Professional Information for METFORMIN CR ZYDUS range

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

METFORMIN CR ZYDUS extended-release tablets

METFORMIN CR 750 ZYDUS extended-release tablets

METFORMIN CR 1 000 ZYDUS extended-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each extended-release **METFORMIN CR ZYDUS** tablet contains 500 mg metformin hydrochloride.

Each extended-release **METFORMIN CR 750 ZYDUS** tablet contains 750 mg metformin hydrochloride.

Each extended-release **METFORMIN CR 1 000 ZYDUS** tablet contains 1 000 mg metformin hydrochloride.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Extended-release tablets.

METFORMIN CR ZYDUS: White to off-white, capsule shaped, uncoated tablets, debossed with '63' on one side and 'Z' on the other side.

METFORMIN CR 750 ZYDUS: White to off-white, capsule shaped, biconvex tablets, plain on both sides.

METFORMIN CR 1 000 ZYDUS: White to off-white, capsule shaped, bevelled, biconvex tablets, plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

METFORMIN CR ZYDUS is indicated for the treatment of type 2 diabetes mellitus in adults. It is particularly useful in treating overweight patients, when diet and exercise alone does not result in adequate control of hyperglycaemia. **METFORMIN CR ZYDUS** can be given on its own as initial therapy, or it can be administered in combination with other oral antidiabetic medicines, or with insulin.

4.2 Posology and method of administration

Posology

METFORMIN CR ZYDUS:

The usual starting dose is one tablet daily given with the evening meal. 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 is 4 tablets daily. Dosage increases should be made in increments of 500 mg every 10 to 15 days, up to a maximum of 4 tablets (2 000 mg) once daily with the evening meal.

If glycaemic control is not achieved with 2 000 mg (4 tablets) of **METFORMIN CR ZYDUS** given once daily, 1 000 mg (2 tablets) of **METFORMIN CR ZYDUS** given twice daily should be considered, with both doses given with food.

If glycaemic control is still not achieved, patients may be switched to metformin immediate-release tablets with a maximum daily dosage of 3 000 mg.

METFORMIN CR 750 ZYDUS:

The usual starting dose is one tablet daily given with the evening meal. 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 recommended dosage is 2 tablets once daily, with the evening meal.

If glycaemic control is not achieved with **METFORMIN CR 750 ZYDUS** 2 tablets once daily, **METFORMIN CR 750 ZYDUS** may be increased to a maximum dose of 3 tablets once daily with the evening meal.

If glycaemic control is not achieved on **METFORMIN CR 750 ZYDUS** 3 tablets once daily, one

tablet of **METFORMIN CR 750 ZYDUS** in the morning and two tablets of **METFORMIN CR 750 ZYDUS** 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 3 000 mg daily.

METFORMIN CR 1 000 ZYDUS:

METFORMIN CR 1 000 ZYDUS is intended as maintenance therapy for patients already treated with either 1 000 mg (2 tablets of 500 mg **METFORMIN CR ZYDUS**) or 2 000 mg (4 tablets of 500 mg **METFORMIN CR ZYDUS**) of sustained-release metformin hydrochloride. If glycaemic control is not achieved, patients may be switched to standard metformin hydrochloride tablets to a maximum dose of 3 000 mg daily.

Switching patients already treated with metformin tablets

In patients already treated with metformin immediate release tablets, the starting dose of **METFORMIN CR ZYDUS** should be equivalent to the daily dose of metformin immediate-release tablets.

In patients treated with metformin immediate release at a dose above 2 000 mg, switching to **METFORMIN CR ZYDUS** is not recommended.

Switching patients from other oral antidiabetic medicines

If transfer from another oral antidiabetic medicine is intended, discontinue the other medicine and initiate **METFORMIN CR ZYDUS** at the doses indicated above.

Combination therapy with insulin

METFORMIN CR ZYDUS and insulin may be used in combination therapy to achieve better blood glucose control. The usual starting dose is 500 mg of **METFORMIN CR ZYDUS** once daily with the evening meal, while insulin dosage is adjusted on the basis of blood glucose measurements. After titration, 1 000 mg of **METFORMIN CR ZYDUS** may be considered.

Other combination therapy

See section 4.4.

Special populations

Elderly patients

Due to the potential for decreased renal function in elderly patients, the dosage for **METFORMIN CR ZYDUS** should be adjusted based on renal function. Regular assessment of renal function is necessary (see section 4.4).

Paediatric population

In the absence of available data, **METFORMIN CR ZYDUS** should not be used in children.

Method of administration

Oral.

4.3 Contraindications

- Hypersensitivity to metformin hydrochloride or to any of the inactive ingredients of **METFORMIN CR ZYDUS** (see section 6.1).
- Any type of acute metabolic acidosis (diabetic coma and ketoacidosis).
- Diabetic precoma.
- Renal failure or renal function impairment (creatinine clearance < 60 mL/min). **METFORMIN CR ZYDUS** may increase the risk of developing lactic acidosis when given to patients with these conditions (see section 4.4).
- Acute conditions that may alter renal function, e.g. dehydration, severe infection, shock, intravascular administration of iodinated contrast media (see section 4.4).
- Diseases which may cause tissue hypoxia (especially acute diseases or worsening of chronic diseases), such as cardiac or respiratory failure, recent myocardial infarction or shock.
- Hepatic insufficiency, acute alcohol intoxication, alcoholism (acute or chronic).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Lactic acidosis

METFORMIN CR ZYDUS can increase the risk of developing lactic acidosis. This is a rare, but serious metabolic complication that can occur because of the accumulation of metformin, as in **METFORMIN CR ZYDUS**. There is a high risk of mortality when treatment is not carried out immediately.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), **METFORMIN CR ZYDUS** should be temporarily discontinued and it is recommended that a health care provider be contacted.

The incidence of lactic acidosis may be reduced by assessing and managing other associated risk factors, such as inadequately controlled diabetes mellitus type 2, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any condition associated with hypoxia.

The characteristics of lactic acidosis is acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia, followed by coma. Diagnostic laboratory test results will indicate decreased blood pH (< 7,3), plasma lactic levels above 5 mmol/L and an increased anion gap and lactate/pyruvate ratio. Treatment with **METFORMIN CR ZYDUS** should be stopped immediately and the patient hospitalised if metabolic acidosis is suspected.

Renal function

Serum creatinine levels should be determined before treatment with **METFORMIN CR ZYDUS** is started and regularly thereafter, since **METFORMIN CR ZYDUS** is excreted by the kidneys.
In patients with normal renal function, testing should be done at least annually. In patients with serum creatinine levels at the upper limit of normal and in elderly patients, testing should be done at least two to four times a year.

METFORMIN CR ZYDUS range therapy should be stopped 2 – 3 days before surgery and before clinical investigations such as intravenous urography and intravenous angiography, and reinstated only after control of renal function has been regained.

The use of **METFORMIN CR ZYDUS** formulations is not advised in conditions which may cause dehydration, or in patients suffering from serious infections, trauma or on low calorie intake. Patients on long-term treatment with **METFORMIN CR ZYDUS** formulations should have an annual estimation of vitamin B_{12} levels, since **METFORMIN CR ZYDUS** range may cause malabsorption of vitamin B_{12}, which may result in megaloblastic anaemia.

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, **METFORMIN CR ZYDUS** may be used with regular monitoring of cardiac and renal function. **METFORMIN CR ZYDUS** is contraindicated in patients with acute and unstable heart failure (see section 4.3).

Elderly patients

Due to the potential for decrease renal function in elderly subjects, the dosage of **METFORMIN CR ZYDUS** should be adjusted based on renal function. Regular assessment of renal function is necessary. Serum creatinine levels should be determined before initiating treatment, and at least two to four times a year in elderly patients. Decreased renal function in elderly patients 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 NSAIDs (see section 4.5).

Administration of iodinated contrast agents

As the intravascular administration of iodinated contrast materials in radiological studies can lead to renal failure, **METFORMIN CR ZYDUS** treatment should be stopped before, or at the time of the test. It should also not be reinstituted until 48 hours afterwards, and only after renal function has

been found to be stable after re-evaluation (see section 4.5).

Surgery and clinical investigations

METFORMIN CR ZYDUS should be discontinued 48 hours before elective surgery with general, spinal or epidural anaesthesia, and not resumed earlier than 48 hours after surgery.

METFORMIN CR ZYDUS should be discontinued two to three days before surgery and before clinical investigations such as intravenous urography and intravenous angiography. Treatment should only be resumed once the control of renal function has been regained.

Hypoglycaemia

METFORMIN CR ZYDUS on its own may not cause hypoglycaemia, but caution is advised when it is used in combination with insulin or other oral antidiabetic medicines (e.g. sulphonylureas). Stabilisation of diabetic patients with **METFORMIN CR ZYDUS** and insulin should be carried out in hospital because of the possibility of hypoglycaemia, until the ratio of the two medicines has been obtained. Contraindications should be carefully observed.

Routine monitoring

All patients should continue to monitor their diet with the regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy restricted diet. Laboratory tests for diabetes monitoring should be performed regularly.

Tablet elimination

The tablet shells may be excreted in faeces. Patients should be advised that this is normal.

4.5 Interaction with other medicines and other forms of interaction

Inadvisable combinations

Alcohol

Consuming alcohol with **METFORMIN CR ZYDUS** increases the risk of developing hypoglycaemia and lactic acidosis in acute alcohol intoxication. This risk is even higher when the patient is fasting,

malnourished or suffer from hepatic insufficiency (see section 4.3).

Iodinated contrast agents

Intravascular administration of iodinated contrast agents may lead to renal failure, resulting in **METFORMIN CR ZYDUS** accumulation and a risk of lactic acidosis. Treatment with **METFORMIN CR ZYDUS** should be discontinued before, or at the time of the test. It should not be reinstituted until 48 hours afterwards, and only after renal function has been re-evaluated and results indicate that it is stable (see section 4.3).

Combinations requiring precautions for use

Some medicines can adversely affect renal function which may increase the risk of lactic acidosis, e.g. nonsteroidal anti-inflammatory medicines (NSAIDs), including selective cyclo-oxygenase (COX) II inhibitors, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using these medicines in combination with **METFORMIN CR ZYDUS**, close monitoring of renal function is necessary.

Glucocorticoids, beta2-agonists and diuretics

Caution is advised when administering **METFORMIN CR ZYDUS** with glucocorticoids (systemic and local routes), beta2-agonists and diuretics, as these medicines have intrinsic hyperglycaemic activity. The patient should be informed, and blood glucose monitoring should be performed more frequently, especially at the initial stages of treatment. If necessary, the dosage of **METFORMIN CR ZYDUS** should be adjusted with the concomitant use of these medicines during therapy, and after treatment is stopped.

ACE inhibitors:

Since ACE inhibitors may decrease the blood glucose levels, caution is advised when co-administering with **METFORMIN CR ZYDUS**. If necessary, the dosage of **METFORMIN CR ZYDUS** should be adjusted during therapy when used in combination with these medicines, and after treatment is stopped.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT_1 and OCT_2.

Co-administration of **METFORMIN CR ZYDUS** with

- Inhibitors of OCT_1 (such as verapamil) may reduce efficacy of **METFORMIN CR ZYDUS**.
- Inducers of OCT_1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of **METFORMIN CR ZYDUS**.
- Inhibitors of OCT_2 (such as cimetidine, dolutegravir, ranolazine, trimethoprim, vandetanib, isavuconazole) may decrease the renal elimination of **METFORMIN CR ZYDUS** and thus lead to an increase in metformin plasma concentration.
- Inhibitors of both OCT_1 and OCT_2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of **METFORMIN CR ZYDUS**.

Caution is advised, especially in patients with renal impairment, when these medicines are co-administered with **METFORMIN CR ZYDUS**, as metformin plasma concentration may increase. If needed, dose adjustment of **METFORMIN CR ZYDUS** may be considered as OCT inhibitors/inducers may alter the efficacy of **METFORMIN CR ZYDUS**.

Anticoagulants

METFORMIN CR ZYDUS has been reported to reduce the activity of anticoagulants, and a dose adjustment of warfarin should be considered when administered concomitantly with anticoagulants.

Sulphonylureas

Caution is advised when **METFORMIN CR ZYDUS** is co-administered with sulphonylureas, as this combined therapy may cause hypoglycaemia.

Vitamins

Long-term treatment with **METFORMIN CR ZYDUS** may cause vitamin B_{12} malabsorption in the gastrointestinal tract, thus a dose reduction of **METFORMIN CR ZYDUS** should be considered.

Paediatric population

No data available.

4.6 Fertility, pregnancy and lactation

The use of **METFORMIN CR ZYDUS** during pregnancy and lactation is contraindicated (see section 4.3).

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 CR ZYDUS** in pregnant women does not indicate an increased risk of congenital abnormalities. It is recommended that impaired glycaemic control or diabetes is not treated with **METFORMIN CR ZYDUS** if a patient plans to become pregnant or during pregnancy. For diabetes it is recommended that insulin be used to maintain blood glucose levels as close to normal as possible to reduce the risk of malformations of the fetus.

Breastfeeding

METFORMIN CR ZYDUS is excreted into human breast milk. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breastfeeding is not recommended during treatment with **METFORMIN CR ZYDUS**.

4.7 Effects on ability to drive and use machines

METFORMIN CR ZYDUS monotherapy does not cause hypoglycaemia and therefore is not expected to have an effect on the ability to drive or to use machines. However, patients should be alerted to the risk of hypoglycaemia when **METFORMIN CR ZYDUS** is used in combination with other antidiabetic medicines (such as sulphonylureas, insulin, repaglinide).

4.8 Undesirable effects

Summary of the safety profile

During treatment initiation, the most frequent adverse reactions were nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, which resolve spontaneously in most cases.

Metabolism and nutrition disorders

Less frequent: Hypoglycaemia, lactic acidosis, megaloblastic anaemia, decrease of vitamin B_{12} and folic acid 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

Frequent: Taste disturbance.

Gastrointestinal disorders

Frequent: Nausea, vomiting, diarrhoea, abdominal pain and loss of appetite, weight loss. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders

Less frequent: Liver function test abnormalities or hepatitis resolving upon **METFORMIN CR ZYDUS** discontinuation.

Skin and subcutaneous tissue disorders

Less frequent: Erythema, pruritus and urticaria.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of **METFORMIN CR ZYDUS** is important. It allows continued monitoring of the benefit/risk balance of **METFORMIN CR ZYDUS**. Health care providers are asked to report any suspected adverse reactions via the **Adverse Drug**

Reaction Reporting Form, found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Hypoglycaemia can occur when **METFORMIN CR ZYDUS** is given concomitantly with an oral hypoglycaemic, insulin or alcohol. Lactic acidosis may develop in case of excessive dosage intake, and particularly if there is a possibility of accumulation.

Lactic acidosis is a medical emergency which needs to be treated in the hospital.

The most effective way to remove lactate and **METFORMIN CR ZYDUS** is haemodialysis. In addition, therapy should be symptomatic and supportive, particularly aimed at correcting fluid loss and blood glucose levels.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 21.2 Oral hypoglycaemics

Pharmacotherapeutic group: Oral anti-diabetics

ATC code: A10BA02: Gastrointestinal tract and metabolism

5.1 Pharmacodynamic properties

Metformin is a biguanide with antihyperglycaemic effects. It lowers both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via three mechanisms:

- lowering 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

Metformin is absorbed primarily from the small intestine.

After administration of a single oral dose of metformin extended-release tablets 500 mg, peak plasma levels (C_{max}) are achieved with a median value of 7 hours. Following a single oral dose of 1 500 mg of metformin extended-release 750 mg tablets, a mean plasma concentration of 1 193 ng/mL is achieved after a median value of 5 hours (range of 4 to 12hours). At steady-state, both Cmax and AUC of metformin do not increase proportionally to the administered dose. The area under the curve with metformin extended-release tablets administered as 2 000 mg once daily, is similar to that observed with metformin immediate-release tablets.

The intra-subject variability of Cmax and AUC with metformin extended-release tablets is comparable with metformin immediate release tablets. Although the AUC is decreased by 30 % when metformin extended-release tablet is given under fasting conditions, the peak is not modified or delayed by fasting conditions.

Meal composition does not influence the absorption.

Distribution

After repeated administration of a dose of up to 2 000 mg of **METFORMIN CR ZYDUS**, metformin does not accumulate in the plasma.

Plasma protein binding is insignificant, and metformin enters erythrocytes. The blood peak concentration is lower than the plasma peak concentration and appears approximately at the same time. The red blood cells are a secondary compartment of distribution. The mean volume of distribution ranges between 63 and 276 L.

Biotransformation

Metformin does not undergo metabolism and is excreted unchanged in the urine. No metabolite has been identified in humans.

Elimination

Metformin renal clearance (> 400 mL/min) shows an elimination by glomerular filtration and by tubular secretion. After oral administration, the biological elimination half-life is approximately 6,5 hours. There is no biliary excretion.

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 (see section 4.2).

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glyceryl behenate

Hypromellose

Microcrystalline cellulose

Povidone.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

METFORMIN CR ZYDUS: 48 months.

METFORMIN CR 750 ZYDUS: 24 months.

METFORMIN CR 1 000 ZYDUS: 24 months.

6.4 Special precautions for storage

METFORMIN CR ZYDUS: Store at or below 25 °C.

METFORMIN CR 750 ZYDUS: Store at or below 30 °C.

METFORMIN CR 1 000 ZYDUS: Store at or below 30 °C.

Keep blister strips in outer carton until required for use.

Protect from light and moisture.

6.5 Nature and contents of container

Clear, transparent PVC/PVDC/silver aluminium blister strips, containing 10 tablets each. Blister strips are packed in an outer cardboard box.

METFORMIN CR ZYDUS: Pack sizes: 90, 120 or 360 tablets.

METFORMIN CR 750 ZYDUS: Pack sizes: 60 or 90 tablets.

METFORMIN CR 1 000 ZYDUS: Pack sizes: 60 or 90 tablets.

6.6 Special precautions for disposal

Any unused medicine should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare S.A. (Pty) Ltd

Southdowns Office Park, Building B, Ground Floor

22 Karee Street

Centurion

0157

8. REGISTRATION NUMBERS

METFORMIN CR ZYDUS: 51/21.2/0684.683

METFORMIN CR 750 ZYDUS: 55/21.2/0674

METFORMIN CR 1 000 ZYDUS: 55/21.2/0675

9. DATE OF FIRST AUTHORISATION

METFORMIN CR ZYDUS: 1 August 2019

METFORMIN CR 750 ZYDUS: 18 July 2023

METFORMIN CR 1 000 ZYDUS: 18 July 2023

10. DATE OF REVISION OF THE TEXT

18 July 2023