Applicant/PHCR: **AUROGEN SA (PTY) LTD**
Product proprietary name: **DIRBAFIN XR 500 mg and DIRBAFIN 750 mg**
Dosage form and strength: **EXTENDED RELEASE TABLETS 500 mg, 750 mg**
Approved 4 March 2023

1.3.1.1 Professional Information for Medicines for Human Use

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

DIRBAFIN XR 500 mg (tablet)

DIRBAFIN XR 750 mg (tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DIRBAFIN XR 500 mg:

Each extended - release tablet contains metformin hydrochloride USP 500 mg. Sugar free.

DIRBAFIN XR 750 mg:

Each extended - release tablet contains metformin hydrochloride USP 750 mg. Sugar free.

3. PHARMACEUTICAL FORM

DIRBAFIN XR 500 mg:

White to off-white, capsule shaped, bevelled edge, biconvex uncoated tablets debossed with 'C' on one side and '29' on the other side.

DIRBAFIN XR 750 mg:

White to off-white, capsule shaped, bevelled edge, biconvex uncoated tablets debossed with 'A' on one side and '19' on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

DIRBAFIN XR can be given alone as initial therapy or can be administered in combination with other oral antidiabetic medicines or with insulin.

4.2. Posology and method of administration

Posology

DIRBAFIN XR 500 mg:

The usual starting dose is one tablet daily. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastro-intestinal tolerability. The maximum recommended dosage is 4 tablets daily. Dosage increases should be made in increments of 500 mg every 10 to 15 days, up to a maximum of 2 000 mg once daily with an evening meal.

If glycaemic control is not achieved with **DIRBAFIN XR 500 mg** 4 tablets once daily, **DIRBAFIN XR 500 mg** 2 tablets twice daily should be considered, with both doses given with food. If glycaemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3 000 mg daily.

DIRBAFIN XR 750 mg:

The usual starting dose is one tablet daily. After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastro-intestinal tolerability. The recommended dosage is 2 tablets once daily, with an evening

meal. If glycaemic control is not achieved with **DIRBAFIN XR 750 mg** 2 tablets once daily, **DIRBAFIN XR 750 mg** may be increased to a maximum dose of 3 tablets once daily with the evening meal. If glycaemic control is not achieved with **DIRBAFIN XR 750 mg** 3 tablets once daily, one tablet of **DIRBAFIN XR 750 mg** in the morning and two tablets of **DIRBAFIN XR 750 mg** in the evening should be considered, with both doses being given with food. If glycaemic control is still not achieved, patients may be switched to standard metformin tablets to a maximum dose of 3000 mg daily.

Switching patients already treated with metformin tablets: In patients already treated with metformin tablets, the starting dose of **DIRBAFIN XR** should be equivalent to the daily dose of metformin immediate release tablets. In patients treated with metformin at a dose above 2 000 mg, switching to **DIRBAFIN XR** is not recommended.

Switching patients from other oral antidiabetic medicines: If transfer from another oral antidiabetic medicines is intended, discontinue the other medicines and initiate **DIRBAFIN XR** prolonged release tablets at the doses indicated above.

Combination therapy with insulin:

DIRBAFIN XR prolonged release tablets and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose is **DIRBAFIN XR 500 mg** once daily with the evening meal, while insulin dosage is adjusted on the basis of blood glucose measurements. After titration, **DIRBAFIN XR 500 mg** two tablets daily may be considered.

Other combination therapy: See section 4.4

Elderly

Due to the potential for decreased renal function in elderly subjects, the dosage for **DIRBAFIN XR** should be adjusted based on renal function.

Regular assessment of renal function is necessary.

Paediatric Population

In the absence of available data, [PN] XR should not be used in children.

Method of administration

For oral use:

DIRBAFIN XR should be taken with food.

4.3. Contraindications

- Hypersensitivity to metformin hydrochloride or any of the other ingredients.
- Diabetic ketoacidosis, diabetic pre-coma.
- Renal failure or renal dysfunction (creatinine clearance < 60 mL/min)
- Acute conditions with the potential to alter renal function e.g. dehydration, severe infection, shock, intravascular administration of iodinated contrast media.
- Acute or chronic disease which may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, shock, pancreatitis.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism (acute or chronic)
- The use of **DIRBAFIN XR** during pregnancy is not advised.

4.4. Special warnings and precautions for use

- Contraindications should be carefully observed.

- 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.

Lactic acidosis

Lactic acidosis is associated with the use of **DIRBAFIN XR**, range. Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to **DIRBAFIN XR** administration. In patients presenting with a metabolic acidosis and not having evidence of ketoacidosis (ketonuria and ketonaemia), lactic acidosis should be suspected and **DIRBAFIN XR** range therapy should be stopped. Lactic acidosis is a medical emergency, which must be treated in hospital. **DIRBAFIN XR** range is excreted by the kidney and regular monitoring of renal function is advised in all diabetic patients with type 2 diabetes mellitus. The incidence of lactic acidosis may be reduced by assessing also other associated risk factors such a poorly controlled diabetes mellitus, type 2: ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

The risk of metformin accumulation and metformin-associated lactic acidosis increases with the severity of renal impairment because metformin is substantially excreted by the kidney. Clinical recommendations based upon the patient's renal function include:

- Before initiating **DIRBAFIN XR**, obtain an estimated glomerular filtration rate (eGFR).
- **DIRBAFIN XR** is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2.

- Initiation of **DIRBAFIN XR** is not recommended in patients with eGFR between 30-45 mL/min/1.73 m^2.
- Obtain an eGFR at least annually in all patients taking **DIRBAFIN XR**. In patients at risk for the development of renal impairment (e.g., the elderly), renal function should be assessed more frequently.
- In patients taking **DIRBAFIN XR** whose eGFR falls below 45 mL/min/1.73 m^2, assess the benefit and risk of continuing therapy.
- Interactions — The concomitant use of **DIRBAFIN XR** with specific medicines may increase the risk of metformin-associated lactic acidosis: those that impair renal function, result in significant hemodynamic change, interfere with acid-base balance, or increase metformin accumulation. Consider more frequent monitoring of patients.
- Age 65 or greater — The risk of metformin-associated lactic acidosis increases with the patient's age because elderly patients have a greater likelihood of having hepatic, renal, or cardiac impairment than younger patients. Assess renal function more frequently in elderly patients.
- Radiologic studies with contrast — Administration of intravascular iodinated contrast medicines in radiological studies (such as intravenous urography and intravenous angiography) in metformin-treated patients has led to an acute decrease in renal function and failure and the occurrence of lactic acidosis. Stop **DIRBAFIN XR** at the time of, or prior to, an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; in patients with a history of hepatic impairment, alcoholism or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure, and restart **DIRBAFIN XR** if renal function is stable.

- Hypoxic states — Several of the post marketing cases of metformin-associated lactic acidosis occurred in the setting of acute congestive heart failure (particularly when accompanied by hypoperfusion and hypoxemia). Cardiovascular collapse (shock), acute myocardial infarction, sepsis, and other conditions associated with hypoxemia have been associated with lactic acidosis and may cause prerenal azotaemia. When such an event occurs, discontinue **DIRBAFIN XR**.

Diagnosis: Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by a coma. Diagnostic laboratory findings include a decreased pH, decreased blood pH, plasma lactate levels above 5mmol/L and an increased anion gap and lactate/ pyruvate ratio. If metabolic acidosis is suspected, **DIRBAFIN XR** should be discontinued and the patient should be hospitalised immediately.

Renal function

As **DIRBAFIN XR** is excreted by the kidney, serum creatinine levels 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 serum creatinine levels at the upper limit of normal and in elderly subjects.

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 when initiating antihypertensive therapy or diuretic therapy and when starting therapy with a NSAID.

Dehydration

The use of **DIRBAFIN XR** formulations is not advised in conditions which may cause dehydration, or in patients suffering from serious infections, trauma or on low calorie intake.

Vitamin B12

Patients on long-term treatment with **DIRBAFIN XR** formulations should have an annual estimation of vitamin B12 levels, since **DIRBAFIN XR** range may cause mal-absorption of vitamin B12, which may result in megaloblastic anaemia.

Surgery

DIRBAFIN XR should be discontinued 48 hours before elective surgery with general anaesthesia and should not be resumed earlier than 48 hours afterwards.

Concomitant medicines

During concomitant treatment with a sulphonylurea, blood glucose should be monitored because combination therapy may cause hypoglycaemia. Stabilisation of diabetic patients with **DIRBAFIN XR** and insulin should be carried out in hospital because of the possibility of hypoglycaemia until the ratio of the two medicines has been obtained.

4.5 Interaction with other medicines and other forms of interaction

Inadvisable combinations:

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 medications.

Iodinated contrast medicines

Intravascular administration of iodinated contrast medicines may lead to **DIRBAFIN XR** accumulation and a risk of lactic acidosis. **DIRBAFIN XR** should be discontinued prior to, or at the time of the test and not reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal.

Medicines requiring precautions for use

Glucocorticoids (systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. Medical practitioners should inform the patient and perform more frequent blood glucose monitoring, especially at the beginning of treatment. If necessary, the dosage of the antidiabetic medicines should be adjusted during therapy with the other medicine and upon its discontinuation.

ACE-inhibitors may decrease the blood glucose levels. If necessary, the dosage of the antidiabetic medicine should be adjusted during therapy with the other medicine and upon its discontinuation.

Cimetidine: Reduced renal clearance of **DIRBAFIN XR** has been reported during cimetidine therapy, so a dose reduction should be considered.

Anticoagulants: **DIRBAFIN XR** has been reported to diminish the activity of warfarin and so dose adjustments and increased frequency of INR determinations should be considered.

Sulphonylurea: Concomitant therapy of **DIRBAFIN XR** with sulphonylurea may cause hypoglycaemia (see section 4.4).

Vitamins: Long-term treatment with **DIRBAFIN XR** may cause vitamin B12 mal-absorption in the gastro-intestinal tract, thus a dose reduction of **DIRBAFIN XR** should be considered (see section 4.4).

Carbonic Anhydrase Inhibitors such as topiramate, zonisamide, acetazolamide or dichlorphenamide frequently cause a decrease in serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these medicines with **DIRBAFIN XR** may increase the risk for lactic acidosis.

Medicines that reduce DIRBAFIN XR Clearance: Concomitant use of medicines that interfere with common renal tubular transport systems involved in the renal elimination of metformin (ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis.

4.6 Fertility, pregnancy and lactation

Pregnancy:

The use of **DIRBAFIN XR** during pregnancy is not recommended.

Lactation:

There is no information available concerning the safety of **DIRBAFIN XR** during lactation.

Fertility

There are no data available on the effect of **DIRBAFIN XR** on human fertility

4.7 Effects on ability to drive and use machines

DIRBAFIN XR range therapy on its own has no effect on the ability to drive or to use machines. Care should however be taken when **DIRBAFIN XR** range is combined with other anti-diabetic medicines such as sulphonylureas or insulin, as this may cause low blood glucose levels and might interfere with your driving ability.

4.8 Undesirable effects

a. *Summary of the safety profile*

Adverse reactions reported are listed below by system organ class and by frequency.

b. *Tabulated list of adverse reactions*

MedDRA System Organ Class	**Frequency Category**
Metabolic and nutrition disorders:	
Decrease of vitamin B12 absorption with decrease of serum levels during long-term use of the **DIRBAFIN XR** range (should be considered if patient presents with megaloblastic anaemia).	frequent
Lactic acidosis (see section 4.4).	
Nervous system disorders:	
Taste disturbance	Frequent

Gastrointestinal disorders:	
Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, flatulence	Frequent
Hepatobiliary disorders	
Liver function test abnormalities or hepatitis resolving on **DIRBAFIN XR** range discontinuation	Less frequent
Skin and subcutaneous tissue disorders	
Skin reactions such as erythema, pruritus and urticaria.	Less frequent

c. ***Description of selected adverse reactions***

Lactic acidosis

Post marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin-associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain.

d. ***Reporting of suspected adverse reactions***

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Medicine Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Hypoglycaemia can occur when **DIRBAFIN XR** range 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 correcting blood glucose levels.

Treatment of overdosage

There is no specific antidote for overdose with **DIRBAFIN XR** range. Treatment is supportive and symptomatic and should be directed at correcting fluid loss and metabolic disturbances.

Haemodialysis is the most effective way to remove lactate and metformin.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A 21.2 Oral hypoglycaemics, ATC code: A10BA02

Metformin is a biguanide with anti-hyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via three mechanisms:

- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis;
- in muscle, by increasing glucose sensitivity, improving peripheral glucose uptake and utilisation; 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.

5.2 Pharmacokinetic properties

Absorption

Following a single oral dose of **DIRBAFIN XR 500 mg** peak plasma levels (C_{max}) are achieved with a median value of 7 hours.

Following a single oral dose of 1500 mg of **DIRBAFIN XR 750 mg**, a mean plasma concentration of 1193 ng/mL is achieved after a median value of 5 hours (range of 4 to 12 hours).

DIRBAFIN XR 750 mg was shown to be bioequivalent to **DIRBAFIN XR 500 mg**, at a total daily dose of 1500 mg, with respect to C_{max} and AUC in healthy fed and fasted subjects.

At steady-state, both C_{max} and AUC of metformin do not increase proportionally to the administered dose.

Although the AUC is decreased by 30 % when the metformin prolonged release tablet is given under fasting conditions, the peak is neither modified nor delayed by fasting conditions.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak concentration is less than the plasma peak and appears approximately at the same time.

The mean volume of distribution (Vd) ranged between 63 – 276 L.

Metabolism

Metformin is eliminated unchanged in the urine. No metabolite has been identified in humans.

There is no biliary excretion.

Elimination

Metformin renal clearance (>400 mL/min) shows elimination by glomerular filtration and by tubular secretion. After oral intake, the apparent terminal elimination half-life is approximately 6, 5 hours.

Special Populations

Renal Impairment

In patients with decreased renal function the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased (see section 4.3 and section 4.4).

5.3 Preclinical safety data

No data is available as per the Innovator PI and US Innovator PI.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The other ingredients of **DIRBAFIN XR** are:

cellulose microcrystalline, hypromellose, hydroxy propyl cellulose, isopropyl alcohol, carbomer 941, magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25°C.

Keep the blisters in the carton until required for use.

Keep HDPE containers tightly closed.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

DIRBAFIN XR 500 mg and 750 mg

1) Blister Pack:

Blister pack comprises of 250 µm PVC film laminated with 50 µm aclar and 25 µ aluminium foil with 7 gsm heat seal lacquer as the lidding material**.**

Pack size:

60's: Printed cardboard carton containing 6 blisters of 10 tablets each.

90's: Printed cardboard carton containing 9 blisters of 10 tablets each.

120's: Printed cardboard carton containing 12 blisters of 10 tablets each.

2) HDPE Pack:

DIRBAFIN XR 500 mg

For 90's count:

Tablets are packed in white opaque round 150 ml HDPE container

with 38 mm neck finish closed with 38 mm white opaque polypropylene stock ribbed closure or continuous thread closure with wad having induction sealing liner. The HDPE container also contains 9 gram per yard rayon coil.

For 120's count:

Tablets are packed in white opaque round 200 ml HDPE container with 38 mm neck finish closed with 38 mm white opaque polypropylene stock ribbed closure or continuous thread closure with wad having induction sealing liner. The HDPE container also contains 9 gram per yard rayon coil.

Pack size: 90's - One HDPE container contains 90 tablets.

Pack size: 120's - One HDPE container contains 120 tablets.

DIRBAFIN XR 750 mg

For 90's count:

Tablets are packed in white opaque round 200 ml HDPE container

with 38 mm neck finish closed with 38 mm white opaque polypropylene stock ribbed closure or continuous thread closure with wad having induction sealing liner. The HDPE container also contains 9 gram per yard rayon coil.

For 120's count:

Tablets are packed in white opaque round 250 ml HDPE container

with 53 mm neck finish closed with 53 mm white opaque polypropylene stock ribbed closure or continuous thread closure with wad having induction sealing liner. The HDPE container also contains 9 gram per yard rayon coil.

Pack size: 90's - One HDPE container contains 90 tablets.

Pack size: 120's - One HDPE container contains 120 tablets.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements for the disposal and handling of **DIRBAFIN XR**.

7 NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

AUROGEN SA (Pty) Ltd

Woodhill Office Park, Building 1, First Floor

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

8 REGISTRATION NUMBER

DIRBAFIN XR 500 MG: 47/21.2/0392

DIRBAFIN XR 750 MG: 47/21.2/0393

9 DATE OF FIRST AUTHORISATION

17 AUGUST 2021

10 DATE OF REVISION OF TEXT

4 MARCH 2023