SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

GLYFORMIN/Metformin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Metformin Hydrochloride BP 500.00 mg

3 PHARMACEUTICAL FORM

Film-Coated Tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Maturity onset diabetes when diet alone has failed.
Obese diabetic patients who are not well controlled on insulin but who are insulin-dependent may occasionally benefit when GLYFORMIN is used as an adjunct.

4.2 Posology and method of administration

Adults: Usually one 500mg tablet 3 times a day to be taken with meals. Should control of diabetes be incomplete a gradual increase in dosage to a maximum of 3g daily in divided doses taken together with meals may be instituted

This dosage regimen should not be increased above 3g.

Children: Not recommended

Elderly: Metformin, while indicated in the elderly should not be used when renal function is impaired
Route of adminstration: Oral

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
The drug is contraindicated in diabetic coma and ketoacidosis. Chronic liver disease. Impaired renal function. Cardiac failure. Recent myocardial infarction. Shock or pulmonary insufficiency and conditions associated with lactic acidosis. Acute or chronic alcoholism. Those conditions associated with hypoxaemia.
Acute conditions with the potential to alter renal function such as: severe infection or trauma, dehydration. Peripheral vascular disease. Hypersensitivity to the drug.
Severe renal failure (GFR < 30 mL/min).

4.4 Special warnings and precautions for use

Lactic acidosis

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 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 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 (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, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking metformin 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.

Patients with known or suspected mitochondrial diseases:

In patients with known mitochondrial diseases such as Mitochondrial Encephalopathy with Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome and Maternal inherited diabetes and deafness (MIDD), metformin is not recommended due to the risk of lactic acidosis exacerbation and neurologic complications which may lead to worsening of the disease.

In case of signs and symptoms suggestive of MELAS syndrome or MIDD after the intake of metformin, treatment with metformin should be withdrawn immediately and prompt diagnostic evaluation should be performed.

Renal function

GFR should be assessed before treatment initiation and regularly thereafter, see section 4.2. Metformin is contraindicated in patients with GFR<30 mL/min and should be temporarily discontinued in the 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 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 (see section 4.3).

Administration of iodinated contrast agents

Glyformin should not be used: in conditions which may cause dehydration. Intravascular contrast studies with iodinated materials can lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Therefore, in patients in whom any such studies are planned, metformin should be discontinued at the time of, or prior to, the procedure and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal, see sections 4.2 and 4.5.

In any of the above conditions Glyformin should be temporarily suspended and particularly if acidosis is suspected. Only after lactic acidosis or ketoacidosis have been excluded should treatment be resumed. Glyformin is excreted by the kidney therefore regular monitoring of renal function should be undertaken in all diabetics, especially the elderly.

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 reevaluated 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.

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.

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

Vitamin B12

Metformin may reduce vitamin B12 serum levels. The risk of low vitamin B12 levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B12 deficiency. In case of suspicion of vitamin B12 deficiency (such as anaemia or neuropathy), vitamin B12 serum levels should be monitored. Periodic vitamin B12 monitoring could be necessary in patients with risk factors for vitamin B12 deficiency. Metformin therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B12 deficiency provided in line with current clinical guidelines.

An annual vitamin B12 level estimation may be considered desirable in patients on continuous metformin therapy.

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

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of metformin with
- Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

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 the efficacy of metformin.

There may be interactions between Glyformin and anticoagulants; accordingly patients receiving the two drugs may need adjustment of the anticoagulant dosage.

Patients receiving Glyformin over prolonged periods should have an annual estimation of b12 because of decreased b12 absorption.

Combined therapy of Glyformin with a sulphonylurea or insulin may cause hypoglycaemia. Glyformin and insulin therapy stabilisation should be carried out in hospital. During cimetidine therapy reduced renal clearance of metformin has been reported and accordingly a dose reduction should be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy

Uncontrolled hyperglycaemia in the periconceptional phase and during pregnancy is associated with increased risk of congenital abnormalities, pregnancy loss, pregnancy-induced hypertension, preeclampsia, and perinatal mortality. It is important to maintain blood glucose levels as close to normal as possible throughout pregnancy, to reduce the risk of adverse hyperglycaemia-related outcomes to the mother and her child.

Metformin crosses the placenta with levels that can be as high as maternal concentrations.

A large amount of data on pregnant women (more than 1000 exposed outcomes) from a register-based cohort study and published data (meta-analyses, clinical studies, and registries) indicates no increased risk of congenital abnormalities nor feto/neonatal toxicity after exposure to metformin in the periconceptional phase and/or during pregnancy.

There is limited and inconclusive evidence on the metformin effect on the long-term weight outcome of children exposed in utero. Metformin does not appear to affect motor and social development up to 4 years of age in children exposed during pregnancy although data on long term outcomes are limited. If clinically needed, the use of metformin can be considered during pregnancy and in the periconceptional phase as an addition or an alternative to insulin.

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 based on body surface area comparisons.

4.7 Effects on 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

While Glyformin is usually well tolerated, gastro-intestinal disturbances sometimes occur and although they are usually minor they can normally be avoided by taking Glyformin with or after food. It may, however, be necessary temporarily to lower the dose of Glyformin. Glyformin treatment should not be abandoned at the first sign of intolerance because this has been found to resolve spontaneously.

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

Common: Vitamin B12 decrease/deficiency (see section 4.4).
Very rare: Lactic acidosis (see section 4.4).

Lactic acidosis has been associated with Glyformin, but in the rare cases reported it has occurred in patients with contraindications to therapy.

In patients with a metabolic acidosis lacking evidence of ketoacidosis (ketoneuria and ketonaemia)lactic acidosis should be suspected and Glyformin therapy stopped. Lactic acidosis is a medical emergency which must be treated in hospital.

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, 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 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 via Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Hypoglycaemia does not occur if Glyformin is taken alone in overdosage, but it can occur when Glyformin is given concomitantly with a sulphonylurea, insulin or alcohol. In excessive dosage lactic acidosis may develop. The

treatment includes intensive supportive therapy and correcting fluid loss and metabolic disturbance.

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

Metformin is a biguanide oral anti-hyperglycaemic agent which is thought to act through delayed uptake of glucose from the gastro-intestinal tract and by increased peripheral glucose utilisation mediated by increased insulin sensitivity and inhibition of increased hepatic and renal gluconeogenesis.

5.2 Pharmacokinetic properties

Metformin is completely absorbed from the gastro-intestinal tract and is excreted unchanged in the urine. 37.6% of an oral dose was recovered in the urine after 48 hours. Metformin is not protein bound in plasma or metabolised.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Silicon Dioxide
Gelatin
Sodium Starch Glycollate
Purified Water
Magnesium Stearate
Hydroxypropylmethylcellulose
Ethylcellulose

Titanium Dioxide E171
Diethylphthalate
Methanol
Dichloromethane

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months for all packs.

6.4 Special precautions for storage

Store below 25°C in a dry place.
Keep containers securely closed.

6.5 Nature and contents of container

High density polystyrene containers with polythene lids and/or polypropylene containers with polypropylene or polythene lids and polyurethane/polythene inserts.
Pack sizes: 28, 30, 50, 56, 60, 84, 250,500 and 1000
250 micron PVC glass-clear/bluish rigid PVC (pharmaceutical grade). 20 micron hard-tempered aluminium foil coated on the dull side with 6-7 gsm heat seal lacquer and printed on the bright side.
Pack sizes: 28, 30, 50, 56, 60, 84, 100, 250, 500 and 1000

6.6 Special precautions for disposal

No special instructions

7 MARKETING AUTHORISATION HOLDER

Chelonia Healthcare Limited
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8 MARKETING AUTHORISATION NUMBER(S)

PL 33414/0059

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/02/2009

10 DATE OF REVISION OF THE TEXT

14/04/2025