Product Trade Name	**GLYFERON® 1000**
Drug Product name , strength and pharmaceutical form	**Metformin Hydrochloride 1000 mg, Film coated tablet**
Dossier ID	CPR-RAD- **SGLYFT1- RW**
Module 1.6.1	**Product information – Prescribing information (SmPC)**

MODULE 1 ADMINISTRATIVE INFORMATION AND PRODUCT INFORMATION

1.6 Product Information

1.6.1 Prescribing information (SmPC)

Enclosed is the section 1.5.1 Summary of Product Characteristics (SmPC) from the dossier CPR-RAD-SGLYFT1-EACv1.0.

Product Trade Name	**GLYFERON® 1000**
Drug Product name , strength and pharmaceutical form	**Metformin Hydrochloride 1000 mg, Film coated tablet**
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Module 1.6.1	**Product information – Prescribing information (SmPC)**

1.5.1 Summary of Product Characteristics

Full copy of the SmPC is attached hereafter.

MA information of the EAC countries: New MAA in procedure.

8. MARKETING AUHORISATION NUMBER

8.1. Burundi :

8.2. Kenya:

8.3. Rwanda:

8.4. Tanzania:

8.5. Uganda:

9. DATE OF FIRST REGISTRATION

9.1. Burundi:.

9.2. Kenya:

9.3. Rwanda:

9.4. Tanzania:

9.5. Uganda:

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Glyferon 1000

Metformin Hydrochloride

1.1. Strength

1000 mg

1.2. Pharmaceutical form

Film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1. Qualitative declaration

Metformin Hydrochloride DC granules equivalent with Metformin HCl.

For the full list of excipients, see section 6.1.

2.2. Quantitative declaration

Each tablet contains Metformin Hydrochloride DC granules 1162.79 mg equivalent with Metformin HCl 1000 mg.

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, Glyferon 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, Glyferon 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 mode of administration

4.2.1. Posology

Adults

Monotherapy and combination with other oral antidiabetic agents

The usual starting dose is 500 mg or 850 mg metformin 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 metformin hydrochloride 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.

Combination with insulin

Metformin and insulin may be used in combination therapy to achieve better blood glucose control. Metformin 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.

4.2.2. Special populations

Elderly

Due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary.

Patients with renal impairment

Metformin may be used in patients with moderate renal impairment, stage 3a (creatinine clearance [CrCl] 45– 59 mL/min or estimated glomerular filtration rate [eGFR] 45 -59 mL/min/1.73m2) only in the absence of other conditions that may increase the risk of lactic acidosis and with the following dose adjustments:
The starting dose is 500 mg or 850 mg metformin hydrochloride, once daily. The maximum dose is 1000 mg daily, given as 2 divided doses. The renal function should be closely monitored (every 3-6 months).
If CrCl or eGFR fall <45 ml/min or <45 ml/min/1.73m2 respectively, metformin must be discontinued immediately.

4.2.3. Pediatric population

Monotherapy and combination with insulin

- Glyferon can be used in children from 10 years of age and adolescents.
- The usual starting dose is 500 mg or 850 mg metformin 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 metformin hydrochloride is 2 g daily, taken as 2 or 3 divided doses.

4.2.4. Method of administration

Oral route

4.3. Contraindications

- Hypersensitivity to metformin or to any of the excipients listed in section 6.1.
- Diabetic ketoacidosis, diabetic pre-coma.
- Moderate (stage 3b) and severe renal failure or renal dysfunction (CrCl < 45 ml/min or eGFR < 45 ml/min/1.73m2).
- 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 warning and precautions for use

4.4.1. General information

Lactic acidosis

Lactic acidosis is a very rare, but serious (high mortality rate in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with impaired renal failure or acute worsening of renal function. Special caution should be paid to situations where renal function may become impaired, for example in case of dehydration (severe diarrhoea or vomiting), or when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID). In the acute conditions listed, metformin should be temporarily discontinued. Other associated risk factors should be considered to avoid lactic acidosis such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia (such as decompensated cardiac failure, acute myocardial infarction).

The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps, digestive disorders as abdominal pain and severe asthenia. Patients should be instructed to notify these signs immediately to
their physicians if they occur, notably if patients had a good tolerance to metformin before. Metformin should be discontinued, at least temporarily, until the situation is clarified. Reintroduction of metformin should then be discussed taking into account the benefit/risk ratio in an individual basis as well as renal function.

Diagnosis:

Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. In case of lactic acidosis, the patient should be hospitalised immediately.
Physicians should alert the patients on the risk and on the symptoms of lactic acidosis.

Renal function

As metformin is excreted by the kidney, creatinine clearance (this can be estimated from serum creatinine levels by using the Cockcroft-Gault formula) or eGFR should be determined before initiating treatment and regularly thereafter:

- at least annually in patients with normal renal function,
- at least two to four times a year in patients with creatinine clearance at the lower limit of normal and in elderly subjects.

In case CrCl is <45 ml/min (eGFR < 45 ml/min/1.73m2), metformin is contraindicated.
Decreased renal function in elderly subjects is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example in case of dehydration, or when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a non-steroidal anti-inflammatory drug (NSAID). In these cases, it is also recommended to check renal function before initiating treatment with metformin.

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.

Administration of iodinated contrast media

The intravascular administration of iodinated contrast media in radiologic studies can lead to renal failure. This may induce metformin accumulation and may increase the risk for lactic acidosis. In patients with eGFR > 60 ml/min/1.73 m2, metformin must be discontinued prior to, or at the time of the test and not be reinstituted until at least 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further.
In patients with moderate renal impairment (eGFR between 45 and 60 ml/min/1.73m2), metformin must be discontinued 48 hours before administration of iodinated contrast media and not be reinstituted until at least 48 hours afterwards and only after renal function has been re-evaluated and has not deteriorated further.

Surgery

Metformin must be discontinued 48 hours before elective surgery under general, spinal or peridural anaesthesia.
Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and only if normal renal function has been established.

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).

4.4.2. Pediatric 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.

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 metformin 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.

4.5. Interactions with other medicinal products and other forms of interactions

4.5.1. General information

Concomitant use not recommended

Alcohol

Acute alcohol intoxication is associated with an increased risk of lactic acidosis, particularly in case of fasting or malnutrition, hepatic insufficiency.
Avoid consumption of alcohol and alcohol-containing medicinal product.

Iodinated contrast media

Intravascular administration of iodinated contrast media may lead to renal failure, resulting in metformin accumulation and an increased risk of lactic acidosis.
In patients with eGFR > 60 ml/min/1.73m2,metformin must be discontinued prior to, or at the time of the test and not be reinstituted until at least 48 hours afterwards, and only after renal function has been re-evaluated and has not deteriorated further.
In patients with moderate renal impairment (eGFR between 45 and 60 ml/min/1.73m2), metformin must be discontinued 48 hours before administration of iodinated contrast media and not be reinstituted until at least 48 hours afterwards and only after renal function has been re-evaluated and has not deteriorated further.

Combinations requiring precautions for use

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 metformin dosage during therapy with the respective medicinal product and upon its discontinuation.

Diuretics, especially loop diuretics

They may increase the risk of lactic acidosis due to their potential to decrease renal function.

4.5.2. Additional information on special populations

See section 4.5.1

4.5.3. Pediatric population

See section 4.5.1

4.6. Fertility, pregnancy and lactation

4.6.1. 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 metformin 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 foetal development, parturition or postnatal development. When the patient plans to become pregnant and 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, to reduce the risk of malformations of the foetus.

4.6.2. Lactation

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.

4.6.3. 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 based on body surface area comparisons.

4.7. Effects on the ability to drive and use machines

Metformin 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 metformin 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 metformin in 2 or 3 daily doses and to increase slowly the doses.
The following adverse reactions may occur under treatment with metformin. 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.

• Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of metformin. 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 metformin 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 metformin discontinuation.

Skin and subcutaneous tissue disorders

Very rare

• Skin reactions such as erythema, pruritus, urticarial

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.

4.9. Overdose

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g, although lactic acidosis has occurred in such circumstances. High overdose of metformin 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 metformin is haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group and ATC code : Blood glucose lowering drugs. Biguanides. A10BA02

Mechanism of action

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:

- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilization.
- and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

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

Pharmacodynamic effects

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.

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 metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetes-related complication in the metformin 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: metformin 7.5 events/1000 patient-years, diet alone 12.7 events/1000 patient-years, p=0.017;
- a significant reduction of the absolute risk of overall mortality: metformin 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: metformin 11 events/1000 patient-years, diet alone 18 events/1000 patient-years (p=0.01).
- Benefit regarding clinical outcome has not been shown for metformin used as second-line therapy, in combination with a sulfonylurea.

In type 1 diabetes, the combination of metformin 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 metformin hydrochloride tablet, maximum plasma concentration (Cmax) is reached in approximately 2.5 hours (tmax). Absolute bioavailability of a 500 mg or 850 mg metformin 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, metformin absorption is saturable and incomplete. 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 48 hours and are generally less than 1 microgram/ml. In controlled clinical trials, maximum metformin plasma levels (Cmax) did not exceed 5 microgram/ml, even at maximum doses. Food decreases the extent and slightly delays the absorption of metformin. 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. 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 (Vd) 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.

Characteristics in specific groups of patients

- Renal impairment The available data in subjects with moderate renal insufficiency are scarce and no reliable estimation of the systemic exposure to metformin in this subgroup as compared to subjects with normal renal function could be made. Therefore, the dose adaptation should be made upon clinical efficacy/tolerability considerations.
- Paediatric population
  - Single dose study: After single doses of metformin 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 paediatric 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, repeateddose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

The active substance is 1000 mg Metformin HCl.

Other ingredients:

- sodium starch glycolate,
- povidone,
- colloidal silica,
- maize starch,
- magnesium stearate.

Excipients of coating:

- hypromellose,

- macrogol 6000,
- propylene glycol,
- talc,
- titanium dioxide.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store below 30°C.

6.5. Nature and contents of container

The tablets are packaged in blisters consisting of transparent polyvinyl chloride (PVC) coated with polyethylene (PE)- polyvinyl chloride (PVDC) and aluminium foil.

The blisters are placed with instruction leaflet in cardboard box.

6.6. Special precautions for disposal and other handlings

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER AND MANUFACURING SITE ADDRESS

7.1. Marketing Authorisation Holder

Dafra Pharma GmbH, Mühlenberg 7, 4052 Basel, Switzerland

7.2. Manufacturer

Bilim Pharmaceuticals, GOSB, 1900 Sokak, No: 1904,
41480 Gebze, Kocaeli/Turkey

8. MARKETING AUHORISATION NUMBER

See list of MAs per country

9. DATE OF FIRST REGISTRATION

See list of MAs per country

10. DATE OF REVISION OF TEXT

January 2019