1.3 Product information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed

SUMMARY OF PRODUCTS CHARACTERISTICS

1. Name of the medicinal product

GLUCODIX-ER-1000 (METFORMIN HYDROCHLORIDE EXTENDED - RELEASE TABLETS USP)

2. Qualitative and quantitative composition

Sr. No.	Ingredients	Label Claim	Qty./Tablet (mg)	Actual Qty/batch (kg)	Functions
Dry mixing					
1	Metformin HCl USP*	1000.000	1000.000	100.000	Anti-hyperglycemic Agent
2	HPMC K100M BP	----	174.000	17.400	Extended -release agent
3.	Microcrystalline cellulose (PH-102) BP**	----	46.000	4.600	Diluent
Binding					
4.	Povidone K-30 BP	----	50.000	5.000	Binder
5.	Isopropyl Alcohol BP***	----	0.680 ml	68.000 Ltr	Solvent
Blending & Lubrication					
6.	Colloidal anhydrous silica BP	----	15.000	1.500	Glidant
7.	Magnesium stearate BP	----	15.000	1.500	Lubricant
Total weight of uncoated tablet			**1300.000mg**	**130.000 kg**	

*Quantity to be calculated on the basis of its potency.
**Quantity to be compensates on increasing quantity of active material
***The materials that will not remain in the final product.

3. Pharmaceutical forms

Oral Uncoated Extended-Release 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, it 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, It 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

It is important that GLUCODIX-ER-1000 tablet be taken in divided doses with meals. Dosage increases should be made in increments of 500 mg every 10-15 days, up to a maximum of 2000 mg once daily with the evening meal. If glycaemic control is not

achieved on 2000 mg once daily, and 1000 mg twice daily should be considered, with both doses being given with food. If glycaemic control is still not achieved, patients may be switched to standard GLUCODIX-ER-1000 tablets to a maximum dose of 3000 mg daily.
In patients already treated with GLUCODIX-ER-1000 tablets, the starting dose should be equivalent to the daily dose of GLUCODIX-ER-1000 tablets. In patients treated with metformin at a dose above 2000 mg daily, switching to is not recommended.

Elderly:
Metformin is indicated in the elderly, but not when renal function is impaire.

Method of Administration:
Oral administration

4.3 Contraindications

- Hypersensitivity to metformin or any excipients.
- Diabetic ketoacidosis, diabetic pre-coma.
- Moderate (stage 3b) and severe renal failure or renal dysfunction (CrCL < 45 mL/min or eGFR < 45 ml/min/1.73m^2).
- 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 precaution for use

Lactic acidosis is a very rare, but serious metabolic complication 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.
As metformin is excreted by the kidney, creatinine clearance, eGFR should be determined before initiating treatment and regularly thereafter. In patients with stable chronic heart failure, metformin should be used with a regular monitoring of cardiac and renal function.
Metformin must be discontinued 48 hours before elective surgery under general, spinal or peridural anaesthesia.
Metformin alone does not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetics.

4.5 Paediatric population

Not applicable

4.6 Interaction with other medicinal products and other forms of interactions

Concomitant use not recommended
Alcohol:
Increased risk of lactic acidosis in acute alcohol intoxication, particularly in case of:
-Fasting or malnutrition.
-Hepatic insufficiency.
-Avoid consumption of alcohol and alcohol-containing medicinal product.
Iodinated contrast agents:

Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in metformin hydrochloride accumulation and an increased risk of lactic acidosis.
Metformin hydrochloride must be discontinued prior to, or at the time of the test and not be reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

4.7 Additional information on special populations

Not Applicable

4.8 Fertility, pregnancy and lactation

Pregnancy:

Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased risk of congenital abnormalities and perinatal mortality. There are limited data to suggest that metformin does not increase the risk of congenital abnormalities and does not adversely affect pregnancy outcome in diabetic women. Insulin is generally preferred for treatment of diabetes in women planning on becoming pregnant and during pregnancy to maintain blood glucose levels as close to normal as possible, to reduce the risk of malformations of the foetus.

Lactation:

Metformin is excreted into breast milk, and that the possible effects on the infant should be considered if women wish to breastfeed while receiving the drug. Since 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 breastfeeding and the potential risk to adverse effects on the child.

4.9 Effects on ability to drive and use machines

Not Applicable

4.10 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 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.
Gastrointestinal disorders: Gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, malabsorption syndrome
Metabolism and nutrition disorders: 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: Taste disturbance, asthenia, headache
Skin and subcutaneous tissue disorders: Skin reactions such as erythema, pruritus, urticaria.

4.11 Overdose

Hypoglycaemia can occur when metformin is given concomitantly with a sulphonylurea, insulin or alcohol. In excessive dosage, and particularly if there is a possibility of accumulation, lactic acidosis may develop. Intense symptomatic and

supportive therapy is recommended which should be particularly directed at correcting fluid loss and metabolic disturbance.

5. Pharmacological properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Biguanides
ATC code: 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.
- 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.

5.2 Pharmacokinetic Properties

Absorption
After an oral dose of the prolonged release tablet, metformin absorption is significantly delayed compared to the immediate release tablet with a reported Tmax at approximately 7 hours (Tmax for the immediate release tablet is 2.5 hours).
At steady state, similar to the immediate release formulation, Cmax and AUC are not proportionally increased to the administered dose. The AUC after a single oral administration of 2000 mg of metformin prolonged release tablets is similar to that observed after administration of 1000 mg of metformin immediate release tablets b.i.d.
Intrasubject variability of Cmax and AUC of metformin prolonged release is comparable to that observed with metformin immediate release tablets.
No accumulation is observed after repeated administration of up to 2000 mg of metformin as prolonged release tablets.
Following a single oral administration of one tablet of GLUCODIX-ER-1000 under fasting conditions, mean AUC of 10927 ng.hr/ml and a mean peak plasma concentration of 1488 ng/ml is achieved 4 hours (range 2 to 6.5 hours) after administration.
Following a single oral administration of one tablet of GLUCODIX-ER-1000 under fed conditions, mean AUC of 15577 ng.hr/ml and a mean peak plasma concentration of 1397 ng/ml is achieved 6.5 hours (range of 3.5 to 12 hours) after administration.
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.

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 toxicity to reproduction.

6. Pharmaceutical Particulars

6.1 List of Excipients

HPMC K100M
Microcrystalline cellulose (PH-102)
Povidone K-30
Isopropyl Alcohol
Colloidal anhydrous silica
Magnesium stearate

6.2 Incompatibilities

Not known.

6.3 Shelf Life

36 months from the date of manufacturing

6.4 Special precautions for storage

Store at a temperature not exceeding 30ºC in a dry place. Protect from light. Keep out of reach of children.

6.5 Nature and contents of container

10 X 10 Tablets in Alu-PVC Blister Pack

6.6 Special precautions for disposal and other handling

None

7. Marketing authorisation holder

Name : Stallion Laboratories Pvt. Ltd.
Address : C-1B, 305/2, 3, 4& 5, G.I.D.C.
Kerala (Bavla),
Dist.: Ahmedabad,
Gujarat, India.
Phone : (02714)-268315, 268386
Fax : (02714)-268769
E-mail : info@stallionlabs.com

8. Marketing authorisation number(s)

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9. Date of first authorisation/renewal of the authorisation

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10. Date of revision of the text
