GLUCONORM SR 1000MG

1. Name of the medicinal product
Glucornorm Ipca 1000 mg film coated tablets

2. Qualitative and quantitative composition
Glucornorm Ipca 1000mg film-coated tablets:

One film-coated tablet contains 1000mg Glucornorm hydrochloride corresponding to 780 mg Glucornorm base.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form
Film-coated tablet.

Glucornorm Ipca 1000mg film-coated tablets:

White to off-white, oval shaped 19.00mm x 10.50mm biconvex film-coated tablets debossed with '10' and '00' on either side of deep notch on one side and breakline on other side. The tablet can be divided into equal doses.

4. Clinical particulars
4.1 Therapeutic indications
Treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

• In adults, Glucornorm may be used as monotherapy or in combination with other oral antidiabetic agents or with insulin.

• In children from 10 years of age and adolescents, Glucornorm may be used as monotherapy or in combination with insulin.

A reduction of diabetic complications has been shown in overweight type 2 diabetic adult patients treated with Glucornorm as first-line therapy after diet failure (see section 5.1).

4.2 Posology and method of administration
Posology

Adults with normal renal function (GFR≥ 90 mL/min)

Monotherapy and combination with other oral antidiabetic agents:

Glucornorm Ipca 500 mg film-coated tablets and Glucornorm Ipca 850 mg film-coated tablets

The usual starting dose is 500 mg or 850 mg Glucornorm hydrochloride 2 or 3 times daily given during or after meals. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability.

The maximum recommended dose of Glucornorm hydrochloride is 3 g daily, taken as 3 divided doses.

Glucornorm Ipca 1000 mg film-coated tablets

For patients taking high doses of Glucornorm hydrochloride (2 to 3 g daily), two Glucornorm 500 mg tablets may be replaced with Glucornorm 1000 mg film-coated tablets. The maximum recommended daily dose is 3 g Glucornorm hydrochloride divided into 3 daily doses.

If transfer from another oral antidiabetic agent is intended: discontinue the other agent and initiate Glucornorm at the dose indicated above.

Combination with insulin:

Glucornorm and insulin may be used in combination therapy to achieve better blood glucose control. Glucornorm hydrochloride is given at the usual starting dose of 500 mg or 850 mg 2 or 3 times daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

Elderly:

Due to the potential for decreased renal function in elderly subjects, the Glucornorm dosage should be adjusted based on renal function. Regular assessment of renal function is necessary (see section 4.4).

Renal impairment:

GFR should be assessed before treatment with Glucornorm -containing medicinal products begins and at least every year thereafter. In patients with increased risk of further impairment of renal function and in elderly, renal function should be assessed more often, eg. every 3-6 months.

GFRml/min	Total maximum daily dose (to be divided into 2-3 doses daily)	To consider
60-89	3000 mg	Dose reduction may be considered in relation to declining renal function.
45-59	2000 mg	Factors that may increase the risk of lactate acidosis (see section 4.4) should be– reviewd before considering initiation of Glucornorm .The starting dose is at most half of the maximum dose.
30-44	1000 mg	
< 30	-	Glucornorm is contraindicated.

Children and adolescents:

Paediatric population

Monotherapy and combination with insulin

• Glucornorm can be used in children from 10 years of age and adolescents.

• The usual starting dose is 500 mg or 850 mg Glucornorm hydrochloride once daily, given during or after meals.

After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability. The maximum recommended dose of Glucornorm hydrochloride is 2 g daily, taken as 2 or 3 divided doses.

4.3 Contraindications

• Hypersensitivity to Glucornorm or to any of the excipients listed in section 6.1.

• Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).

• Diabetic pre-coma.

• Sever renal failure (GFR < 30 ml/min).

• Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock.

• Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock.

• Hepatic insufficiency, acute alcohol intoxication, alcoholism.

4.4 Special warnings and precautions for use

Lactic acidosis:

Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis.Glucornorm accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), Glucornorm should be temporarily discontinued and contact with a health care professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated with caution in Glucornorm -treated patients. Other risk factors for lactic acidosis are excessive alcohol intake; hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any condition associated with hypoxia as well as concomitant use of medicinal products that may cause lactic acidosis (see sections 4.3 and 4.5).

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea muscle cramps, abdominal pain, asthenia, and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking Glucornorm and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (5 mmol/l), and an increased anion gap and lactate/pyruvate ratio.

Renal function:

GFR should be assessed before treatment initiation and regularly thereafter, see section 4.2 Glucornorm is contraindicated in patients with

GFR <30 ml / min and should be temporarily discontinued in presence of conditions that alter renal function, see section 4.3.

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with chronic stable heart failure, Glucornorm may be used with regular monitoring of cardiac and renal function.

For patients with acute and unstable heart failure, Glucornorm is contraindicated (see section 4.3).

Administration of iodinated contrast media:

Intravascular administration of iodinated contrast agents may lead to contrast-induced nephropathy resulting in Glucornorm accumulation and increased risk of lactate acidosis. Glucornorm should be discontinued before or at the time of imaging procedure and should not be reinstated until at least 48 hours after, provided that renal function has been evaluated and demonstrated to be stable (see section 4.2 and 4.5).

Surgery:

Glucornorm must be discontinued at the time of surgery under general, spinal or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been reevaluated and found to be stable.

Paediatric population:

The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with Glucornorm is initiated.

No effect of Glucornorm on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of Glucornorm on these parameters in Glucornorm -treated children, especially prepubescent children, is recommended.

Children aged between 10 and 12 years:

Only 15 subjects aged between 10 and 12 years were included in the controlled clinical studies conducted in children and adolescents. Although efficacy and safety of Glucornorm in these children did not differ from efficacy and safety in older children and adolescents, particular caution is recommended when prescribing to children aged between 10 and 12 years.

Other precautions:

All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.

The usual laboratory tests for diabetes monitoring should be performed regularly.

Glucornorm alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics (e.g. sulfonylureas or meglitinides).

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended:

Alcohol:

Alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting malnutrition or hepatic impairment.

Iodinated contrast agents

Glucornorm must be discontinued prior to, or at the time of the test and not be restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see section 4.2 and 4.4).

Combinations requiring precautions for use:

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with Glucornorm , close monitoring of renal function is necessary.

Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids (systemic and local routes) and sympathomimetics):

More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the Glucornorm dosage during therapy with the respective medicinal product and upon its discontinuation.

Organic cation transporters (OCT)

Glucornorm is a substrate of both transporters OCT1 and OCT2.

Co-administration of Glucornorm with

• Inhibitors of OCT1 (such as verapamil) may reduce efficacy of Glucornorm .

• Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of Glucornorm .

• Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of Glucornorm and thus lead to an increase in Glucornorm plasma concentration.

• Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of Glucornorm .

Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with Glucornorm , as Glucornorm plasma concentration may increase. If needed, dose adjustment of Glucornorm may be considered as OCT inhibitors/inducers may alter the efficacy of Glucornorm .

4.6 Fertility, pregnancy and lactation

Pregnancy

Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased risk of congenital abnormalities and perinatal mortality.

A limited amount of data from the use of Glucornorm in pregnant women does not indicate an increased risk of congenital abnormalities. Animal studies do not indicate harmful effects with respect to pregnancy, embryonic or fetal development, parturition or postnatal development (see section 5.3).

When the patient plans to become pregnant and during pregnancy, it is recommended that diabetes is not treated with Glucornorm but insulin be used to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the fetus.

Breast-feeding

Glucornorm is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breastfeeding is not recommended during Glucornorm treatment. A decision on whether to discontinue breast-feeding should be made, taking into account the benefit of breastfeeding and the potential risk to adverse effects on the child. .

Fertility

Fertility of male or female rats was unaffected by Glucornorm when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

4.7 Effects on ability to drive and use machines

Glucornorm monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.

However, patients should be alerted to the risk of hypoglycaemia when Glucornorm is used in combination with other antidiabetic agents (e.g. sulfonylureas, insulin or meglitinides).

4.8 Undesirable effects

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take Glucornorm in 2 or 3 daily doses and to increase slowly the doses.

The following adverse reactions may occur under treatment with Glucornorm . Frequencies are defined as follows:

very common: ≥ 1/10; common ≥ 1/100, <1/10; uncommon ≥ 1/1,000, <1/100; rare ≥ 1/10,000, <1/1,000; very rare <1/10,000.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Metabolism and nutrition disorders:

Very rare:

Lactic acidosis (see section 4.4).

Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of Glucornorm . Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.

Nervous system disorders:

Common: Taste disturbance

Gastrointestinal disorders:

Very common: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that Glucornorm be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders:

Very rare: Isolated reports of liver function tests abnormalities or hepatitis resolving upon Glucornorm discontinuation.

Skin and subcutaneous tissue disorders:

Very rare: Skin reactions such as erythema, pruritus, urticaria

Paediatric population

In published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year, adverse event reporting was similar in nature and severity to that reported in adults.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after approval is of great importance. It allows continuous monitoring of the benefit-risk balance of the drug. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose
Hypoglycaemia has not been seen with Glucornorm hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of Glucornorm or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and Glucornorm is haemodialysis.

5. Pharmacological properties
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Blood glucose lowering drugs. Biguanides; ATC code: A10BA02

Mechanism of action

Glucornorm is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Glucornorm may act via 3 mechanisms:

1) reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.

2) in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization.

3) and delay of intestinal glucose absorption.

Glucornorm stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Glucornorm increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.

Pharmacodynamic effects

In clinical studies, use of Glucornorm was associated with either a stable body weight or modest weight loss.

In humans, independently of its action on glycaemia, Glucornorm has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: Glucornorm reduces total cholesterol, LDL cholesterol and triglyceride levels.

Clinical efficacy:

The prospective randomised study (UKPDS) has established the long-term benefit of intensive blood glucose control in adult patients with type 2 diabetes.

Analysis of the results for overweight patients treated with Glucornorm after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the Glucornorm group (29.8 events/1000 patient-years) versus diet alone (43.3 events/1000 patient-years), p=0.0023, and versus the combined sulfonylurea and insulin monotherapy groups (40.1 events/1000 patient-years), p=0.0034;

- a significant reduction of the absolute risk of diabetes-related mortality: Glucornorm 7.5 events/1000 patient-years, diet alone 12.7 events/1000 patientyears, p=0.017;

- a significant reduction of the absolute risk of overall mortality: Glucornorm 13.5 events/1000 patient-years versus diet alone 20.6 events/1000 patient-years (p=0.011), and versus the combined sulfonylurea and insulin monotherapy groups 18.9 events/1000 patient-years (p=0.021);

- a significant reduction in the absolute risk of myocardial infarction: Glucornorm 11 events/1000 patient-years, diet alone 18 events/1000 patient-years (p=0.01).

Benefit regarding clinical outcome has not been shown for Glucornorm used as secondline therapy, in combination with a sulfonylurea.

In type 1 diabetes, the combination of Glucornorm and insulin has been used in selected patients, but the clinical benefit of this combination has not been formally established.

Paediatric population

Controlled clinical studies in a limited paediatric population aged 10-16 years treated during 1 year demonstrated a similar response in glycaemic control to that seen in adults.

5.2 Pharmacokinetic properties

Absorption:

After an oral dose of Glucornorm hydrochloride tablet, maximum plasma concentration (Cmax) is reached in approximately 2.5 hours (tmax). Absolute bioavailability of a 500 mg or 850 mg Glucornorm hydrochloride tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, Glucornorm absorption is saturable and incomplete. It is assumed that the pharmacokinetics of Glucornorm absorption is non-linear.

At the recommended Glucornorm doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are

generally less than 1 microgram/ml. In controlled clinical trials, maximum Glucornorm plasma levels (Cmax) did not exceed 5 microgram/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of Glucornorm . Following oral administration of a 850 mg tablet, a 40% lower plasma peak concentration, a 25% decrease in AUC (area under the curve) and a 35 minute prolongation of the time to peak plasma concentration were observed. The clinical relevance of these findings is unknown.

Distribution:

Plasma protein binding is negligible. Glucornorm partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (Vd) ranged between 63-276 l.

Metabolism:

Glucornorm is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination:

Renal clearance of Glucornorm is> 400 ml/min, indicating that Glucornorm is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of Glucornorm in plasma.

Characteristics in specific group of patients

Renal impairment

The available data in persons with moderate renal insufficiency are sparse and no reliable estimation of systemic Glucornorm exposure in this subgroup could be made compared to persons with normal renal function. Therefore, dose adjustment should be based on clinical efficacy / tolerability (see section 4.2).

Paediatric population

Single dose study: After single doses of Glucornorm hydrochloride 500 mg paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults.

Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg twice daily for 7 days in pediatric patients the peak plasma concentration (Cmax) and systemic exposure (AUC0-t) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who

received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

5.3 Preclinical safety data
Preclinical data reveal no special hazard for humans based on conventional studies on safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

6. Pharmaceutical particulars
6.1 List of excipients
Tablet core

Sodium Starch Glycolate (Type A)

Povidone K-30

Maize Starch

Colloidal Anhydrous Silica

Magnesium stearate

Film-coating hypromellose,

Isopropyl alcohol

Titanium dioxide E171

Purified Talc

Macrogol – 6000

Propylene glycol

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions

6.5 Nature and contents of container
Glucornorm Ipca 1000mg film coated Tablets are supplied in Clear

PVC/PVDC/Aluminium blister of 14 Tablets. Pack size: 14, 28, 56 or 84 Tablets

Glucornorm Ipca 1000mg film coated Tablets are supplied in HDPE bottle. Pack size: 30, 63, 210 and 1000 tablets

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder
Zolon Healthcare Limited located at No 11 planning way Ilupeju, Lagos
8. Marketing authorisation number(s)
NA

9. Date of first authorisation/renewal of the authorisation
NA

10. Date of revision of the text
NA