Glimepiride Tablets USP 1mg/2mg/3mg/4mg

1. Name of the medicinal product

Glimepiride 1mg Tablets USP Taj Pharma
Glimepiride 2mg Tablets USP Taj Pharma
Glimepiride 3mg Tablets USP Taj Pharma
Glimepiride 4mg Tablets USP Taj Pharma

2. Qualitative and quantitative composition

a) Each uncoated tablet contains:

Glimepiride USP	1mg
Excipients	q.s.

b) Each uncoated tablet contains:

Glimepiride USP	2mg
Excipients	q.s.

c) Each uncoated tablet contains:

Glimepiride USP	3mg
Excipients	q.s.

d) Each uncoated tablet contains:

Glimepiride USP	4mg
Excipients	q.s.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet

4. Clinical particulars

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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.

Posology

Dose is determined by the results of blood and urinary glucose determinations.

The starting dose is 1 mg Glimepirideper day. If good control is achieved this dose should be used for maintenance therapy.

For the different dose 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 Glimepirideper day.

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

In patients not adequately controlled with the maximum daily dose of metformin, concomitant Glimepiridetherapy can be initiated.

While maintaining the metformin dose, the Glimepiridetherapy is started at 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 (TajPharma), concomitant insulin therapy can be initiated if necessary. While maintaining the Glimepiridedose, 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 Glimepirideis 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.

If a patient has a hypoglycaemic reaction on 1 mg Glimepiridedaily, 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, Glimepiriderequirements 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 (TajPharma)

A switch over from other oral hypoglycaemic agents to Glimepiridecan generally be done. For the switch over to Glimepiridethe strength and the half life of the previous medication has to be taken into account. In some cases, especially in antidiabetic medicines 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 hypoglycaemic reactions due to the additive effect.

The recommended starting dose is 1 mg Glimepirideper day. Based on the response the Glimepiridedose may be increased stepwise, as indicated earlier.

Switch over from Insulin to Glimepiride (TajPharma)

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

Special Populations

Patients with renal or hepatic impairment:

See section 4.3.

Paediatric population

There are no data available on the use of Glimepiridein patients under 8 years of age. For children aged 8 to 17 years, there are limited data on Glimepirideas monotherapy (see sections 5.1 and 5.2).

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

Method of administration

Tablets should be swallowed without chewing with some liquid.

4.3 Contraindications

Glimepirideis contraindicated in patients with the following conditions:

- hypersensitivity to Glimepiride (TajPharma), other sulfonylureas or sulfonamides or to any of the excipients listed in section 6.1,

- 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.

4.4 Special warnings and precautions for use

Glimepiridemust be taken shortly before or during a meal.

When meals are taken at irregular hours or skipped altogether, treatment with Glimepiridemay 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 sulphonylureas 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 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 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 Glimepiride (TajPharma),

- 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 (see Interactions 4.5).

Treatment with Glimepiriderequires 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 (TajPharma).

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 Glimepiridein 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 haemolyticanaemia. Since Glimepiridebelongs to the class of sulfonylurea agents, caution should be used in patients with G6PD-deficiency and a non-sulfonylurea alternative should be considered.

Glimepiridecontains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactosemalabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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

Glimepirideis 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 GlimepirideAUC is increased approximately 2-fold by

fluconazole, one of the most potent CYP2C9 inhibitors.

Based on the experience with Glimepirideand with other sulphonylureas 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,

- 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, 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 counter-regulation to hypoglycaemia may be reduced or absent.

Alcohol intake may potentiate or weaken the hypoglycaemic action of Glimepiridein an unpredictable fashion.

Glimepiridemay either potentiate or weaken the effects of coumarin derivatives.

Colesevelam binds to Glimepirideand reduces Glimepirideabsorption from the gastro-intestinal tract. No interaction was observed when Glimepiridewas taken at least 4 hours before colesevelam. Therefore, Glimepirideshould be administered at least 4 hours prior to colesevelam.

4.6 Fertility, 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 (TajPharma)

There are no adequate data from the use of Glimepiridein pregnant women. Animal studies have shown reproductive toxicity which likely was related to the pharmacologic action (hypoglycaemia) of Glimepiride(see section 5.3).

Consequently, Glimepirideshould not be used during the whole pregnancy.

In case of treatment by Glimepiride (TajPharma), 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. Glimepirideis 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 (TajPharma).

4.7 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.

4.8 Undesirable effects

The following adverse reactions from clinical investigations were based on experience with Glimepirideand other sulfonylureas, were listed below by system organ class and in order of decreasing incidence (very common: ≥1/l0; 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

Rare: thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, erythropenia, haemolyticanaemia 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: leukocytoclasticvasculitis, 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 (see further under section 4.4).

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

Symptoms

After ingestion of an overdosagehypoglycaemia 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.

Management

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) overdosagehospitalisation 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 Glimepiridein 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Oral blood glucose lowering drugs: Sulfonamides, urea derivatives. Glimepirideis an orally active hypoglycaemic substance belonging to the sulphonylurea group. It may be used in non-insulin dependent diabetes mellitus.

Mechanism of action

Glimepirideacts mainly by stimulating insulin release from pancreatic beta cells.

As with other sulphonylureas this effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, Glimepirideseems to have pronounced extrapancreatic effects also postulated for other sulphonylureas.

Insulin release

Sulphonylureas 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.

Glimepiridebinds 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 sulphonylurea 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. Glimepirideincreases very rapidly the number of active glucose transport molecules in the plasma membranes of muscle and fat cells, resulting in stimulated glucose uptake.

Glimepirideincreases 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.

Glimepirideinhibits 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 Glimepirideis dose-dependent and reproducible. The physiological response to acute physical exercise, reduction of insulin secretion, is still present under Glimepiride (TajPharma).

There was no significant difference in effect regardless of whether the drug 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 Glimepiridecaused 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 Glimepiridetherapy 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 (TajPharma), 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

An active controlled clinical trial (Glimepirideup to 8 mg daily or metformin up to 2,000 mg daily) of 24 weeks duration was performed in 285 children (8-17 years of age) with type 2 diabetes.

Both Glimepirideand metformin exhibited a significant decrease from baseline in HbA1c (Glimepiride (TajPharma)-0.95 (se 0.41); metformin -1.39 (se 0.40)). However, Glimepiridedid not achieve the criteria of noninferiority to metformin in mean change from baseline of HbA1c. The difference between treatments was 0.44% in favour of metformin. The upper limit (1.05) of the 95% confidence interval for the difference was not below the 0.3% non-inferiority margin.

Following Glimepiridetreatment, 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.

5.2 Pharmacokinetic properties

Absorption

The bioavailability of Glimepirideafter 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

Glimepiridehas 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).

In animals, Glimepirideis excreted in milk. Glimepirideis 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 radiolabelled Glimepiride (TajPharma), 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 (TajPharma), 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

Older people

Pharmacokinetics were similar in males and females, as well as in young and older people (above 65 years) patients.

Renal impairment

In patients with low creatinine clearance, there was a tendency for Glimepirideclearance 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 Glimepiridein 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 $t_{1/2}$ similar to that previously observed in adults.

5.3 Preclinical safety data

Preclinical effects observed occurred at exposures sufficiently in excess of the maximum human exposure as to indicate little relevance to clinical use, or were due to the pharmacodynamic action (hypoglycaemia) of the compound. This finding is based on conventional safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and reproduction toxicity studies. In the latter (covering embryotoxicity, teratogenicity and developmental toxicity), adverse effects observed were considered to be secondary to the hypoglycaemic effects induced by the compound in dams and in offspring.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose Monohydrate, Sodium lauryl sulphate, Povidone, Sodium starch glycolate, Magnesium Stearate, Microcrystalline cellulose.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Special precautions for disposal and other handling
No special requirements.

7. Manufactured In India By:
TAJ PHARMACEUTICALS LTD.
Mumbai, India
Unit No. 214.Old Bake House,
Maharashtra chambers of Commerce Lane,
Fort, Mumbai - 400001
at:Gujarat, INDIA.
Customer Service and Product Inquiries:
1-800-TRY-FIRST (1-800-222-434 & 1-800-222-825)
Monday through Saturday 9:00 a.m. to 7:00 p.m. EST
E-mail: tajgroup@tajpharma.com