations:
Paediatric population:
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 paediatric patients.
Pharmacokinetics:
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 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 Cmax and AUC (area under the time/concentration curve).
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 (approx. 48 ml/min).
Glimepiride is excreted in milk. Glimepiride is transferred to the placenta. Passage of the blood brain barrier is low.
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 radiolabelled 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 intraindividual 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 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 paediatric patients (4 children aged 10-12 years and 26 children aged 12-17 years) with type 2 diabetes showed mean AUC(0-last) , Cmax and t1/2 similar to that previously observed in adults.
Indications for use:
Iindicated for the treatment of type 2 diabetes mellitus, when diet, physical exercise and weight reduction alone are not adequate.
Contraindications:
- Hypersensitivity to glimepiride or any other component of the drug, to sulfonylurea derivatives or other sulfonamides.
- Insulin-dependent diabetes mellitus type 1;
- Diabetic ketoacidosis;
- Diabetic coma;
- Severe liver or kidneys dysfunctions;
- In case of severe liver or kidney dysfunction it is recommended to transfer the patient to insulin treatment.

Precaution: caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.
Pregnancy and lactation:
There are no adequate data from the use of glimepiride in pregnant women.
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.
The excretion in human milk is unknown. 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.
Dosage and directions for use:
Successful treatment of diabetes mellitus depends on patient's adherence to an appropriate diet, regular physical activity and continuous monitoring of glucose levels in blood and urine. Patient's failure to adhere to the diet is not compensated by taking tablets or insulin. The drug is used in adults. The tablet should be swallowed without chewing, followed by liquid.
The dosage depends on serum and urine glucose levels. Generally, Gvardens is used once daily. It is recommended to use the drug shortly before or with a substantial breakfast or, if breakfast is not taken, shortly before or with the main meal. If you have missed a regular dose, do not increase the next dose.
Monotherapy:
The initial dose is 1 mg of glimepiride daily. If such dose helps to adequately control the sugar level, it should be used as a supporting dose.
If glycemic control is not optimal, the dose should be gradually increased (with an interval of 1-2 weeks) to 2, 3 or 4 mg of glimepiride daily. If the patient experiences hypoglycemic reaction to 1 mg of Gvardens per day, this means that the disease may be controlled only by the diet. The dose of more than 4 mg daily gives better results only in isolated cases. The maximum recommended dose is 6 mg of Gvardens daily.
Combination with metformin:
If the maximum daily dose of metformin does not provide a sufficient glycemic control, a concomitant therapy with glimepiride may be started. Adhering to the previous dose of metformin, Gvardens therapy should be started with a low dose (1 mg), which may be gradually increased later to maximum daily dose, focusing on the desired level of metabolic control. The combined therapy should be conducted under close medical supervision.
Combination with insulin:
If maximum daily dose of Gvardens does not provide adequate glycemic control, if necessary, a concomitant treatment with insulin may be started. Adhering to the previous dose of glimepiride, insulin therapy should be started with the lowest dose, which may be gradually increased later to maximum daily dose, focusing on the desired level of metabolic control. The combined therapy should be conducted under close medical supervision.
Improved controllability of diabetes is accompanied by increased insulin sensitivity, therefore, during the therapy the need for glimepiride may decrease. To avoid hypoglycemia, the dose should be decreased or the therapy should be discontinued. It may be also necessary to revise the dosage if the patient's body weight or life style has changed, or if there are other factors that increase the risk of hypo- or hyperglycemia.
Transfer from oral hypoglycemic agents to Gvardens:
Usually, it is possible to transfer to Gvardens therapy from other oral hypoglycemic agents. During such transfer, the effect and half-life of the previous agent should be taken into account. In some cases, especially if the anti-diabetic drug has long half-life period (such as chlorpropamide), it is recommended to wait several days before starting Gvardens. This will help reduce the risk of hypoglycemic reactions due to the additive action of two agents. The recommended initial dose is 1 mg of glimepiride daily. The dose may be gradually increased, taking into account reaction to the drug.
Transfer from insulin to Gvardens:
In exceptional cases, patients with diabetes mellitus type 2 taking insulin may be recommended to transfer to Gvardens. Such transfer should be performed only under close medical supervision.
Side-effects:
Gastrointestinal disturbances: Vomiting, gastrointestinal pain, and diarrhea have been reported, but the incidence in placebo-controlled trials was less than 1%. In rare cases, there may be an elevation of liver enzyme levels. In isolated instances, impairment of liver function (e.g. with cholestasis and jaundice), as well as hepatitis, which may also lead to liver failure have been reported with sulphonylureas, including glimepiride.
Dermatological effects: Allergic skin reactions, e.g., purities, erythematic, urticaria, and morbilliform or maculopapular eruptions, occur in less than 1% of treated patients. These may be transient and may disappear despite continued use of glimepiride. If those hypersensitivity reactions persist or worsen, the drug should be discontinued. Porphyries cutanea tarda, photosensitivity reactions, and allergic vasculitis have been reported with sulphonylureas, including glimepiride.
Haematologic reactions: Leucopenia, agranulocytosis, thrombocytopenia, haemolytic anaemia, aplastic anaemia, and pancytopenia have been reported with sulfonylurea, including glimepiride.
Metabolic reactions: Hepatic porphyria reactions and disulfiram-like reactions have been reported with sulfonylureas, including glimepiride. Cases of hyponatremia have been reported with glimepiride and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with sulfonylureas, including glimepiride, and it has been suggested that certain sulfonylurea may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.
Hypoglycaemia: Glimepiride appears to be associated with a low incidence of hypoglycaemia. Glimepiride may have the potential to produce adverse cardiovascular effects; however glimepiride has been established agent for the treatment of type 2 diabetes for a number of years without adverse cardiovascular effects.
Overdose:
An overdose may cause hypoglycemia, which lasts from 12 to 72 hours, and may recur after the first relief. The symptoms may appear within 24 hours after absorption of the drug. Typically, such patients should be in the in-patient department.
Symptoms of hypoglycemia: nausea, vomiting and pain in the stomach, headache, tremor, blurred vision, loss of coordination, drowsiness, sleep disturbances, anxiety, aggressiveness, impaired concentration and reaction rate, depression, disorientation, speech disorders, aphasia, paresis, sensory disturbances, dizziness, helplessness, loss of self-control, delirium, cerebral convulsions, loss of consciousness up to development of coma, shallow respiration and bradycardia. Moreover, such symptoms of reverse adrenergic reaction, as excessive sweating, anxiety, tachycardia, hypertension, palpitations, angina pectoris and cardiac arrhythmia may be observed.
Treatment. The treatment first of all consists in prevention of absorption of the drug. For this, induce vomiting, and then during water or lemonade with activated carbon (adsorbent), laxative is indicated. In case of severe overdose, hospitalization to the intensive therapy unit is necessary. Administration of glucose should be started as soon as possible: if necessary, first, a one-time injection of 50 mL of a 50% solution, and then intravenous infusion of 10% solution, with constant control of blood glucose level. The further treatment is symptomatic.
Drug interactions:
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 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 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,
- 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:
- oestrogens and progestogens,
- saluretics, thiazide diuretics,
- thyroid stimulating agents, glucocorticoids,
- phenothiazine derivatives, chlorpromazine,
- adrenaline and sympathicomimetics,
- nicotinic acid (high doses) and nicotinic acid derivatives,
- laxatives (long term use),
- phenytoin, diazoxide,
- glucagon, barbiturates and rifampicin,
- acetazolamide.

H2 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 4 hours before colesevelam. Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.
Cautions:
When meals are taken at irregular hours or skipped altogether, treatment with Gvardens 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, require immediate medical treatment and occasionally hospitalisation.
Factors favouring 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 in diet,
- imbalance between physical exertion and carbohydrate intake,
- consumption of alcohol, especially in combination with skipped meals,
- impaired renal function,