SUMMARY OF PRODUCT CHARACTERISTICS

Glimepiride Teva 1 mg
Glimepiride Teva 2 mg
Glimepiride Teva 3 mg
Glimepiride Teva 4 mg

Tablets

1. NAME OF THE MEDICINAL PRODUCT

Glimepiride Teva 1 mg
Glimepiride Teva 2 mg
Glimepiride Teva 3 mg
Glimepiride Teva 4 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of Glimepiride Teva 1 mg contains 1 mg glimepiride.
Each tablet of Glimepiride Teva 2 mg contains 2 mg glimepiride.
Each tablet of Glimepiride Teva 3 mg contains 3 mg glimepiride.
Each tablet of Glimepiride Teva 4 mg contains 4 mg glimepiride.

Excipient with known effect:
Each tablet of Glimepiride Teva 1 mg contains 141.815 mg lactose monohydrate.
Each tablet of Glimepiride Teva 2 mg contains 139.4 mg lactose monohydrate.
Each tablet of Glimepiride Teva 3 mg contains 139.8 mg lactose monohydrate.
Each tablet of Glimepiride Teva 4 mg contains 138.8 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Glimepiride Teva 1 mg: Mottled pink, round tablet, bisected on both sides. One side of the tablet debossed with “9” on one side of score and “3” on the other. The other side of the tablet debossed with “72” on one side of score and “54” on the other.

Glimepiride Teva 2 mg: Mottled green, round tablet, bisected on both sides. One side of the tablet debossed with “9” on one side of score and “3” on the other. The other side of the tablets debossed with “72” on one side of score and “55” on the other.

Glimepiride Teva 3 mg: Light yellow to yellow, round tablet, bisected on both sides. One side of the tablet debossed with “G” on one side of score and “3” on the other.

Glimepiride Teva 4 mg: Mottled light blue, round tablet, bisected on both sides. One side of the tablet debossed with “9” on one side of score and “3” on the other. The other side of the tablet debossed with “72” on one side of score and “56” on the other.

The tablets can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Glimepiride Teva is indicated for non-insulin-dependent diabetes melitus (adult-onset diabetes, type II diabetes), when diet, regular physical exercise and weight reduction alone cannot maintain therapeutically suitable blood glucose levels.

4.2 Posology and method of administration

Glimepiride Teva should be administered with breakfast or the first main meal of the day.

The recommended starting dose of glimepiride is 1 mg or 2 mg once daily. Patients at increased risk for hypoglycemia (e.g., the elderly or patients with renal impairment) should be started on 1 mg once daily (see section 4.4).

After reaching a daily dose of 2 mg, further dose increases can be made in increments of 1 mg or 2 mg based upon the patient's glycemic response. Uptitration should not occur more frequently than every 1 to 2 weeks. A conservative titration scheme is recommended for patients at increased risk for hypoglycemia (see section 4.4).

The maximum recommended dose is 8 mg once daily.

Patients being transferred to glimepiride from longer half-life sulfonylureas (e.g., chlorpropamide) may have overlapping drug effect for 1 to 2 weeks and should be appropriately monitored for hypoglycemia.

When colesevelam is coadministered with glimepiride, maximum plasma concentration and total exposure to glimepiride is reduced. Therefore, glimepiride should be administered at least 4 hours prior to colesevelam.

4.3 Contraindications

Glimepiride is contraindicated in patients with the following conditions:
- hypersensitivity to the active substance, other sulfonylureas or sulfonamides or to any of the excipients listed in section 6.1.
- 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.

4.4 Special warnings and precautions for use

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 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 of 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, require immediate medical treatment and occasionally hospitalisation.

Factors favouring hypoglycemia 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,
- overdose with glimepiride,
- 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 (see section 4.5).

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 anemia. 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.

Excipients

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

If glimepiride 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 metabolised 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:
- 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.

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 gastrointestinal 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.

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
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 (see section 5.3).
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.

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 glimepiride.

Fertility

No data on fertility is available.

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 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.

4.8 Undesirable 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
Rare: thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, erythropenia, hemolytic anemia 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 dyspnea, fall in blood pressure and sometimes shock.
Not known: cross-allergenicity with sulfonylureas, sulfonamides or related substances is possible.

Metabolism and nutrition disorders
Rare: hypoglycemia
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 dose (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
Rare: dysgeusia.
Very rare: nausea, vomiting, diarrhea, abdominal distension, abdominal discomfort and abdominal pain, which seldom lead to discontinuation of therapy.

Hepatobiliary disorders
Very rare: hepatic function abnormal (e.g., with cholestasis and jaundice), hepatitis and hepatic failure.
Not known: hepatic enzymes increased.

Skin and subcutaneous tissue disorders
Rare: alopecia.
Not known: hypersensitivity reactions of the skin may occur such as pruritus, rash, urticaria and photosensitivity.

Investigations
Rare: weight gain.
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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il.

4.9 Overdose

Symptoms
After ingestion of an overdose 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, co-ordination problems, sleepiness, coma and convulsions.

Acute overdosage as well as long term treatment with too high a dose of glimepiride may lead to severe life-threatening hypoglycemia.

Management
As soon as an overdose of glimepiride has been discovered, a physician must be notified without delay. The patient must immediately take sugar, if possible, in the form of glucose, unless a physician has already undertaken responsibility for treating the overdose. Careful monitoring is essential until the physician is confident that the patient is out of danger. It must be remembered that hypoglycemia may recur after initial recovery.

In case of mild episode of hypoglycemia, treatment primarily consists of oral glucose. Severe hypoglycemic reactions requires immediate treatment.

Significant overdoses of glimepiride and severe reactions with signs such as loss of consciousness or other serious neurological disorders are medical emergencies and require immediate treatment. Admission to hospital in an intensive care department is indicated.

If large quantities of glimepiride have been ingested, gastric lavage is indicated within 1 hour of ingestion, followed by activated charcoal, sodium-sulphate and octreotide. 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 for at least 24 hours.
Alternatively, in adults, administration of glucagon may be considered. Further treatment should be symptomatic.

In severe cases with a protracted course, hypoglycemia, or the danger of slipping back into hypoglycemia, may persist for several days.

Pediatric population
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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Blood glucose lowering drugs, excl. insulins: Sulfonylureas.
ATC code: A10B B12

Glimepiride is an orally active hypoglycemic substance belonging to the sulfonylurea group. It may be used in non-insulin dependent diabetes mellitus.

Mechanism of action
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 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 dose 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 dose 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.

5.2 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 litres) 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 radiolabelled 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 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.

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 (hypoglycemia) 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 hypoglycemic effects induced by the compound in dams and in offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Sodium starch glycolate
Microcrystalline cellulose
Povidone
Magnesium stearate

Glimepiride Teva 1 mg: Iron oxide red (E172)
Glimepiride Teva 2 mg: Iron oxide yellow (E172), Indigo carmine aluminium lake (E132)
Glimepiride Teva 3 mg: Iron oxide yellow (E172)
Glimepiride Teva 4 mg: Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25ºC.

6.5 Nature and contents of container

Each package contains 30 tablets in blister pack.

6.6 Special precautions for disposal

No special requirements.

7. LICENCE HOLDER AND MANUFACTURER

Teva Israel Ltd.,
124 Dvora HaNevi'a St., Tel Aviv 6944020, Israel.

8. REGISTRATION NUMBERS

Glimepiride Teva 1 mg: 151.15.33843
Glimepiride Teva 2 mg: 151.16.33859
Glimepiride Teva 3 mg: 151.17.33870
Glimepiride Teva 4 mg: 151.18.33871

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