COMPANY CORE DATA SHEET
No. 0089-02
14 April 2011

GLURENORM

Composition
1 tablet contains 30 mg
1-Cyclohexyl-3-[[p-[2-(3,4-dihydro-7-methoxy-4,4-dimethyl - 1,3-dioxo-2-(1H)-
isoquinolyl]=ethyl][phenyl]sulfonyl]urea (= gliquidone)

Excipients: lactose, maize starch dried, soluble maize starch, magnesium stearate

Indications
Treatment of patients with type 2 diabetes mellitus who do not respond adequately to
exercises and dietary control.

Dosage and administration
The physician's instructions as to dosage and diet should be strictly observed. The patient
should not discontinue treatment without consulting the physician.

Initial therapy
Treatment with Gliquidone (GLURENORM) is usually initiated with ½ tablet (15 mg) at
breakfast. If this proves inadequate, the dose should be gradually increased, upon the
physician’s instruction. It should be noted that total daily doses over 4 tablets (120 mg) do not
usually produce further improvement in control.

GLURENORM tablets should be taken at the beginning of the meal. After intake of the
GLURENORM tablet, the meal should not be skipped.

If treatment with ½ a tablet at breakfast proves inadequate, the dose should be gradually
increased, upon the physician's instructions. When not more than two tablets (60 mg) are
prescribed, the daily dose of GLURENORM may be taken as a single dose at breakfast.

When higher daily doses are required, better control can be achieved, however, with a twice or
three-time daily dosage. In that case, the highest dosage should be taken at breakfast. Total
daily doses over 4 tablets (120 mg) do not usually produce further improvement in glycaemic
control. Therefore, the maximum recommended daily dose is 4 tablets (120 mg).

Dosing in patients with renal impairment
Based on pharmacokinetic data only about 5% of the metabolites of administered
GLURENORM is excreted via the kidneys. In a clinical study with diabetic patients suffering
from stage 1 to 4 of renal impairment - compared to those without renal impairment - a daily
GLURENORM dose of 40 - 50 mg on average had very similar effects on blood glucose
profiles, no accumulation or hypoglycaemic symptoms were observed. Thus, no dose
adjustment in patients with renal impairment is required.

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GREEN (CCDS 0089-02 - Posology Update Proposed)
Dosing in patients with hepatic impairment
Daily GLURENORM® doses higher than 75 mg require careful medical control. Since 95% of administered GLURENORM® is metabolized by the liver and excreted by the biliary system, GLURENORM® should not be given in patients with moderate and severe hepatic impairment (please refer to “contraindications”).

In two clinical studies with diabetic patients suffering from different grades of liver impairment (including active liver cirrhosis with portal hypertension) GLURENORM did not cause further deterioration of liver function, the number of side effects was low and no marked hypoglycaemic reactions were observed.

Paediatric and adolescents population
GLURENORM is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

Transfer
(From other oral antidiabetic agents with similar mode of action).
The patient's current state of diabetic control will determine the initial dosage. When changing over from other antidiabetic agents it should be noted that the effect of 1 Gliquidone (GLURENORM ) tablet (30 mg) is approximately equivalent to 1000 mg tolbutamide.
The initial dose is usually ½ to 1 tablet. The dosage should be increased only on medical advice.
When not more than two tablets (60 mg) are prescribed, the daily dose of GLURENORM may be taken as a single dose at breakfast.
Better control can be achieved, however, with a twice or three times daily dosage.
Gliquidone (GLURENORM) tablets should be taken at the beginning of the meal.

Contraindications
GLURENORM should not be used in Type 1 diabetes mellitus, diabetic coma and pre-coma, diabetes complicated by acidosis and ketosis, pancreatic resection, during severe infections, before surgery, severe hepatic impairment, acute intermittent (hepatic) porphyria, allergy to sulfonamides.

In case of rare hereditary conditions that may be incompatible with an excipient of the product (please refer to “special warnings and precautions”) the use of the product is contraindicated.

Special warnings and precautions
Treatment of diabetes requires regular medical attention. Caution should be exercised, particularly during the dose titration phase or upon transfer from another preparation (please refer to “effects on ability to drive and use machines”).

Although only about 5% of GLURENORM is excreted by the kidneys and GLURENORM is thus generally well tolerated by patients with renal impairment, in the presence of severe renal impairment particularly careful medical control is necessary. Should signs of hypoglycaemia such as fever, skin rashes, or nausea occur during treatment, the physician should be consulted without delay. Should a patient become pregnant during treatment, GLURENORM should be discontinued and medical advice sought immediately.

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Oral antidiabetic therapy should not be used to replace dietetic therapy, since in diabetes the diet is designed primarily to control the patient's weight and is independent of any drug treatment which the physician may prescribe. The omission of a meal or non-adherence to the physician's dosage recommendations may considerably reduce the blood sugar level and possibly lead to loss of consciousness e.g. if the tablet is taken before a meal instead at starting the meal, the effect on blood glucose is usually more prominent increasing the risk of hypoglycaemia.

Should clinical signs of hypoglycaemia occur, the immediate oral intake of sugar containing foods is the appropriate action. If the hypoglycaemic state persists, immediate intensified treatment and monitoring is necessary.

Physical exertion may intensify the hypoglycaemic effects.

Alcohol or stress may enhance or reduce the blood glucose lowering effect of sulfonylureas.

Treatment of patients suffering from glucose-6-phosphate-dehydrogenase deficiency with sulfonylureas may lead to haemolytic anaemia. As GLURENORM belongs to the class of sulfonylureas, it should be used with caution in patients with glucose-6-phosphate-dehydrogenase deficiency and an alternative therapy should be considered.

Special care should be observed in concomitant use of GLURENORM with many other medications especially those which increase the blood glucose lowering of GLURENORM (please refer to “Interactions”).

One tablet of 30 mg contains 134.6 mg lactose, resulting in 538.4 mg lactose per maximum recommended daily dose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Interactions**

A number of drugs are known to influence glucose metabolism, possible interactions should therefore be taken into account by the physician.

Pharmacokinetic and pharmacodynamic drug-drug interactions with GLURENORM may alter the blood glucose lowering effect. Sulfonylureas are extensively bound to plasma proteins and therefore can be displaced by co-medications also exhibiting high protein binding.

The concomitant use of the following substances may increase the hypoglycaemic effect of GLURENORM: ACE inhibitors, allopurinol, analgesics and nonsteroidal antiphlogistics, antifungals, chloramphenicol, clarithromycin, clofibrate, coumarin anticoagulants, fluoroquinolones, heparin, MAO inhibitors, sulfipyrazone, sulfinpyrazone, tetracyclines and tricyclic antidepressants, cyclophosphamide and derivatives, insulin and other oral antidiabetics with and without intrinsic risk of hypoglycaemia.

Beta-receptor blocking agents, other sympatholytics (including clonidine), reserpine and guanethidine may possibly enhance the hypoglycaemic effect and also mask symptoms of hypoglycaemia.
The concomitant use of the following substances may reduce the hypoglycaemic effect of GLURENORM: aminoglutethimide, corticosteroids, diazoxide, oral contraceptives, sympathomimetics, rifamycins, thiazide and loop diuretics, thyroid hormones, glucagon, phenothiazines and nicotinic acid. Barbiturates, rifampicin and phenytoin may possibly reduce the hypoglycaemic effect of GLURENORM by inducing liver enzymes.

Reduced or enhanced hypoglycaemic effects of GLURENORM have been described for H2 receptor antagonists (cimetidine, ranitidine) and alcohol.

**Fertility, pregnancy and lactation**
There are no studies for glitizone in pregnant or lactating women. Glitizone was not teratogenic in animal studies. However, embryotoxic effects were observed in rabbits at high doses leading to permanent hypoglycaemia (please refer to “toxicology”).

It is not known, whether glitizone or its metabolites are excreted in human milk.

In pregnant diabetics, a particularly close and intensive control of plasma glucose concentration is necessary. No satisfactory control of the carbohydrate metabolism is possible with oral antidiabetic agents in pregnant women.

For that reason GLURENORM should not be used in pregnant or lactating women. Should a patient become pregnant or intend to become pregnant during treatment, GLURENORM should be discontinued and treatment should be switched to insulin.

Clinical and non-clinical studies on the influence of GLURENORM on fertility are not available.

**Effects on ability to drive and use machines**
No studies on the effects on the ability to drive and use machines have been performed. However, patients should be advised that they may experience somnolence, dizziness and accommodation disorders or other clinical signs of hypoglycaemia during treatment with GLURENORM. Therefore, caution should be recommended when driving a car or operate machinery. If patients experience hypoglycaemic effects they should avoid potentially hazardous tasks such as driving or operate machinery.

**Side effects**
Based on clinical trial data and post-marketing experience with GLURENORM the following side effects may occur with hypoglycaemia as most common side effect.

**Blood and lymphatic system disorders**
- agranulocytosis
- leucopenia
- thrombocytopenia

**Metabolism and nutrition disorders**
- hypoglycaemia
- decreased appetite

**Nervous system disorders**
- somnolence
- dizziness

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- headache
- paraesthesia

Eye disorders
- accommodation disorders

Cardiac disorders
- angina pectoris
- extrasystoles

Vascular disorders
- cardiovascular insufficiency
- hypotension

Gastrointestinal disorders
- diarrhoea
- vomiting
- abdominal discomfort
- nausea
- constipation
- dry mouth

Hepato-biliary disorders
- cholestasis

Skin and subcutaneous tissue disorders
- rash
- pruritus
- Stevens-Johnson Syndrome
- photosensitivity reaction
- urticaria

General disorders and administration site conditions
- chest pain
- fatigue

Overdose
Overdose of sulfonylureas may cause hypoglycaemia.

Symptoms
Hypoglycaemic reactions (also prolonged) as unconsciousness, tachycardia, moist skin, motoric restlessness and hyperreflexia; gastric disorders may occur.

Therapy
Immediate oral or i.v. administration of glucose. Control of plasma glucose concentration and further administration of glucose can be required.

Pharmacological properties
GLURENORM is a second generation blood sugar lowering sulfonylurea drug. It exhibits pancreatic and extrapancreatic effects.

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At the pancreas, gliclazide stimulates the release of insulin from the pancreatic beta cells by potentiation of glucose-mediated insulin release.

In animal studies it seems to reduce the insulin resistance in liver and adipose tissue by increase of insulin receptors and by stimulation of post-receptor mechanism induced by insulin.

The blood glucose lowering effect begins 60 to 90 minutes after oral administration and reaches its maximum 2 to 3 hours after intake of the drug with duration of approximately 8 - 10 hours. Gliclazide can thus be considered as a short acting sulfonyleurea and is therefore suitable in Type 2 diabetic patients with increased risk of hypoglycaemia, e.g. the elderly and patients with renal impairment.

Since renal elimination of gliclazide is negligible, GLURENORM may be used in patients with renal impairment or diabetic nephropathy.

In a limited number of diabetic patients eligible for sulfonyleurea therapy, who also have concomitant liver diseases, gliclazide has proven to be effective and safe. Only elimination of metabolically inactive metabolites was delayed.

However, severe hepatic impairment represents a contraindication (please refer to “contraindications”).

During a clinical study with GLURENORM treatment over a period of 18 and 30 months the mean body weight did not increase but rather decreased by 1 - 2 kg. In a comparative study with several sulfonyleureas, patients under GLURENORM therapy had no significant change of body weight after 1 year of treatment.

**Pharmacokinetics**

**Absorption:**
Following oral administration of single doses of 15 and 30 mg, gliclazide is rapidly and almost completely absorbed (80 - 95%) by the gastro-intestinal tract showing a mean peak plasma concentration of 0.65 µg/mL (range: 0.12 - 2.14 µg/mL). The median time to reach the maximum plasma concentration was 2.25 hours (range: 1.25 - 4.75 hours).

Following a two-compartmental model, the resulting mean area under the concentration-time curve from zero to infinity (AUC_{0-∞}) of gliclazide is 5.1 µg h/mL (range: 1.5 - 10.1 µg h/mL).

No differences in the plasma levels between diabetics and healthy subjects have been reported.

**Distribution:**
Gliclazide is highly bound to plasma proteins (> 99%). There are no clinical data available about the passing of gliclazide or its metabolites across the hematocerephalic barrier or through the placenta. Non-clinical data indicate that gliclazide and its metabolites do not pass across these barriers. No data about the presence of gliclazide in human breast milk are available.

**Metabolism:**
Gliquidone is completely metabolised principally by hydroxylation and demethylation in the liver. The blood metabolites of gliquidone show no or very little pharmacological activity as compared to the parent drug.

Elimination:
Gliquidone is mainly excreted as metabolites through the bile with the faeces. Studies with 15 mg of the radiolabeled drug (¹⁴C) demonstrated that approximately 86% of the total radioactivity could be recovered in the faeces after oral administration. Independently from the mode of administration and the amount of substance, only a small proportion of the gliquidone dose is excreted via the kidneys and can be found as metabolised drug in the urine (approximately 5%). Even after repeated doses of gliquidone, the renal excretion remains minimal. Following a two-compartmental model, the mean dominant elimination half-life (t₁/₂a) of gliquidone is 1.2 hours (range: 0.4 - 3.0 hours), whereas its mean terminal elimination half-life (t₁/₂b) is approximately 8 hours (range: 5.7 - 9.4 hours).

Pharmacokinetics in special population groups:

Elderly population:
The pharmacokinetics characteristics are essentially equivalent in elderly and middle-aged people.

Renal or hepatic impairment:
It has been observed that the metabolism of gliquidone is maintained in patients with hepatic insufficiency. Therefore, gliquidone can be safely used in patients with liver disease. On the other hand, taking into account that most of the drug is excreted via bile in the faeces, no accumulation of the drug in patients with impaired renal function occurs. Consequently, it can be safely administered to patients at risk of chronic nephropathy.

Toxicology
Single- and repeat-dose toxicity studies showed that the toxicity of gliquidone is very low.

Oral LD₅₀ values were > 10 g/kg in mice, rats, rabbits and dogs. After i.v. administration, LD₅₀ values were 144 - 180 mg/kg in rats.

Oral repeat-dose toxicity studies in rats at dose levels up to 200 mg/kg/day (dietary admixture, 18 months) and 1000 mg/kg/day (gavage, 6 months) did not reveal any relevant adverse effects. Also in dogs, oral administration of up to 20 mg/kg/day for 18 months did not reveal any relevant adverse effects.

In in vitro and in vivo genotoxicity studies (Ames assay, bone marrow micronucleus test in rats, Chinese hamsters bone marrow and spermatogonia test), gliquidone did not show any mutagenic or clastogenic effects. Gliquidone was also negative in carcinogenicity studies in mice and rats.

Gliquidone was not teratogenic in rats and rabbits. In rabbits, an increase in the resorption rate was observed at ≥ 50 mg/kg/day attributed to permanent hypoglycaemia in the pregnant females.

Availability

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PT. Boehringer Ingelheim Indonesia

Tablets
Box contains 10 strips of 10 tablets

Only on doctor's prescription.
Hanya dengan resep dokter.

Store in below 30 °C.
Store in a safe place, out of the reach of children.

Manufactured by:
PT. Boehringer Ingelheim Indonesia
Bogor, Indonesia

Under license from:
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

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