SUMMARY PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Gludown 850 Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet Contains:

Metformin Hydrochloride.....850mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-Coated Tablet

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, Gludown 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. Gludown 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 metformin as first line therapy after diet failure

4.2 Posology and method of administration

Adults with normal renal function: Monotherapy and combination with other oral antidiabetic agents: The usual starting dose is 500 mg or 850 mg metformin HCI 2 or 3 times daily given during or after meals. After 10 to 15 days lhe dose should be adjusted on lhe basis of blood glucose measurements. As tow Increase of dose may Improve gastrointestinal tolerability. The maximum recommended dose of metformin HCl is 3 g daily, taken as 3 divided doses.

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

receiving Gludown treatment may be safely switched to Gludown SR once daily at the same total daily dose, up to 2000mg once daily. Following a switch from Gludown to Gludown SR, glycemic control should be closely monitored and dosage adjustments made accordingly. If glycemic control is not achieved on. Gludown SR 2000mg once dally, a trial of Gludown SR 1000mg twice daily should be considered. Gludown SA tablets must be swallowed whole and never crushed or chewed. Combination with insulin: Metformin and insulin may be used in combination therapy to achieve better blood glucose control. Metformin HCI is given at the usual starting dose of 500mg or 850mg 2 or 3 times daily, while insulin dosage is 3 adjusted on the basis of blood glucose measurements.

Elderly: Dosage should be adjusted based on renal function. Regular assessment of renal function is necessity.

Paediatric population:

Monotherapy:-and combination with Insulin: Gludown can be used in children from 10 years of age and adolescents. The usual starting dose is 500mg or 850mg metformin HCI 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 metformin HCl is 2g daily, taken as 2 or 3 divided doses.

4.3 Contraindications

Hypersensitivity to metformin or to any of the excipients; Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis); Diabetic pre-coma; Severe 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: A very rare, but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin 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), metformin should be temporarily discontinued and health care professional cont. Drugs that can acutely Impair renal function (such as antihypertensives, diuretics and NSAIDs) should be initiated \\lith caution in metformin -treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic Insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting

and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis.

Renal function: GFR should be assessed before treatment initiation and regularly thereafter. Metformin is contraindicated in patients with GFR<30 mL/min and should be temporarily discontinued in the presence of conditions that alter renal function.

Cardiac function: Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, metformin may be used with a regular monitoring of cardiac and renal function. For patients with acute and unstable heart failure, metformin is contraindicated.

Iodinated contrast agents: IV administration of these may lead to contrast induced nephropathy, resulting in metformin accumulation and-an increased risk of lactic acidosis. Metformin should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable.

Surgery: Metformin 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 re-evaluated and found to be stable.

Paediatric population: The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin is initiated. No effect of metformin 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 metformin on these parameters in metformin-treated children, especially prepubescent children, Is recommended.

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. Metformin 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: Metformin must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after provided that renal function has been re-evaluated and found to be stable.

Combinations requiring precautions for use:

Some drugs can adversely affect renal function and Increase the risk of lactic acidosis, e.g. NSAIDs, including selective COX II inhibitors, ACE Inhibitors, .angiotensin II receptor antagonists and diuretics, especially loop diuretics. When using such products in combination with metformin, close monitoring of renal function is necessary. Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids and sympathomimetics): More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation. Organic cation transporters (OCT):

Metformin is a substrate of OCT1 and OCT2. Co-administration with Inhibitors of OCT1 (e.g.verapamil) may reduce efficacy. Inducers of OCT1 (e.g. rifampicin) may increase gastrointestinal

Absorption and efficacy. Inhibitors of OCT2 (e.g. cimetidine, dolutegravir, trimethoprim) may decrease renal elimination and lead to an increase In plasma concentration. Inhibitors of both OCT1 and OCT2 (e.g. crizotinib) may alter efficacy and renal elimination. Caution is therefore advised, especially in patients with renal impairment, when these drugs are co-administered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter its efficacy.

4.6 Pregnancy and lactation.

Pregnancy: Uncontrolled diabetes during pregnancy is associated with increased risk of congenital abnormalities and perinatal mortality. Data from the use of metformin in pregnant women does not indicate an increased risk of congenital abnormalities. During pregnancy, it is recommended that diabetes is not treated with metformin but insulin be used to maintain blood glucose levels as close to normal as possible.

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

Fertility: Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose.

4.7 Effects on ability to drive and use machines

Metformin hydrochloride has no or negligible influence on the ability to drive or use machines.

However Metformin hydrochloride may cause side effects (see section 4.8) influencing the capacity of reaction and the ability to drive and use machines.

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 metformin in 2 or 3 daily doses and to increase slowly the doses. The following adverse reactions may occur under treatment with metformin. Metabolism and nutrition disorders: Very rare: Lactic acidosis, decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. Nervous system disorders: Common: Taste disturbance. Gastrointestinal disorders; Very common: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite. Hepatobiliary disorders: Very rare: Isolated reports of liver functiontests abnormalities or hepatitis resolving upon metformin discontinuation. Skin and subcutaneous tissue disorders: Very rare: Skin reactions such as erythema, pruritus, urticarial.

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. Healthcare professionals are asked to report any suspected adverse reactions to the National Regulatory Authority via Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org/

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES.

5.1 Pharmacodynamic properties.

Metformin 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. Metformin 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) Delay of intestinal glucose absorption. It stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin increases the transport capacity of all known types of membrane glucose transporters (GLUTs). In clinical studies, use of metformin was associated with either a stable body weight or modest weight loss. In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin reduces total cholesterol, LDL cholesterol and triglyceride levels.

5.2 Pharmacokinetic properties.

Absorption: After an oral dose of metformin HCI tablet, maximum plasma concentration is reached in approx. 2.5 hours. Absolute bioavailability of a 500mg or 850mg metformin HCI tablet is approximately 50-60% in healthy subjects. Following a single oral dose of Metformin HCI SA tablet, Cmax is achieved with a median value of 7 hours (range 4 to B hours). Peak plasma levels are approximately 20% lower compared to the same dose of metformin HCI, however, the extent of absorption (AUG) is similar to metformin HCI. After an oral dose, the non-absorbed fraction recovered in feaces was 20-30%. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the recommended metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48hours and are generally less than 1 meg/mi. Food decreases the extent and slightly delays the absorption of metformin.

Distribution: Plasma protein binding is negligible. Metformin 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 ranged between 63-276 L:

Metabolism: Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination: Renal clearance of metformin is >400 ml/min, indicating that metformin 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 metformin in plasma.

5.3 Preclinical safety data.

Not Applicable

6. PHARMACEUTICAL PARTICULARS.

6.1 List of excipients.

- White Corn Starch
- Sodium Starch Glycolate
- Sodium Lauryl Sulfate
- Povidone K90
- Croscarmellose Sodium
- Purified Talc
- Magnesium Stearate
- Hydroxypropyl Methylcellulose (5 Cps)
- Ethyl Cellulose
- Titanium Dioxide
- Purified Talc
- Polyethylene Glycol 6000
- Isopropyl Alcohol
- Methylene Chloride

6.2 Incompatibilities

None known

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a dry place below 30°C Protect from light

Keep all medicines out of reach of children

6.5 Nature and contents of the container

Packed in blisters of 2 x 14's or 4 x 14's or 3x10's or 10 x 10's and contained in a unit box with literature insert.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING ADRESS

Company name: LABORATORY & ALLIED LTD Address: PLOT NO: 209/10349 OFF MOMBASA ROAD,

P.O BOX 42875, CODE 00100 NAIROBI

Country: KENYA

Telephone: + 254 – 20-8040306

Telefax: 254 – 020 - 8040309

E-Mail: info@laballied.com

Manufacturer

Company name: LABORATORY & ALLIED LTD Address: PLOT NO: 209/10349 OFF MOMBASA ROAD,

P.O BOX 42875, CODE 00100 NAIROBI

Country: KENYA

Telephone: + 254 – 20-8040306

Telefax: 254 – 020 - 8040309

E-Mail: info@laballied.com

8. MARKETING AUTHORIZATION NUMBER

H2022/CTD8725/18989

9. DATE OF FIRST AUTHORIZATION /RENEWAL OF THE AUTHORIZATION

2023 September 06

10. DATE OF REVISION OF TEXT

2023 September 06